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RECIPIENT: Virginia Commonwealth University
Richmond, VA 23284

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14. ABSTRACT: The Chronic Effects of Neurotrauma Consortium (CENC) is a coordinated, multicenter collaboration linking basic science, translational, and clinical neuroscience researchers from the VA, military, and academia to effectively address the diagnostic and therapeutic ramifications of traumatic brain injury (TBI) and its long-term effects. This Consortium is uniquely positioned because of its centralized organization provided by an experienced, professional Coordinating Center directed by senior academic TBI leaders of VA and DOD; 2) linkages between major eight VA TBI/Polytrauma Centers with multiple DoD Centers, and academic research centers 3) extensive, longer term track record of collaborative TBI research 4) access to large military/VA relevant research subject populations and ten innovative and intersecting research projects that are designed to change proactive in the near term and lay the groundwork for subsequent investigation. This consortium brings together a nationwide group of researchers who have extensive track records of internal and external collaborations, demonstrated productivity in knowledge translation and dissemination, and the proven ability to recruit and follow up with research subjects.

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Technical Abstract

Background: The Chronic Effects of Neurotrauma Consortium (CENC) is a coordinated, multicenter collaboration linking basic science, translational, and clinical neuroscience researchers from the VA, military, and academia to effectively address the diagnostic and therapeutic ramifications of traumatic brain injury (TBI) and its long-term effects. This Consortium is uniquely positioned because of its centralized organization provided by an experienced, professional Coordinating Center directed by senior academic TBI leaders of VA and DOD; 2) linkages between major eight VA TBI/Polytrauma Centers with multiple DoD Centers, and academic research centers 3) extensive, longer term track record of collaborative TBI research 4) access to large military/VA relevant research subject populations and ten innovative and intersecting research projects that are designed to change proactive in the near term and lay the groundwork for subsequent investigation. This consortium brings together a nationwide group of researchers who have extensive track records of internal and external collaborations, demonstrated productivity in knowledge translation and dissemination, and the proven ability to recruit and follow up with research subjects.

Objectives: The chronic effects from TBIs, whether single or repeated, on chronic disabling symptoms, on recovery from combat and trauma-related comorbidities, and on long-term brain function in veterans and service members are not known. The overarching goals of CENC are to examine the critical issues related to the identification and characterization of the anatomic, molecular and physiological mechanisms of chronic brain injury and potential neurodegeneration. The specific research studies have been designed to directly address the proposed consortium objectives and focus areas, to build on and leverage existing TBI research activities across the network, to provide meaningful answers to the current questions facing individuals and organizations affected by neurotrauma, and to identify and lead a way ahead.

Research Plan: Current approved studies include the following:

(1) The Observational Study on Late Neurologic Effects of OEF/OIF/OND Combat (CENC0001C) is a large 1400 participant Observational Cohort Study with the objective of identifying and assessing the long-term effects of mild TBI in a population of Veterans and Service Members with a history of deployment and combat exposure in recent conflicts such as Operation Enduring Freedom or Operation Iraqi Freedom. Data collected include a variety of clinical measures, cognitive and neurological functioning assessments, patient-reported outcomes, and biological measures including biospecimen and MRI analysis. This study is taking place at seven Veteran's Affairs Medical Centers located in Richmond, Tampa, Houston, San Antonio, Portland, Minneapolis and Boston as well as one DoD site located at Fort Belvoir, VA.

(2) The Epidemiology of mTBI and Neurosensory Outcomes Study (CENC0004C) is a retrospective cohort study integrating existing federal healthcare databases to study the chronic effects of mTBI on neurodegenerative disease and other comorbidities, and the methods to treat and rehabilitate adverse effects of mTBI in Veterans over time.

(3) The Tau Modifications Study (CENC0005C) is a basic science project to identify the key molecular events in the processing of tau after TBI in rodents and humans, with the goal of developing novel biomarker tools to assess tau dysregulation after TBI.

(4) The Novel White Matter Imaging to Improve Diagnosis of Mild TBI Study (CENC0020P) is an observational cohort study assessing the diagnostic utility of multicomponent-driven equilibrium single pulse observation of T1 and T2 (mcDESPOT) on brain volume after mTBI in Veterans with a history of mTBI, posttraumatic stress or both. This study is located at the VA San Diego Healthcare System.

(5) The Structural and Functional Neurobiology of Veterans Exposed to Primary Blast Forces Study (CENC0034P) is an observational cohort study designed to investigate the microstructural nature and functional effect of diffuse heterogeneous white matter abnormalities following mTBI in Veterans of recent conflicts, using advanced multimodal neuroimaging, structured interview, cognitive testing and questionnaires. This study is located at the WG Hefner VA Medical Center in Salisbury, NC.

(6) The Clinical and Neuroimaging Correlates of Neurodegeneration in Military mTBI Study (CENC0049P) is an observational cohort study designed to test potential markers of mTBI and assess self-report measures by re-assessing an existing cohort of Veterans and Service Members by collecting data through clinical interviews, self-reporting measures, neuroimaging and blood-based protein expression. This study is located at the Minneapolis VA Healthcare System and the University of Minnesota.

(7) The Visual Sensory Impairments and Progression Following Mild Traumatic Brain Injury Study (CENC0056P) is an observational cohort study to identify the spectrum of visual sensory disturbances after mTBI using a new imaging technology, and further to identify potential therapeutic modalities including focal transcranial magnetic stimulation, visual behavioral tasks that may strengthen synaptic connections, chemical neuromodulation, and peripheral and central nerve stimulation. This study is headquartered out of the Iowa City VA Healthcare System with study sites also located in Minneapolis and Palo Alto.

Military/VA Benefit: This project is specifically designed to understand the linkages between blast exposures with TBI, chronic effects, and neurodegeneration to assist in providing current and future care, guide the development of novel interventions to prevent or mitigate cognitive and behavioral decline, and contribute to long-term planning for service member and veterans.

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1. INTRODUCTION: Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

2. KEYWORDS: Provide a brief list of keywords (limit to 20 words):

mTBI
CTE
Neurodegeneration
p-tau
Biomarkers
Blast injuries
Brain concussion
Rehabilitation
Phenotype
Postural Balance
Diffusion Tensor Imaging
Epidemiology
Optical Coherence Tomography (OCT)
Magnetoencephalograpy
mcDESPOT
MRI
Neurosensory
Novel White Matter
Neuroimaging
Comorbidity

3. OVERALL PROJECT SUMMARY: Summarize the progress during appropriate reporting period (single annual or comprehensive final). This section of the report shall be in direct alignment with respect to each task outlined in the approved SOW in a summary of Current Objectives, and a summary of Results, Progress and Accomplishments with Discussion. Key methodology used during the reporting period, including a description of any changes to originally proposed methods, shall be summarized. Data supporting research conclusions, in the form of figures and/or tables, shall be embedded in the text, appended, or referenced to appended manuscripts. Actual or anticipated problems or delays and actions or plans to resolve them shall be included. Additionally, any changes in approach and reasons for these changes shall be reported. **Any change that is substantially different from the original approved SOW (e.g., new or modified tasks, objectives, experiments, etc.) requires review by the Grants Officer's Representative and final approval by USAMRAA Grants Officer through an award modification prior to initiating any changes.**

For clarity, each principal activity is detailed separately below by key Scope of Work domain pertinent to Year 5 activities and requirements.

a. **VCU Coordinating Center:** The Coordinating Center is at VCU and is led by Dr. David Cifu, and serves both to implement specific programs of research designed to provide clinically-relevant answers and interventions for current service members (SMs)

and Veterans and provides leadership in developing innovative research proposals and programs to define the long-term solutions to the chronic effects of TBI, which specifically address the research gaps highlighted in our proposal and subsequent roadmap documents provided to our Government Steering Committee (GSC). The Coordinating Center at VCU insures the overall function of all components of the CENC and will be the primary point of contact to the sponsors. The primary goal of the VCU Coordinating Center is to insure completion of all activities; sponsor required reporting; and compliance for the CENC.

(1) Continued subcontracts for approved studies and sites.
(2) Continued to work towards the successful transition of the Neuropathology Core from USUHS to the Boston VA under the direction of Dr. Ann McKee.
(3) Continued assurance of all IRB and IACUC protocols were obtained and maintained.
(4) Ensured that relevant regulatory, reporting and fiscal documents were completed and submitted.
(5) Hosted all telecommunications between consortium members and appropriate parties.
(6) Coordination with the Eisenhower Army Medical Center resulted in them providing Active Service Members as participants in the Longitudinal Study (Study 1) in order to increase the number of Current Service Members. This effort along with other initiatives increased our Current Service Member percentage.
(7) Edited and Published the Special Edition of *Brain Injury* in September which included 15 articles and an introduction. See Appendices 1-16.
(8) Held meetings of the Consumer Advisor Board and the Scientific Advisory Board.
(9) Published research and presented on CENC at major conferences (see below).
(10) Continued to improve our social media presence to include Facebook, Twitter and Instagram.
(11) Submitted/monitored IRB status of protocol approval for VINCI for Dr. Dismuke's collaborative health economics study using Richmond as pilot site; sharing of PHI to extract data approved at their IRB.
(12) VCU staff worked with RTI and Study PIs in order to lock down the timelines for the transition from enrollment/data gathering to analysis and dissemination.
(13) The CENC Leadership initially recommended that Study 56 (Kardon) end their study at the end of FY 18 like the other remaining studies. After further review and recommendations from CENC Leadership, it was decided to allow Study 56 (Kardon) to continue follow-ups through Dec-18 with analysis and dissemination to continue through Feb-19.
(14) VCU staff worked with both the Program/Science Officer (Dr. Christie Vu) and the Grants Officer Representative (Mr. Kenneth Greer) in order to get our request for extension without funding approved.
(15) VCU staff worked with FITBIR operations staff in order to develop a plan for inputting CENC data into FITBIR in a timely fashion keeping in mind other operational requirements.
(16) VCU staff participated in a symposium at the Federal Interagency Conference on Traumatic Brain Injury.

b. **Neuroimaging Core:** The Neuroimaging Core is located at the Baylor College of Medicine (BCM) and the Michael E. DeBakey VA Medical Center in Houston, Texas. It is led by Drs. Elisabeth Wilde and Harvey Levin, but utilizes a model of sub-cores for data analysis, including some forms of volumetric and FLAIR analysis by Drs. Erin Bigler and Mr. Tracy Abildskov (Brigham Young University), diffusion analysis by Dr. David Tate (University of Missouri, St. Louis), additional diffusion and volumetric analysis by Drs. James Stone and Nick Tustison (University of Virginia) and functional connectivity analysis by Dr. Mary Newsome (Baylor College of Medicine and MEDVAMC). The Core includes experts from the fields of neuroradiology, neuropsychology, magnetic resonance imaging (MRI) physics, information technology (IT) and computer programming, and statistics. The Core has facilitated sequence development and pulse programming, training and supervision of technologists and support personnel, and quality assurance (QA) in support of CENC. At the time of this report, the Core has worked on the following four areas:

(1) Standardization and Quality Control. The Imaging Core has established standardized imaging acquisition parameters and imaging data collection policies and procedures where applicable, as well as provided support and guidance on key imaging components. Core personnel have continued testing of the imaging sequences at existing and new Study 1 sites, as well as imaging obtained for other CENC studies involving imaging. Core personnel continue to monitor imaging data acquisition quality and transfer (both QA and human subject data), and Dr. Taylor (now VCU) continues to review quality assurance (QA) phantom test data. Imaging-related artifacts are reported to Core personnel involved in data analysis as well as members of the project team at the site where the imaging data is collected. To date, imaging quality has generally been deemed to be acceptable, though there have been some expected issues with subject motion or artifacts in a subset of participants. In the current reporting period, Drs. Wilde and Taylor performed site visits at Portland VA (July 2018) and Boston VA (September 2018). Additional visits related to scanner updates are planned to examine pre-post upgrade human and phantom data and to monitor changes induced by software or hardware upgrades are planned for Tampa, Portland, and Houston as well as annual visit to each of the other sites.

(2) Data Transfer. Over the course of the past year, Drs. Wilde, Scheibel and other members of the Imaging Core from RTI continued communication with Dan Marcus (Radiologics) as well as Baylor College of Medicine IT specialists and key personnel, and Thomas Fleissner, who is the CEO of the VA-approved vendor (Houston Information Team LLC) regarding the Radiologics platform for data transfer. During the current reporting period, mapping of the project architecture and permissions for each project involving imaging data and XNAT installation were completed, we obtained appropriate security clearances, and the system passed rigorous security testing. Mr. Abildskov was involved in migrating the existing data to the new system.

(3) Data Analysis. Volumetric data analysis remains fairly up to date for subjects that have been transferred to the Core using a few different analysis pipelines (FreeSurfer and Advanced Normalizaton Tools or ANTs). Dr. Bigler/Dr. Wilde's team has performed

in-depth analyses of differences between the previous software version and the current one, and this has been a basis for a publication under review.

Data analysis for DTI is also fairly current using two separate pipelines (ENIGMA and VistaSoft; Dr. Tate), with additional data analysis underway also using ANTs (Drs. Stone and Tustison) and TORTOISE (Dr. Pierpaoli). Drs. Wilde, Tate and Taylor continue to meet by teleconference with Dr. Pierpaoli and his staff to address analytic progress using the TORTOISE pre-processing pipeline and to further review data quality. We have worked with each site to incorporate suggested changes including 1) the use of fat suppressed T2-weighted imaging (as opposed to non-fat-suppressed T2) and 2) the use of 2 diffusion acquisitions obtained in opposite phase encoding directions to further reduce distortion at sites where this was logistically possible.

FcMRI analysis is also underway utilizing seed-based correlation, independent components analysis and graph theory analytic methods (Dr. Newsome's team and Dr. Stone/Tustison's team.

Throughout this reporting period, bi-weekly conference calls included review of initial analysis results and planning manuscripts. Several Imaging Core investigators are also heavily involved in several analysis working groups for study 1 as well as other CENC studies.

(4) Clinical Reads and Common Data Element Coding. Drs. York, Nathan, Betts, and Duncan continue to perform Common Data Element (CDE) codings for all data collected under CENC. Through this reporting period, we have had additional biweekly or monthly conference calls to review the coding procedures and data entry procedures and to review specific cases to test consistency in the CDE coding. Dr. Wilde and the CENC neuroradiologists were involved in the creation of additional imaging Common Data Elements for TBI that are now included in the recently-released Sports-Related Concussion set; these additional elements reflect more subtle findings that may be important for mild TBI in both sports-related concussion and military TBI.

The BYU subcore continues to maintain the PACS system used to facilitate the neuroradiologists' clinical readings and the CDE codings. This system allows the neuroradiologists to more readily access the images (without having to download data) and to utilize a more efficient version of the preferred Osirix software to read the data.

In addition to the CDE coding, Dr. York continues to perform clinical reads for Wake Forest/Salisbury and UCSD/San Diego as there is no neuroradiologist on site to perform these (Note: clinical reads are performed by local neuroradiologists at Houston, San Antonio, Tampa and Richmond Study 1 sites). Dr. Nathan performs clinical reads for the Ft. Belvoir and Boston sites (Study 1). Dr. Duncan performs clinical reads for Portland (Study 1) and 3 projects with imaging in Minneapolis (Study 1 and Davenport and Kardon). We now have less than 100 CDE codings to complete (out of over 1500 subjects).

c. **Neuropathology Core:** The Neuropathology Core is located at VA Boston, led by Dr. Ann McKee, where a new, state-of-the-art brain bank facility has been established. The Neuropathology Core will manage the collection of brain specimens from participants using an existing national network of dieners and neuropathologists. We have developed our methodology for the clinical information. The clinical data will be identified through two clinical phone conversations that have been finalized. These conversations aim to gain characterization of TBI exposure (quantity, severity, frequency, etc.), athletic history (specifying sports played, how long each sport was played, and positions played) military history (identifying when the donor served, where the donor was stationed, how many years of combat the donor served, and exposure to blasts and various other weapons) in vivo diagnoses of cognitive presentation, (e.g. dementia) behavior/mood (e.g. depression) and objective measures of cognition and behavior/mood using validated questionnaires (e.g. Behavioral Rating Inventory of Executive Function-Adult Version). Neuropathological outcomes will include diagnoses of various neurodegenerative diseases based on published pathological criteria and quantitative measures of tau, β-amyloid, α-synuclein, pTDP-43, vascular disease, and neuronal loss. Clinicopathological correlation studies will be performed. Clinical data and well-prepared tissue will be made available to qualified researchers engaged in TBI-related research. During this fiscal year, the Core has:

(1) The CENC VA Brain Bank team has been actively recruiting, registering veterans for donation, harvesting brain donations, analyzing tissue, and gathering clinical and neuropathological data over the past year. To increase recruitment, we've set up tables on the main floor of VA Boston, distributed brochures/ flyers across all VAs in Massachusetts and McKee continued presenting our findings on both our athlete and military cohorts at multiple veteran and non-veteran affiliated events.
(2) The research team has expanded to include a full-time histotechnologist and we are in the process of hiring an administrative coordinator.
(3) The clinical questionnaires have been finalized. Data forms include characterization of TBI exposure (quantity, severity, frequency, etc.), athletic history (specifying sports played, how long each sport was played, and positions played) military history (identifying when the donor served, where the donor was stationed, how many years of combat the donor served, and exposure to blasts and various other weapons), in vivo diagnoses of cognitive presentation, (e.g. dementia) behavior/mood (e.g. depression) and objective measures of cognition and behavior/mood using validated questionnaires (e.g. Behavioral Rating Inventory of Executive Function-Adult Version).
(4) Neuropathological outcomes include diagnoses of neurodegenerative diseases based on published pathological criteria and quantitative measures of tau, β-amyloid, α-synuclein, pTDP-43, vascular disease, and neuronal loss. Clinicopathological correlation studies are in process. Clinical data and well-prepared tissue samples will be made available to qualified researchers engaged in TBI-related research.
(5) The CENC team is in the process of writing a comprehensive clinicopathological manuscript on the OEF/OIF cases that have been harvested through the CENC brain bank. Several other manuscripts are in preparation for submission.
(6) The CENC Neuropath Core is working closely with Dr. Kathryn M. Beasley, PhD, FACHE, Captain, United States Navy (Ret), Director, Government Relations: Health

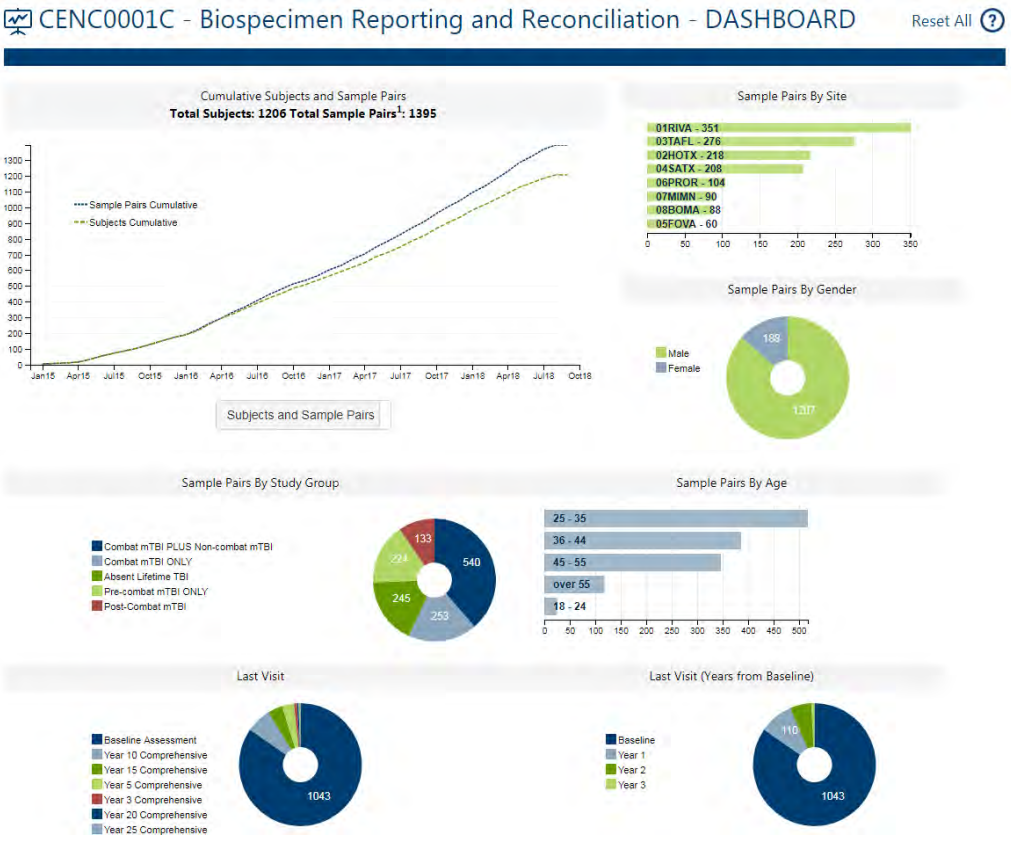
Affairs, The Military Officers Association of America (MOAA). Dr. Beasley is writing an MOAA publication to encourage Women Veterans and service members to sign up for CENC brain donation.

CENC VA Boston:
Current brain donations from military veterans: n=132, 22-98 years (m 72 years).

d. **Biorepository Core:** The Biomarker Core is located at USUHS, and is led by Dr. Brian Cox and Dr. Kimbra Kenney. During the fiscal year, the Core has:

(1) Received biomarker samples from all Longitudinal Study sites, as follows:

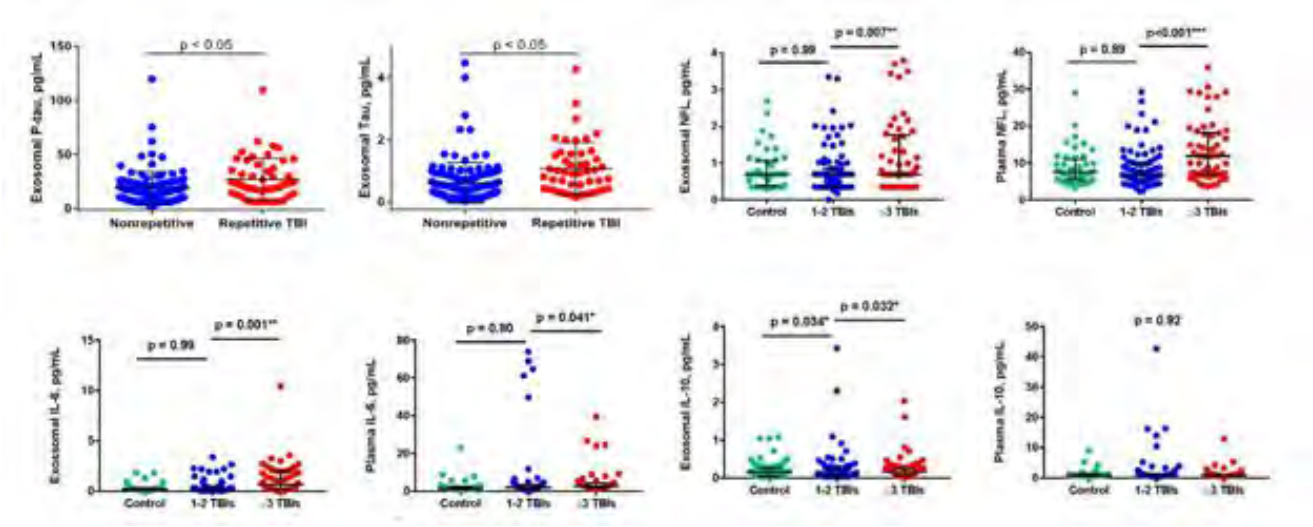
a. 49 shipments from all 8 active Study 1 sites (Cifu/Walker). (See table below) for a total of >22,000 specimen aliquots from 1,431 participants at their baseline visit and from 174 participants at follow-up visits.
b. 7 shipments of samples from Study 49 (Davenport) for a total of 144 specimens from Study 49 (enrollment complete).
c. Carried out genetic analyses of DNA samples from 20 participants from Study 20 (Jak) for a total of 20 specimens from Study 20.
d. Distributed 195 samples for a Biomarker Discovery Project (CENC PI-Kimbra Kenney, MD).



(2) Clinical Service Support to Longitudinal Studies: Provided information to each site regarding quality control, and process issues with the samples:

a. Carried out DNA extraction from 1,009 buffy coat samples
b. Completed APOE genotyping on 759 extracted DNA samples
c. Determined that APOE e4 allele is over-represented in CENC Study 1 population at ~ twice the rate expected (28.4% versus 14%) and that the homozygous E4 allele is over-represented at 1.5 times the expected rate (2.7% versus 1.8%). Analysis is on-going with correlation among neurocognitive outcomes, plasma and exosomal candidate biomarkers and APOE genotyping
d. Completed neuroendocrine screen of 1,431 Study 1 subjects through CLIA-certified laboratory. TSH continues to be the most common neuroendocrine abnormality detected among Study 1 subjects (at 10%). No cases of growth hormone deficiency have been identified among the cohort.

(3) Completed protein analysis of plasma samples from biomarker discovery project from 195 CENC well-characterized Study 1 subjects (102 mTBI with LOC, 48 mTBI without LOC and 45 no TBI) with correlation of 9 plasma and exosomal protein biomarkers [total tau (t-tau), phosphorylated-tau (p-tau), amyloid β40, amyloid β42, neurofilament light chain (NFL), Interleukin-6, Interleukin-10, tumor necrosis factor- α and vascular endothelial grown factor (VEGF)]. We found that repetitive (≥ 3 mTBI) is associated with elevations of exosomal p-tau, t-tau, NFL, IL-6 and IL-10 and plasma NFL compared to those with 1-2 mTBI or no TBI. Plasma and exosomal Aβ40, Aβ42, TNF-α, and VEGF are not associated with repetitive mTBI. Further, elevations of exosomal t-tau, p-tau, NFL, IL-6 and IL-10 correlate with chronic neuropsychological symptoms (as measured by the following: neurobehavioral symptom inventory or NSI, PTSD checklist for DSM-5 or PCL-5 and Patient Health Questionnaire or PHQ-9), suggesting that repetitive mTBI may contribute to chronic neurological symptoms.



(4) We found no significant differences between plasma and total circulating exosomal proteins assayed among Longitudinal study participants with or without remote combat-deployed mTBI or blast versus blunt TBI. These results were presented at the National Neurotrauma Society annual meeting in Toronto Canada in August, 2018 and as a platform presentation and panel discussion at the Military Health System Research Symposium in Kissimee, Florida in August, 2018. A manuscript of exosomal t-tau and p-tau results was published in the CENC 2018 special issue of *Brain Injury* and a manuscript of the NFL, neuroinflammatory and vascular biomarker results is being prepared for submission to a peer-reviewed journal in early FY2019. Results from this analysis will be presented at the NOV 2018 State of the Science Meeting on Blood Based Biomarkers for TBI at Fort Detrick, MD.

(5) We are currently completing imaging (DTI, gray and white matter volumetrics and white matter hyperintensities) and neuropsychological testing correlations with mTBI status and candidate biomarker levels in collaboration with CENC neuroimaging core personnel, Lisa Wilde and David Tate.

(6) We initiated our biomarker project of salivary and exosomal microRNA profiles from this same cohort and microRNA survey of over 800 microRNAs with miRNA profile correlation with TBI, imaging, clinical and TBI outcomes currently ongoing with anticipated completion in the first quarter of the NCE CENC year 6.

(7) In collaboration with industry partner, Meso-Scale Discovery (MSD), we launched a CDMRP funded grant (W81XWH-16-PRARP-CSRA) for a biomarker discovery project of neurodegeneration after TBI and in SEPT 2018 submitted a Biomarker project proposal to the CENC Research Committee that expands our current protein biomarker analyses to 66 candidate proteins in serum samples from up to 700 participants from the CENC Longitudinal study and Study 49 (Clinical and Neuroimaging Correlates of Neurodegeneration in Military mTBI) in collaboration with Bill Walker, Nick Davenport, Lisa Wilde and MSD)

e. **Biostatistics [B], Data Management [DM], and Study Management [SM] Core:**
The Biostatistics, Data Management, and Study Management Core (BDMSM) is located at RTI and led by Dr. Rick Williams (continue overall leadership role with Drs. Cifu and Hinds) and Dr. Tracy Nolen (role changed to PI of BDMSM; had been biostatics lead for the CENC project in prior years). The Core serves as a statistics support, data management, and study management resource for the CENC and all consortium members. During this fiscal year, the BDMSM Core has:

(1) Administrative activities to support the overall coordination of BDMSM Core activities within the CENC consortium, including reporting requirements and presentations to the GSC.

(2) Support of the Data Monitoring Committee (teleconferences held 10/25/2017 and 7/18/2018). There was an additional review of Study 1 done during April 2018.

Additionally, coordinated the committee review and comment on Study 56 continuing in follow-up visits until 12/31/2018.

(3) Research computing and data management groups have continued with support, maintenance to the CENC website. This year studies 8,20,34, and 49 were completed and data was cleaned and locked; datasets provided to study teams.

(4) Ongoing data management and call center support has continued for Study 1. Monthly site performance statistics and reporting continued.

(5) Longitudinal data snapshot for Study 1 was provided to Dr. Walker/VCU on 7/20/2018. BDMSM team has continued to share imaging and study data to support analyses and manuscripts. Copy of final FITBIR submission provided to Dr. Walker/VCU on 10/11/2018.

(6) FITBIR submissions continued, with latest upload to database encompassing 171,841 records added for subjects across studies 1, 08, 20, 25, 34, 49, and 56. Ongoing data clarification/query management activities, and study dashboard updates were done across all studies. Maintenance and end-user support provided across all CENC sites for Medidata Rave, REDCap, and the custom created study management system (SMS) for Study 1.

(7) Monthly data quality reviews (by data management staff, via queries, and coordinated with biostatistics reviews) through June 2018 and ongoing TBI diagnosis committee adjudication and quality review support.

(8) Efforts to coordinate neuroimaging (NI) data (including web based central reads, site-level clinical reads, and database reconciliations of the images themselves), have continued with reporting and meetings held weekly for more than half of FY18.

(9) As of March 2018, the BDMSM was tasked with reducing budget by ~40% for the balance of the fiscal year. The resulting reduction in SOW required to achieve these budget cuts was agreed upon in consultation with VCU. The budgetary goals were reached.

(10) RTI staff were authors on the following publications during this reporting period

a. 3 for Study 5
b. 6 for Study 1
c. 1 for Study 49

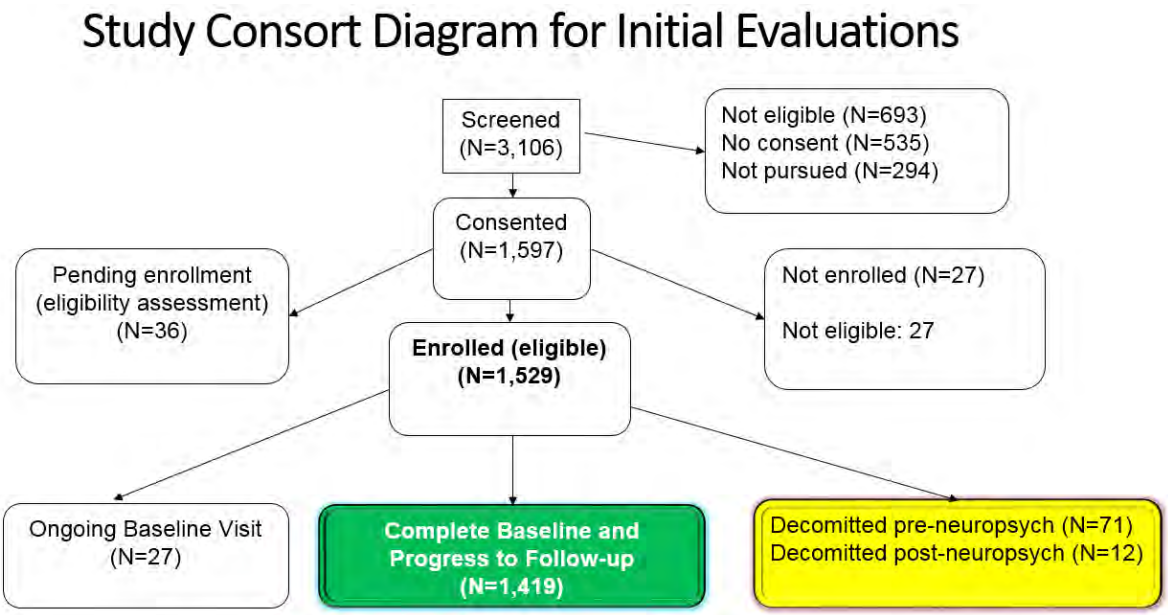
(11) There are an additional 14 manuscripts for which RTI staff have completed analyses and provided statistical reports or draft text for analytic methods and results that are pending lead author completion and/or submission (6 for Study 1, 2 for Study 5, 2 for Study 8, 1 for Study 49 and 3 for the Neuroimaging Core).

(12) RTI staff also provided support to 20 presentations during this reporting period including for the Federal Interagency Conference on TBI, Joint Statistical Meetings, Military Health System Research Symposium, International Society for Magnetic Resonance in Medicine, International Society for Traumatic Stress, and American Congress of Rehabilitation Medicine.

f. **Peer Review Program:** No PRP during this Fiscal Year.

g. **CENC0001C - Observational Study on Late Neurologic Effects of OEF/OIF/OND Combat:** This study's goal is to establish a large cohort (880) of former U.S. OEF/OIF/OND combatants who have had at least one mild Traumatic Brain Injury (mTBI), and follow the members of the cohort long-term to assess specific areas of their physical and mental health. Given the unclear role of mTBI(s) on long term health and the frequent co-occurrence of posttraumatic stress disorder (PTSD) in warfighters, the study will include a group of participants (220) who have experienced combat but have not had an mTBI. During this fiscal year, this study has:

(1) Continued to exceed target enrollment rate and exceeded the original total enrollment target of 1100. During this reporting year, we added 467 participants with 81 of those have a negative lifetime history of mTBI. We also continued to raise the number of key subgroups including current service member participants and female participants.



(2) Successfully balanced rate of enrollments and escalating rate of longitudinal assessments across sites.

(3) Maintained high retention rate (currently 95%) and improved follow-up longitudinal visit completion rate (currently 78% for in-person comprehensive and 84% for interval annual telephonic).

(4) Added new processes to further improve visit completion rates:

a. alternate telephonic version of in-person assessment if feasibility for in-person visit ruled out.

b. further fine-tuned our central notification, communication, and travel assistance system.

c. deployed advance scheduling reminder letter and last-ditch certification letter mailout program at all sites.

d. deployed new certificate for completed telephone visits and CENC coin for completed in-person visit for positive reinforcement. .

(5) Several of the Study 1 Site PIs submitted manuscripts that were included in the Special Edition of *Brain Injury*. For detailed findings, see Appendices 3/4/11/13/15/16 but here is a small sample of what can be found:

a. Preliminary Findings Quantitative EEG (QEEG) Brain Networking Measures Using Graph Theory Analytics: The aim is to test whether chronic mild traumatic brain injury (mTBI) is associated with different graph network properties across frequency bands.

Subjects: 146 subjects from CENC Richmond Snapshot with qEEG data.

		PTSD_2		Total
		0	1	
TBI_Binary	0	24	4	28
	1	78	40	118
Total		102	44	146

With prior research by our group (Walker CDMRP Blast Exposure Study Cohort data), we found that mTBI with post-traumatic amnesia (PTA) was associated with network alterations primarily in the delta band; effects of mTBI were also observed in the beta band. In the delta band, mTBI with PTA was associated with higher density, shorter characteristic path length, and higher global efficiency; however, these networks were less structured than those of participants without PTA, with measures of local connectivity (clustering coefficient and small-world index) more closely resembling these measures in random networks with the same number of edges.

Preliminarily, with the new CENC data, we do see some differences in the delta band. We do not see significant differences in density or global efficiency. We did however observe, in the delta band, some differences in normalized clustering coefficient and small world index. These two measures indicate how closely the measures in participant brain networks resemble these measures in random networks with the same number of edges. The smaller the normalized measure, the closer the measure is to that of a random network. Clustering coefficient and Small World Index are measures of local connectivity and structure.

Figure 1: Consistent with earlier study, those with mTBI have higher edge density on average than those without, but the difference is not significant (p=.17)

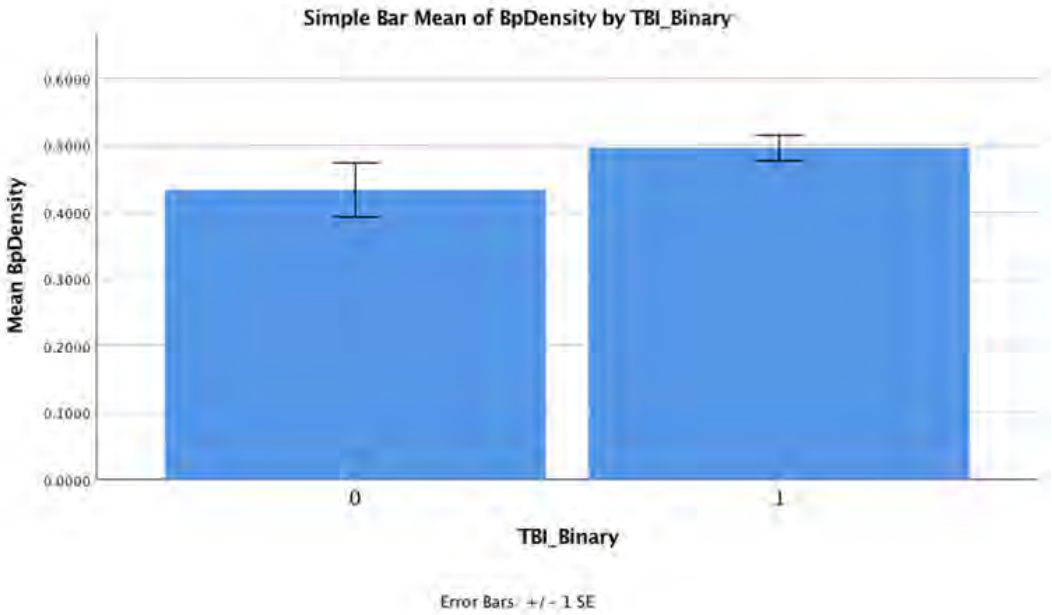


Figure 2: Also consistent with earlier study, those with mTBI have lower normalized clustering coefficient on average than those without, difference is significant at .10 level (p=.10).

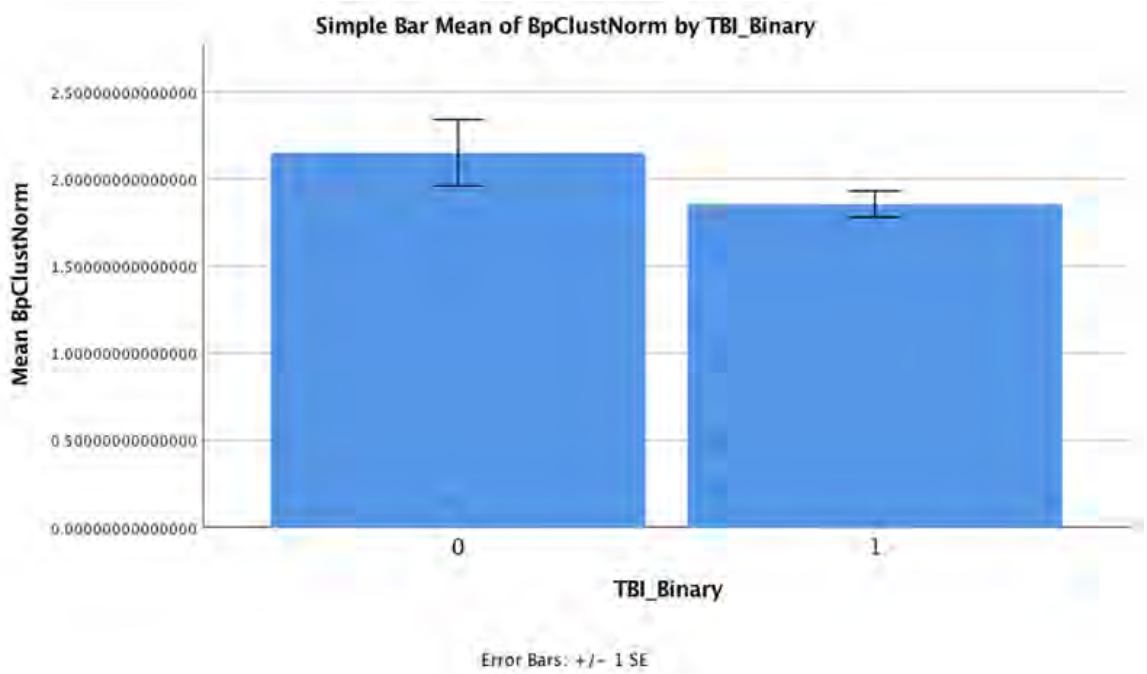
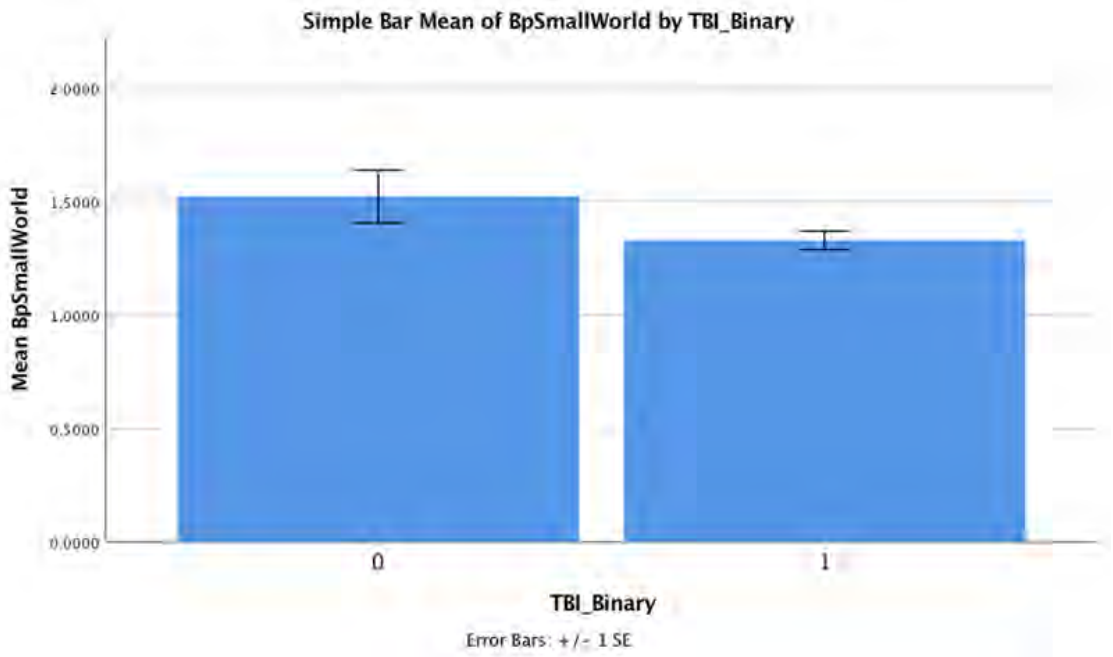


Figure 3: Also consistent with earlier study, those with mTBI have lower small world coefficient on average than those without, difference is significant at .10 level (p=.06).



If we restrict the population to those without PTSD (a possible confounder)(n=102), we find more striking differences.

Figure 4: Consistent with earlier study, those with mTBI have higher edge density on average than those without; difference is significant at .10 level (p=.08)

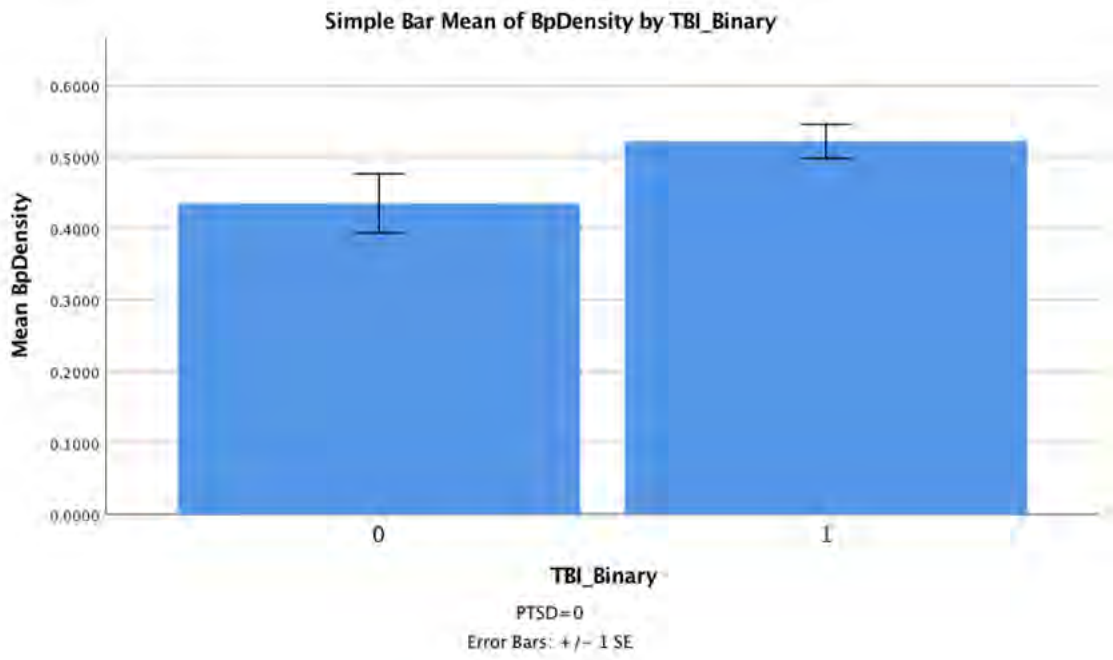


Figure 5: Also consistent with earlier study, those with mTBI have lower normalized clustering coefficient on average than those without, difference is significant at .10 level (p=.08).

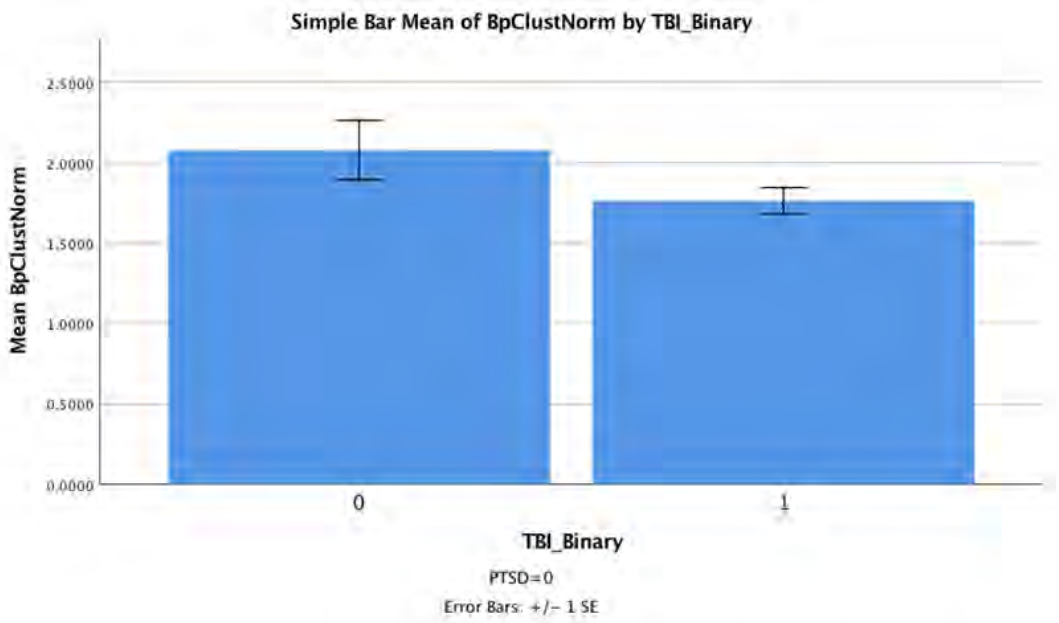
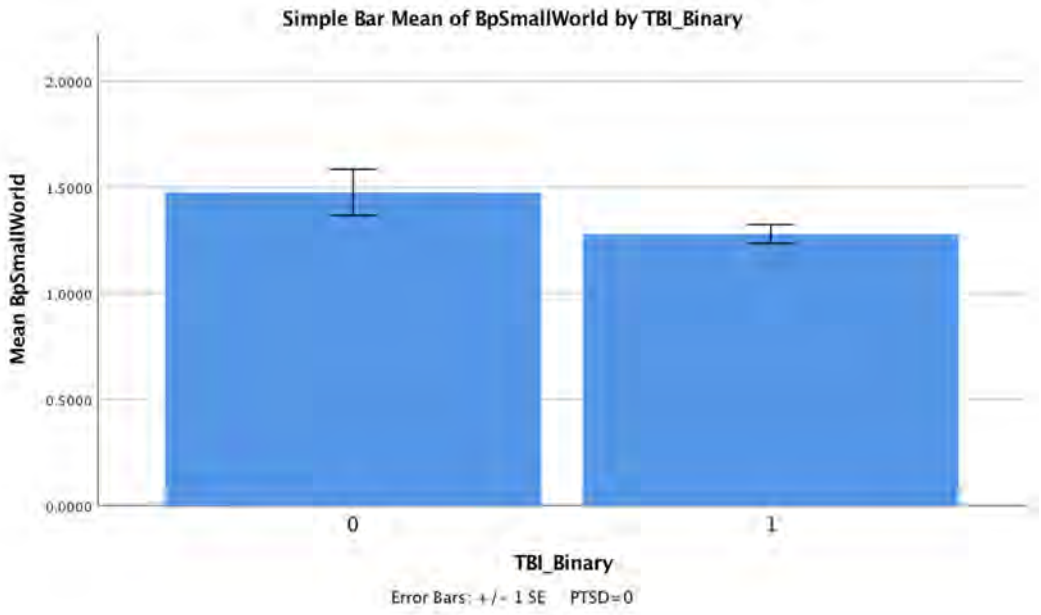


Figure 6: Also consistent with earlier study, those with mTBI have lower small world coefficient on average than those without, difference is significant at .10 level (p=.05).



b. Belanger et al. The Impact of MTBI Burden on Cognitive Performance: A Chronic Effects of Neurotrauma Consortium (CENC) Study: The initial linear regression was not significant. Total mTBI burden did not predict performance on any cognitive factor, p>.05. The SEM results are presented in Table 1. The estimates for the total and

direct effects in most models are positive, though generally not significant. The included mediators were also generally not significant. The one exception was sleep difficulties on Factor 2 (working memory). mTBI burden was predictive of poorer working memory performance in those with sleep difficulties. Other than that, depression was associated with all factors with the direction of the relationship in the direction expected (i.e. presence of depression associated with lower scores). Additionally, PTSD was associated with factor 5 (memory).

Various confounders and covariates (controlled for in the models) were significant. Of note, total combat exposure was associated with TBI exposure, such that greater combat exposure was associated with a greater number of mTBIs. High blood pressure was associated with memory performance such that higher blood pressure was associated with worse memory performance. Not surprisingly, age was negatively associated with cognitive performance across factors and time since index injury was adversely associated with performance on cognitive control. Finally, female gender was associated with better performance on the List Learning factor.

Table 2. Results of the Structural Equation Models (SEM)

SEM Results	Neurocognition Factor 1: List Learning	Neurocognition Factor 2: Working Memory	Neurocognition Factor 3: Cognitive Control	Neurocognition Factor 4: Fluency	Neurocognition Factor 5: Memory
Repetitive TBI, continuous					
Total Effect					
Parameter Estimate	0.08	0.02	-0.03	0.04	0.00
p-value	.0018*	.4342	.2180	.1224	.8714
Direct Effect					
Parameter Estimate	0.09	0.05	0.00	0.06	0.01
p-value	.0010*	.0846	.9887	.0249*	.7660
Indirect Effect					
Parameter Estimate	-0.01	-0.03	-0.03	-0.02	-0.00
p-value	.3527	.0033*	.0005*	.0169*	.6426

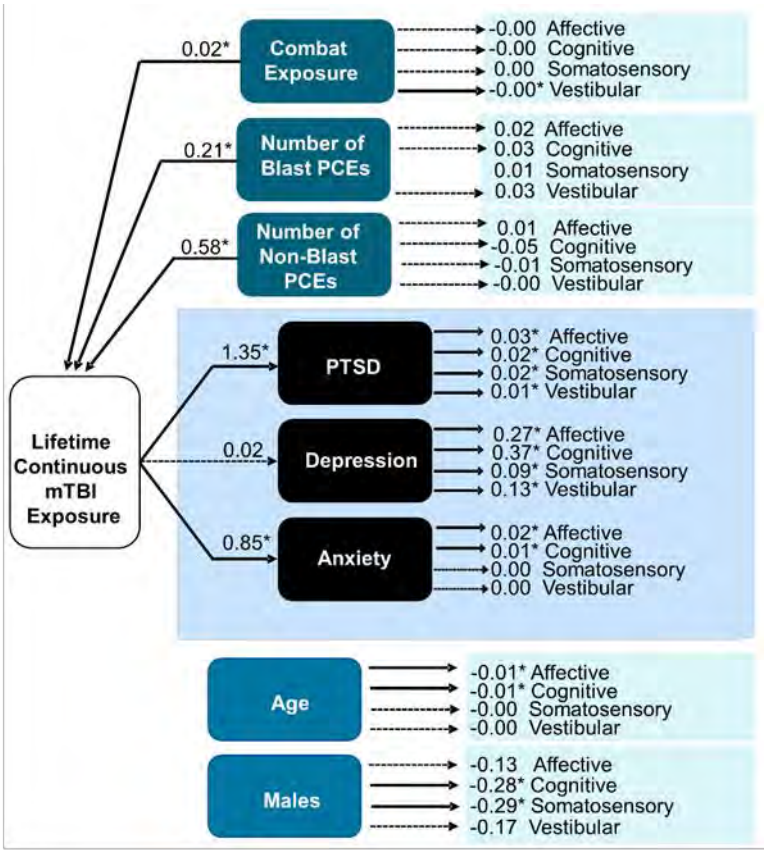
Note. *statistically significant, $p<.05$.

c. Pogoda et al. The Relationship Between Mild Traumatic Brain Injury and Neurobehavioral Symptoms among those who Served in OEF/OIF/OND Combat: A Chronic Effects of Neurotrauma Consortium Study: Here is a list of preliminary conclusions. (1) A higher number of mTBI exposures was associated with more severe NSI symptoms in this OEF/OIF/OND SM and Veteran population. (2) MTBI with co-occurring PTSD, depression, and/or anxiety contributed to increased symptom severity in most NSI domains. (3) These NSI symptom difficulties are being reported nearly 10 years after an index date for most participants, suggesting that systematic symptom assessment, treatment, and evaluation of treatment may be important for OEF/OIF/OND combat SMs and Veterans.

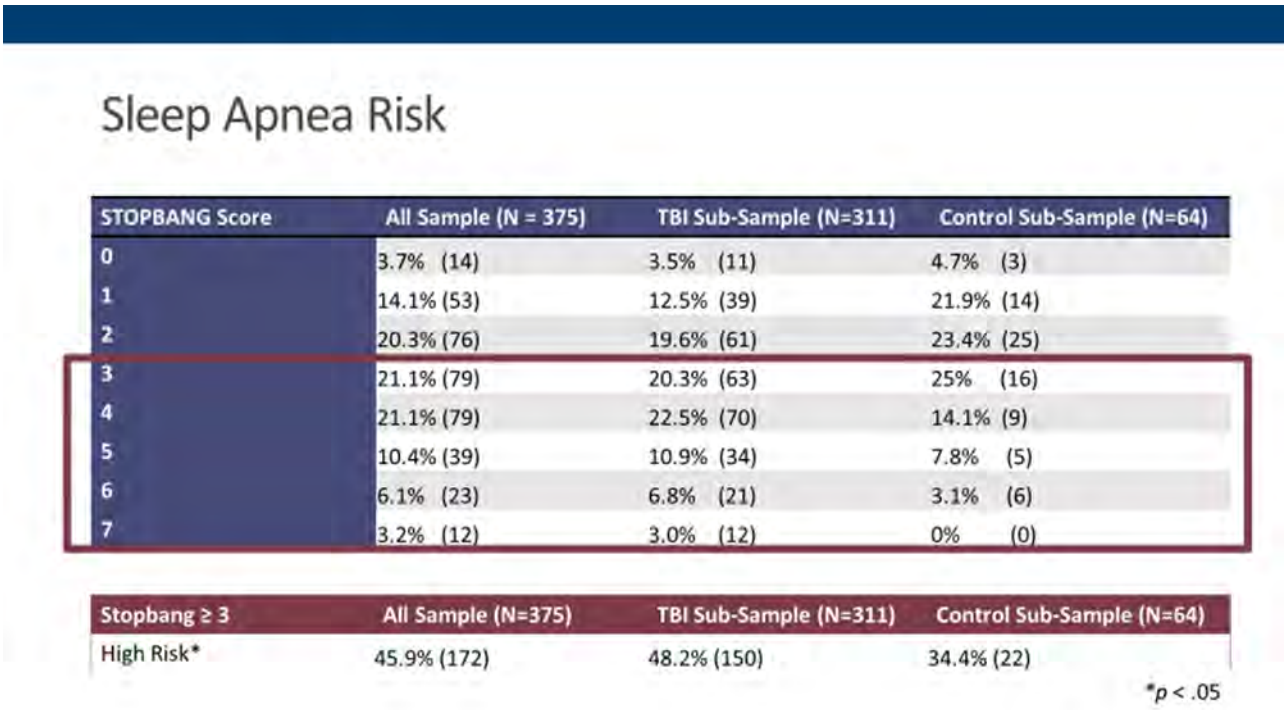
Table 1. SEM directional effects for NSI subscale mean scores, parameter estimates, and p-values.

	Continuous Repetitive mTBI		
NSI Subscales (Means)	Parameter Estimate	(SE)	P-Value
Affective			
Total Effect	0.08	(0.03)	0.006*
Direct Effect	0.02	(0.02)	0.516
Indirect Effect	0.06	(0.02)	0.0002*
Cognitive			
Total Effect	0.13	(0.03)	<.0001*
Direct Effect	0.09	(0.03)	0.005*
Indirect Effect	0.04	(0.01)	0.0003*
Somatosensory			
Total Effect	0.10	(0.02)	<.0001*
Direct Effect	0.07	(0.02)	0.001*
Indirect Effect	0.03	(0.01)	0.003*
Vestibular			
Total Effect	0.09	(0.03)	0.002*
Direct Effect	0.06	(0.03)	0.028*
Indirect Effect	0.03	(0.01)	0.002*

Figure 1: Parameter estimates for pathway analysis of continuous mTBI exposure on the 4 NSI outcomes.



d. Garcia A. et al. Obstructive Sleep Apnea (OSA) Risk is Associated with Cognitive Impairment After Controlling for TBI: A Chronic Effects of Neurotrauma Consortium Study: Here is a list of preliminary conclusions. (1) Mild TBI patients are at significantly higher risk for OSA. (2) Accounting for TBI history, OSA risk independently predicts poorer performance on tasks executive functioning, processing speed, and self-reported cognitive impairment. (3) This offers an avenue for treatment of the most common complaints for mTBI patients.



h. **CENC0004C - Epidemiology of mTBI and Neurosensory Outcomes:** The primary objective of this project is to integrate and analyze existing VA healthcare data to study the chronic effects of mild traumatic brain injury (mTBI) on neurodegenerative disease and other comorbidities, and the methods to treat and rehabilitate adverse effects of mTBI, in Veterans over time. To this end, we have combined multiple VA datasets to create a database of 1.6 million veterans, including all Veterans with TBI and a 2% random sample of Veterans with no TBI. We also generated an “all sources” TBI severity algorithm resulting in seven distinct and clinically meaningful categories of TBI severity using modified 2012 DVBIC/AFHSB criteria. Utilizing these resources, we are examining outcomes of mild TBI in both younger Veterans (OEF/OIF) and all-era Veterans. Although mTBI is the most common type of TBI, little is known about the intermediate and longer-term effects. This study aims to provide information for clinicians and patients, as well as other researchers, on the intermediate and long-term neurological effects of mTBI. During the past fiscal year this study has:

(1) **San Francisco VAMC/NCIRE:**

(a) TBI and Impact on Younger Veterans: With the recent focus on the dangers of opioid abuse and possible changes needed to opioid prescribing practices, we examined risk of receiving opioid therapy for chronic pain in younger Veterans with a history of TBI and persistent postconcussive symptoms. In a manuscript published in the CENC Special Issue of Brain Injury, we found that self-reported severe and very severe postconcussive symptoms predicted initiation of long-term and short-term opioid use for chronic pain in both unadjusted and adjusted analyses. In adjusted analyses, all four postconcussive symptom domains (Emotional, Vestibular, Cognitive, and Somatic/Sensory) significantly predicted initiation of long-term opioid therapy, with Emotional symptoms being the strongest predictor [ARR = 1.68 (1.52, 1.86); see Table]. Increased opioid prescribing in Veterans with self-reported severe persistent postconcussive symptoms indicates a need to educate prescribers and make non-opioid pain management options available for Veterans with TBI and neuropsychological sequelae.

Table: Neurocognitive predictors of new prescription opioid use in 53,124 Iraq and Afghanistan veterans in the year following the Comprehensive TBI Evaluation (CTBIE) and Neurobehavioral Symptom Inventory (NSI)

	Unadjusted[1]	Fully Adjusted[2]
	ARR/95% CI	ARR/95% CI
NSI Vestibular		
Short-Term Opioid Therapy	1.28 (1.16,1.42)	1.17 (1.06,1.30)
Long-Term Opioid Therapy	1.69 (1.40,2.05)	1.56 (1.29,1.90)
NSI Somatic/Sensory		
Short-Term Opioid Therapy	1.34 (1.21,1.48)	1.22 (1.10,1.35)
Long-Term Opioid Therapy	1.69 (1.39,2.05)	1.56 (1.28,1.90)
NSI Cognitive		
Short-Term Opioid Therapy	1.22 (1.16,1.28)	1.11 (1.05,1.16)
Long-Term Opioid Therapy	1.66 (1.50,1.83)	1.44 (1.30,1.59)
NSI Emotional		
Short-Term Opioid Therapy	1.25 (1.19,1.31)	1.11 (1.06,1.16)
Long-Term Opioid Therapy	1.94 (1.76,2.14)	1.68 (1.52,1.86)

[1] Multiple (polytomous) logit models estimated both short-term and long-term opioid use.
[2] Adjusted for age, sex, race/ethnicity, marital status, rank and education, military component, branch of service, number of deployments, alcohol disorders, and drug disorders; also for self-rated pain disability, and prior use of non-opioid treatment modalities (0, 1, or 2 or more).

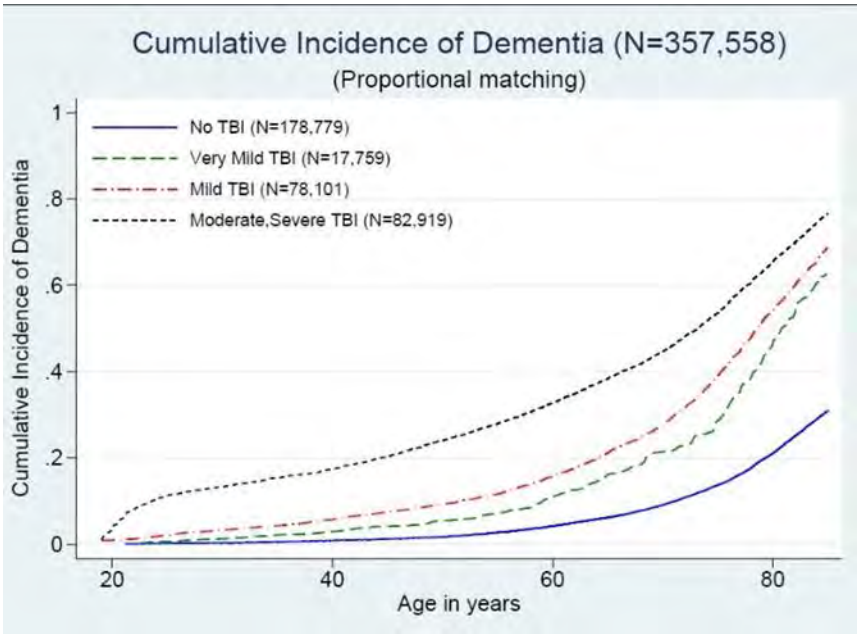
(b) mTBI and Risk for Dementia in All-Era Veterans: While studies have found an association between TBI and dementia, few have examined if mTBI alone increases risk of dementia. In a manuscript recently published in JAMA Neurology, we examined the association between TBI severity (classified using DVBIC 2012 criteria) and incident dementia. Even after adjusting for demographics and medical and psychiatric comorbidities, mild TBI without loss of consciousness (LOC) and mTBI with LOC both increased the risk of dementia 2-3 times that of people with no TBI (see table and figure

below). In this large cohort study of VHA patients, we observed a dose-response relationship between TBI severity and dementia diagnosis. Additional research is critically needed to determine the mechanisms underlying the association observed between TBI and dementia—including mild TBI without LOC—so that effective treatment and prevention strategies can be developed.

Table: Unadjusted and adjusted risk of dementia by TBI severity (N=357,558)

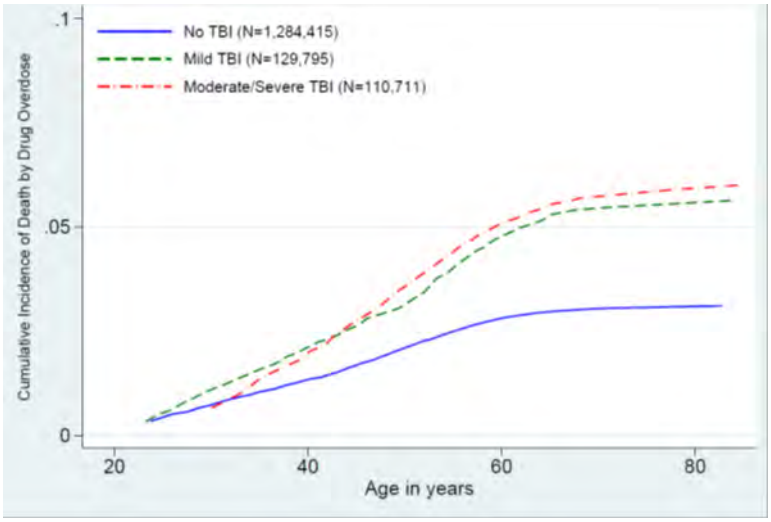
			Hazard Ratio (95% Confidence Interval)		
	No TBI	**Any TBI**	**Mild TBI, Without LOC**	**Mild TBI, With LOC**	**Moderate/Severe TBI**
Unadjusted	Ref	3.41 (3.29-3.53)**	2.29 (2.04-2.58)**	2.48 (2.26-2.72)**	3.75 (3.61-3.89)**
Model 1 [a]	Ref	3.41 (3.30-3.53)**	2.32 (2.06-2.61)**	2.49 (2.27-2.73)**	3.73 (3.60-3.88)**
Model 2 [b]	Ref	3.45 (3.33-3.57)**	2.36 (2.10-2.66)**	2.51 (2.29-2.76)**	3.77 (3.63-3.91)**

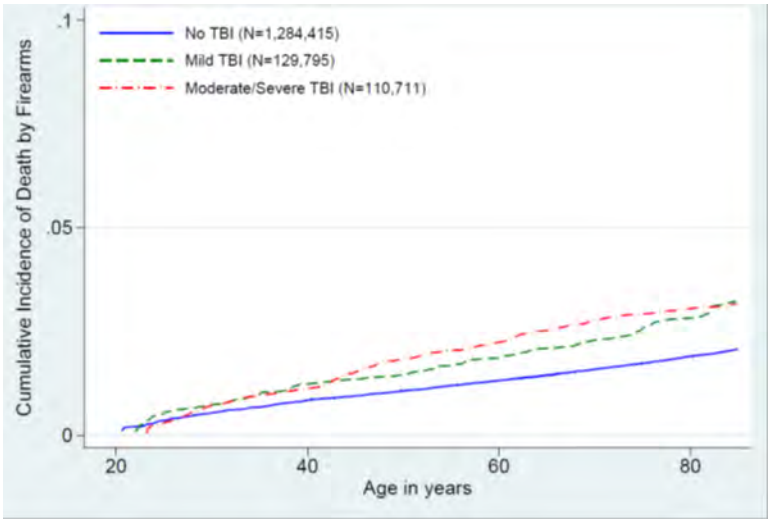
[a] Model 1: adjusted for demographic (gender, race, education, income).
[b] Model 2: adjusted for demographic, medical conditions (diabetes, hypertension, myocardial infarction, cerebrovascular disease, peripheral vascular disease), and psychiatric disorders (mood disorder, anxiety, posttraumatic stress disorder, substance use disorder, tobacco use, and sleep disorder).
**$p<.0001$



(c) <u>TBI and Intentional and Unintentional Death in All-Era Veterans:</u> TBI increases the risk of suicide, but few studies have considered mTBI. Additionally, little is known about whether deaths by drug overdose and firearms are related to TBI and TBI severity. In a recently submitted manuscript, we investigated the association between TBI severity and risk of suicide, death by drug overdose, and death by firearms in Veterans 18 years and older [5]. After adjusting for demographic factors, medical and psychiatric comorbidities, and accounting for the competing risk of other deaths, risk of suicide by any means was 23% higher for Veterans with mild TBI than Veterans without TBI, while the risk of suicide by any means was 46% higher for those with

moderate/severe TBI. When considering death by suicide related to drug overdose, Veterans with mild TBI had a statistically significant increased risk of 65%. In contrast, when considering death by suicide related to firearms, veterans with moderate/severe TBI had a 45% increased risk (see figures below). The findings of this study emphasize the importance of closely monitoring all levels of traumatic brain injury for development of suicidality and risk of death by drug overdose. Further study of potential mechanisms linking mild and moderate/severe TBI to suicide-related outcomes and lethality of method and intent is required in order to target intervention, prevention, and health care needs.





(d) Health Economics Depression and TBI in All-Era and OEF/OIF Veterans: (In collaboration with Dr. Libby Dismuke): Depression has been shown to be a major cause of disability and poor prognosis after TBI. Despite its demonstrated high prevalence in individuals diagnosed with TBI, the association of comorbid depression with VA health care costs of Veterans diagnosed with TBI is unknown. The objective of this study was

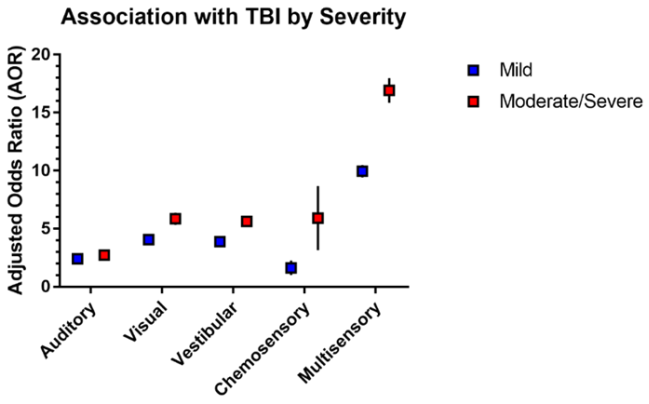
to examine the association of a clinical diagnosis of depression with total, inpatient, outpatient and pharmaceutical costs in VHA, for all era Veterans, non OEF/OIF Veterans, and OEF/OIF Veterans. After adjustment for demographic, TBI severity, and comorbidities, depression was significantly associated with an additional $1,775 in total costs per year for all era Veterans, $1,847 for non OEF/OIF Veterans, and $1,228 for OEF/OIF Veterans. While depression was not significantly associated with inpatient costs for all era and non OEF/OIF Veterans, it was significantly associated with $648 lower costs for OEF/OIF Veterans. Based on predicted mean per Veteran per year and the prevalence of depression, we estimated that Veterans with comorbid TBI and depression cost the VHA approximately $1.1 billion per year. Although our results may suggest depression treatment in OEF/OIF Veterans reduces inpatient costs, high prevalence of depression with TBI and associated costs indicate importance of adhering to evidenced based treatment and guidelines. A manuscript detailing these results was revised and resubmitted to Brain Injury.

(2) **University of Utah/Salt Lake City VAMC:** Over the past year we have completed analyses on multisensory on analyses of neurosensory comorbidity and the overall aim of identifying phenotypes of comorbidity more broadly in our Warfighter Cohort (3 or more years of VA care FY02-14 with at least one year after TBI screening implementation in FY07; merged DoDTR, VA and Military Health System data).

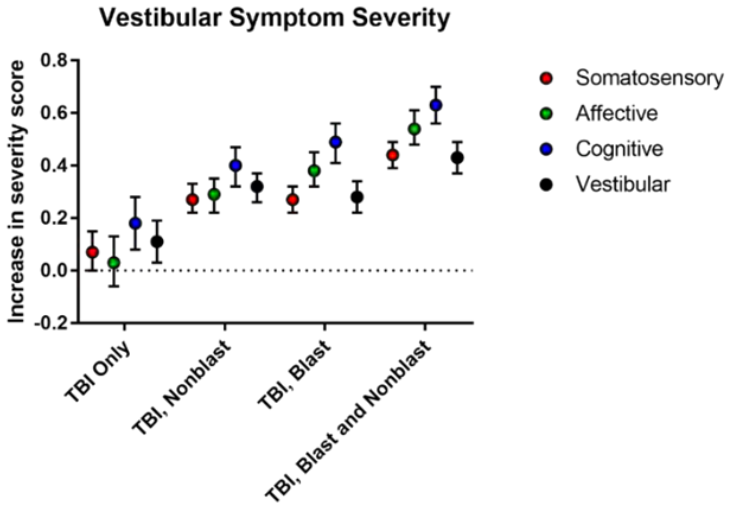
(a) For our studies we developed an “all sources” TBI algorithm to identify individuals with mTBI and TBI severity more broadly in our Warfighter Cohort. We designed an algorithm using both the Department of Defense Trauma Registry (DoDTR) VA administrative data, and the Comprehensive TBI Evaluation to identify the severity of TBI recorded among a hierarchy of these sources prioritizing sources more proximal to injury (DoDTR) or with more clinical detail (CTBIE; See Figure 1) using guidance on TBI severity from both the VA clinical practice guidelines and the Armed Forces Health Surveillance Center. TBI severity was identified using data between FY02-FY15. Severity was classified as No TBI, Historically Resolved (i.e., exposure to TBI where the subsequent symptoms were not problematic at the time of screening indicated on the VA TBI Screening), Screen Positive (i.e., on the VA TBI Screening, indicated exposure to TBI as well as subsequent and current symptoms, but no TBI history diagnosed at the Comprehensive TBI Evaluation), mild TBI (mTBI), moderate/severe TBI, penetrating TBI (pTBI), and TBI of unclassified severity (hereafter, Unclassified TBI) based on the Comprehensive TBI Evaluation. We plan to update this algorithm with data from the Military Health System inpatient, outpatient and Theatre Data Management Store (TMDS) when TMDS data are available.

(b) Neurosensory Dysfunction after TBI in Post 9/11 Veterans: Neurosensory Dysfunction after TBI in Post-9/11 Veterans: Our team developed a manuscript for the CENC Special Issue, Sensory dysfunction and traumatic brain injury severity among deployed post-9/11 Veterans: A Chronic Effects of Neurotrauma Consortium study that included co-authors across the consortium with expertise in neurosensory dysfunction. Using our CENC Warfighter cohort, we described the prevalence of auditory, visual, vestibular, chemosensory and multiple sensory problems and explore their associations

with traumatic brain injury (TBI) severity and injury mechanism among deployed Post-9/11 Veterans. We found that the odds for all types of sensory dysfunction were greater among those with any TBI relative to those with no TBI.



(c) We are revising a paper on dizziness and vestibular dysfunction in which we examined the prevalence, comorbidities, and association of vestibular dysfunction and dizziness with TBI. Of the 570,248 Iraq and Afghanistan war Veterans in this sample, 0.45% were diagnosed with vestibular dysfunction and 2.57% with non-specific dizziness. Those with either vestibular dysfunction or dizziness were significantly more likely to have comorbid TBI, tinnitus, headache, and balance problems. Individuals with self-reported blast exposure were less likely to have vestibular dysfunction or dizziness. We further evaluated the impact of TBI and Blast exposure on symptomology reported in the CTBIE (vestibular, cognitive, affective, somatosensory) and found that TBI and Blast and/or Nonblast exposure was associated with increased symptom severity even when controlling for the diagnoses of vestibular dysfunction and dizziness in the analyses. Similar findings were evident for other factors. These results, including the impact on the cognitive factor suggest that further exploration is indicated especially related to multiple exposures and TBI in an expanded dataset that includes DoD exposures.



(d) Prevalence of hearing loss and tinnitus in Iraq and Afghanistan Veterans: A Chronic Effects of Neurotrauma Consortium Study: Using our Warfighter cohort, we described the prevalence of hearing loss and tinnitus with common post-deployment conditions, including traumatic brain injury (TBI), post-traumatic stress disorder (PTSD), and other typical post-concussive conditions such as headaches and vertigo/dizziness. This retrospective observational study used data from the national Veterans Health Administration (VA) data repository from fiscal years 2001-2014. Veteran data was included if there were at least three years of VA care, with one or more years of care in 2007 or after. We identified comorbidities that may be associated with post-deployment hearing loss or tinnitus including TBI, PTSD, depression, and common post-concussive symptoms using International Classification of Diseases, 9th Revision, Clinical Modification codes. A multinomial logistic regression analysis was used to examine conditions associated with hearing loss or tinnitus. Among IAV, 570,332 were included in the final analysis. Of these, 7.78% of these were diagnosed with hearing loss alone, 6.54% with tinnitus alone, and 6.24% with both hearing loss and tinnitus. Comorbid TBI, PTSD, and depression were significantly associated with increased rates of hearing loss, tinnitus, or both conditions together. Older individuals, males, and those with TBI, PTSD, or vertigo/dizziness were significantly more likely to have hearing loss, tinnitus, or both. In order to provide more holistic post-deployment support, this myriad of conditions should be carefully considered in the planning of clinical care and beyond.

(e) Phenotypes of Comorbidity in Veterans with TBI: Our paper examining associations between TBI severity and neurodegenerative and mental health outcomes using latent class analysis and found distinct comorbidity phenotypes unique to TBI, and several phenotypes that diverge over time (see below). Of interest the trajectory indicating decline (Sort of Healthy+Polytrauma) was no different on adverse outcomes of suicidal ideation/attempt, overdose or homelessness than Polytrauma or Mental Health phenotypes, while the Polytrauma+Improve phenotype was significantly less likely to have these outcomes than even the Sort of Healthy comparator group. This paper is currently under review. We are also working with CENC investigators in the neuroimaging and biomarker cores to develop new projects that link phenotypes to serum repository biomarkers before and after TBI exposure while in DoD (Dr. Kenney), and current variation in neuroimaging parameters (Drs. Tate and Wilde).

(f) Sex Differences in Phenotypes among Men and Women with mTBI: A mentee of Dr. Pugh (Rocio Norman PhD) received a small seed grant to extend our analyses examining variation in phenotypes for men and women. We submitted a paper describing sex differences in phenotypes for Post-9/11 Veterans with mTBI to a VA special issue on Women's Health Issues. Our findings were very similar for men and women with the exception that women did not demonstrate at phenotype of Polytrauma+Improvement, but rather revealed a phenotype that was characterized by mood disorders and pain. We also found that phenotypes were not predictive of adverse outcomes of mortality, overdose, and homelessness for women, whereas phenotypes predicted all adverse outcomes in men. Based on these findings we are examining variation in self-reported outcomes on the CTBIE including NSI scale and subscale scores, pain, pain interference, and employment by phenotype and gender, in addition

to examining variation in prescribing patterns among men and women that may help understand these differences for men and women.

(g) Early onset dementia and TBI: We are developing a manuscript examining the relationship between TBI severity using the "all sources" algorithm and Early Onset Dementia (EOD) defined using a revised algorithm for younger Veterans. Findings from a VA funded study revealed that the positive predictive value of the ICD-9 code algorithm published by the VA Dementia Work Group was only 45% in Post 9/11 deployed Veterans under the age of 65. We developed an algorithm with an 85% PPV, and are evaluating the association of TBI of different severities including historically resolved TBI (see above) using a cleaner (but not perfect) algorithm for EOD. Our pilot evaluation using cases validated by chart review and controls matched on age, sex, race ethnicity, year of entering VA care and branch of service found that, the strongest predictors of EOD were Moderate/Severe or Penetrating TBI (AOR 21.3 95% CI 8.4-54.3), stroke (AOR 15.5 95% CI 5.6-42.9), Other TBI (unclassified, screen positive but no ICD diagnosis; AOR 14.7 95% CI 6.0-36.2), and mTBI (AOR 4.5 95% CI 2.4-8.7). Depression and bipolar disorder were also significantly associated with EOD. We are now implementing the algorithm in our Warfighter Cohort to examine these relationships temporally in the population.

(h) TBI and amyotrophic lateral sclerosis (ALS): Using the Population of Post-9/11 Veterans who received VA care during fiscal years 2002 to 2015 (from which the Warfighter Cohort was derived), we identified definite and probable ALS cases using the algorithm developed by the Centers for Disease Control and Prevention. Using a case control study design we also evaluated the association of ALS with TBI and across the major military occupations and adjusting for demographics and co-morbidities. We found that the prevalence of ALS and cumulative incidence of definite ALS were significantly higher among Air Force personnel and among tactical operation officers. TBI was not associated with ALS in this population. We found no evidence supportive of increased occurrence of ALS among those <45 years of age as evidenced among the Gulf war Veterans, however the prevalence of ALS was higher in this relatively young cohort of veterans compared to those reported among elderly civilians. Our addition of military occupations to the Warfighter cohort data will be used to identify individuals at risk for repetitive low-level blast exposure during and outside of combat deployment.

i. **CENC0005C - Tau Modifications Study**: The goal of this study is two-fold: Firstly, to develop animal models of repetitive mild Traumatic Brain Injury (r-mTBI) that recapitulate aspects of human TBI pathology and will allow correlation between neurobehavioral changes and neuropathological and biochemical outcomes. Secondly, to evaluate tau pathology in the brain of humans (Veterans and athletes) who died with a premortem clinical and a postmortem neuropathologic diagnosis of TBI/CTE. The goals complement each other, as human neuropathological findings are restricted to the single timepoint at autopsy, while relevant, validated mouse models enable TBI pathobiology to be tracked over time from the point of injury. Such models can then be used to assess the effects of interventions:

(1) At this time all animal cohorts have been completed in that they have received their injury paradigms at the appropriate ages, and been euthanized for tissue analyses at the appropriate timepoints (see Tables 1 and 2 below) with neurobehavioral testing carried out on all cohorts living to 15 days or more post-injury. Neurobehavioral characterization is ongoing but shows acute effects of injury in young mice, regardless of gender, which do not persist, and are no longer evident by 90 days post injury. In aged mice the behavioral responses are more complex, with gender specific effects which change over time post injury (see Figure 8 below). At the neuropathological level we demonstrate astrogliosis and microgliosis, which persists to the latest timepoints of investigation in both models. There does appear to be inflection points over time for astrocyte and microglial responses to injury, and these will be investigated in a new collaborative project between Drs. Crawford and Mufson using single transcript analyses. Tau pathology is also evident in our models, persisting to at least 90 days post injury in the cr-mTBI model. Although our animal models do not feature some of the characteristic tau pathology seen in human CTE, such as perivascular or glial tau, the persistence of TBI-dependent tau changes in our cr-mTBI model, long after the cessation of injury, is an important feature of our model and relatively unique in the preclinical space. Our model does recapitulate the persistent and progressive neuroinflammation, axonal injury and white matter damage that is common to human TBI patients providing valid platforms for deeper investigation of molecular targets, and for testing novel therapeutics.

(2) Relating to the aim defining the genetic signature of basal forebrain neurons containing Tau pathology obtained from military personnel and athletes in contact sports exposed to traumatic brain injury leading to chronic traumatic encephalopathy (CTE): Recently, we found that cholinergic basal forebrain (CBF) neurons within the nucleus basalis of Meynert (nbM), which provide the major cholinergic innervation to the cortex and their degeneration results in memory impairments in AD display an increasing number of tau bearing neurons across the pathological stages of CTE (Mufson et al., 2016). However, molecular mechanisms underlying nbM neurodegeneration post CTE remain unknown. During the current grant period, we assessed the genetic signature of nbM neurons containing the p-tau pretangle maker pS422 obtained from CTE subjects who came to autopsy and received a neuropathological staging assessment (Stages II, III, and IV) using the methods of laser capture microdissection and custom-designed microarray methodologies. Results determined using quantitative analysis revealed that cholinergic receptor nicotinic subunit beta-2 gene (Chrnb2), monoaminergic catechol-Omethyltransferase (Comt) and dopa decarboxylase (Ddc) enzymes, chloride channels Clcn4 and Clcn5, endocytosis caveolin 1 (Cav1), cortical development/cytoskeleton lissencephaly 1 (Ls1) and intracellular signaling adenylate cyclase 3 (Adcy3) gene transcripts were significantly downregulated in the pS422 nbM neurons in patients with CTE. By contrast, calpain 2 (Capn2) and microtubule-associated protein 2 (Map2) gene transcript levels were significantly increased in CTE stage IV (Figure 1). We interpret our first of a kind expression profiling data to indicate dysregulation of select genes associated with neurotransmission, signal transduction, cytoskeleton pathology, cell survival/death and microtubule dynamics in nbM Tau positive neurons in the CTE brain (Figure 2). The implications of these expression profiles suggest novel molecular

pathways for drug discovery, which may lead to future treatments and biomarkers of TBI/CTE.

(3) We have now harvested tissue from all 56 cohorts of mice proposed for this study (see tables below) which comprise: a) male hTau transgenic mice aged 3 months receiving a chronic r-mTBI (cr-mTBI) or cr-sham (anesthesia only) twice per week for 3 months from ages 3-6 months with euthanasia for analyses at 24hrs, 15 days, 90 days and 180 days post last injury; b) male and female hTau transgenic mice aged to 12 months and receiving a 5-hit mTBI paradigm (5r-mTBI) or 5r-sham over a 9 day period (48 hr inter-injury interval) with euthanasia for analyses at 24hrs, 5, 10, 15, 90, 180 and 360 days post last injury; c) male and female hTau mice aged 3 months receiving the 5-hit mTBI paradigm (5r-mTBI) or 5r-sham over a 9 day period (48 hr inter-injury interval) with euthanasia for analyses at 24hrs, 5, 10, 15, 90, 180 and 360 days post last injury (note: female mice were only included for the 24hr, 15 day and 360 day timepoints). See Tables 1 and 2 below.

Table 1: cohorts of mice for cr-mTBI study showing time points of euthanasia:

Treatment	1d	15d	90d	180d
Y_cr_sham-m	Completed Oct 2017 (n=12)	Completed June 2018 (n=12)	Completed Sep 2017 (n=12)	Completed Sep 2017 (n=12)
Y_cr_mTBI-m	Completed Oct 2017 (n=12)	Completed June 2018 (n=12)	Completed Sep 2017 (n=12)	Completed Sep 2017 (n=12)

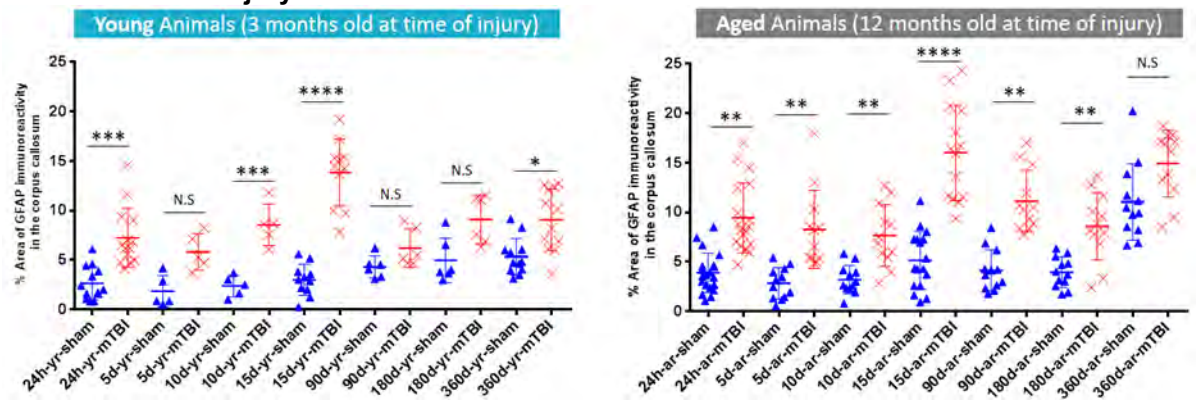
Table 2: cohorts of mice for 5r-mTBI study showing age/gender and time points of euthanasia:

Treatment	1d	5d	10d	15d	90d	180d	360d
yr_sham-f	(n=10) Aug 2016			(n=12) Oct 2015			(n=12) Dec 2017
yr_sham-m	(n=8) July 2016	(n=5) May 2018	(n=5) May 2018	(n=12) Oct 2015	(n=12) July 2017	(n=8) Dec 2017	(n=12) Dec 2017
yr_mTBI-f	(n=11) Aug 2016			(n=12) Oct 2015			(n=12) Dec 2017
yr_mTBI-m	(n=10) Jul 2016	(n=5) May 2018	(n=5) May 2018	(n=12) Oct 2015	(n=12) July 2017	(n=8) Dec 2017	(n=12) Nov 2017
ar_sham-f	(n=12) Mar 2016	(n=10) March 2018	(n=10) Dec 2017	(n=16) July 2015	(n=12) Dec 2016	(n=10) Nov 2017	(n=15) Nov 2016
ar_sham-m	(n=12) Apr 2016	(n=12) June 2018	(n=12) June 2018	(n=12) July 2015	(n=12) Dec 2016	(n=8) Nov 2017	(n=12) Feb 2017
ar_mTBI-f	(n=16) Aug 2016	(n=10) March 2018	(n=10) Dec 2017	(n=14) July 2015	(n=12) Dec 2016	(n=11) Nov 2017	(n=12) Nov 2016
ar_mTBI-m	(n=12) Apr 2016	(n=12) June 2018	(n=12) June 2018	(n=12) July 2015	(n=12) Dec 2016	(n=8) Nov 2017	(n=14) Feb 2017

(4) <u>Neuropathological Analyses of the 5r-mTBI model:</u>
Immunohistochemical analyses for astrogliosis (GFAP) and microgliosis (Iba1) has been carried out for all timepoints though more sections remain to be analyzed. Significant differences, or trends toward increases, in GFAP staining between TBI and sham mice are evident at all timepoints, with peak differences at 15 days post injury in

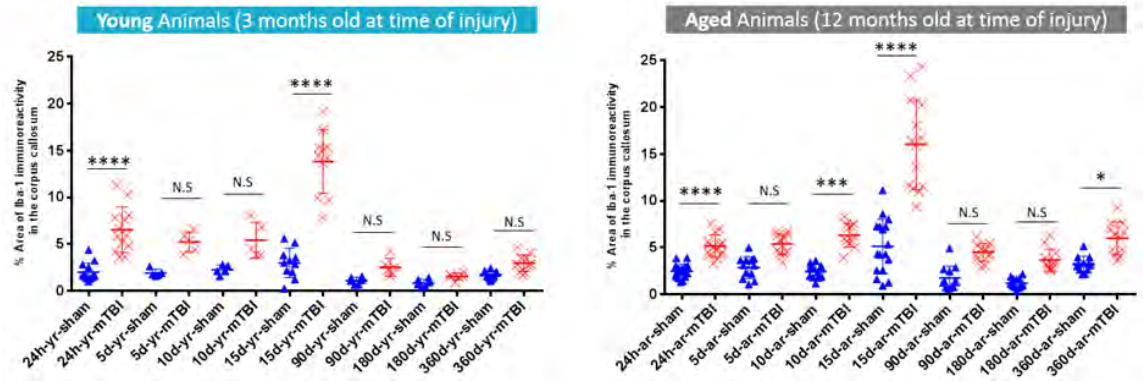
both young and aged mice. Astroglial effects persist for up to one year post injury in both aged and young cohorts (Figure 1). Age-dependent increases in astrogliosis mask the injury effect in aged (> 12 mo. old) mice

Figure 1: GFAP immunohistochemistry in young and aged mice at 24hr-360days following 5r-mTBI or 5r-sham injury.



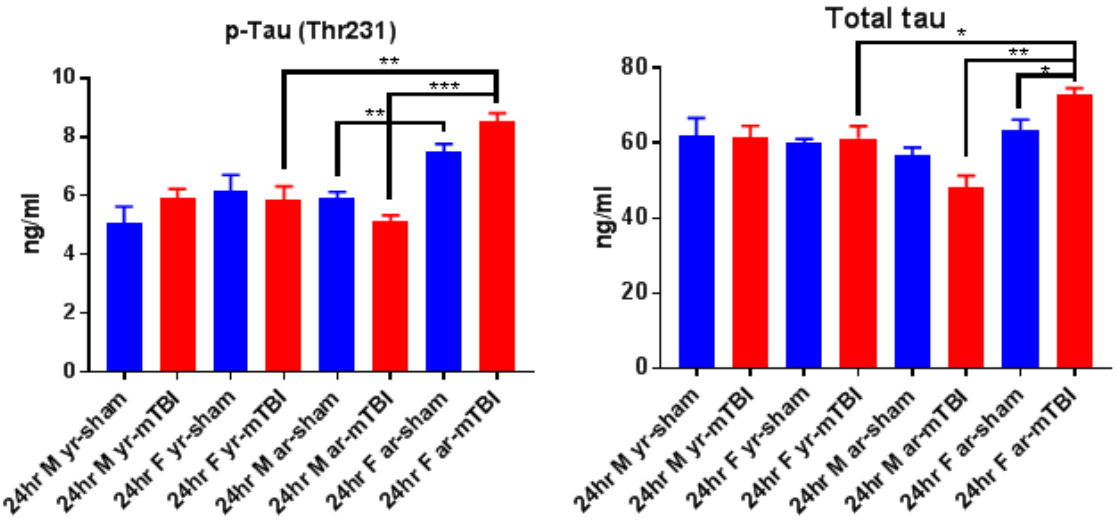
(5) Microglial (Iba1) effects of injury are evident at more timepoints in the aged versus young mice, but a peak at 15 days post injury is again seen in both young and aged mice, with TBI-dependent microgliosis persisting for up to one year post injury in the aged cohorts (Figure 2). Our data for suggest age and time dependent influences on microgliosis and astrocytosis, with apparent inflection points for astrocyte and microglial responses that warrant further investigation.

Figure 2: Iba1 immunohistochemistry in young and aged mice at 24hr-360days following 5r-mTBI or 5r-sham injury.



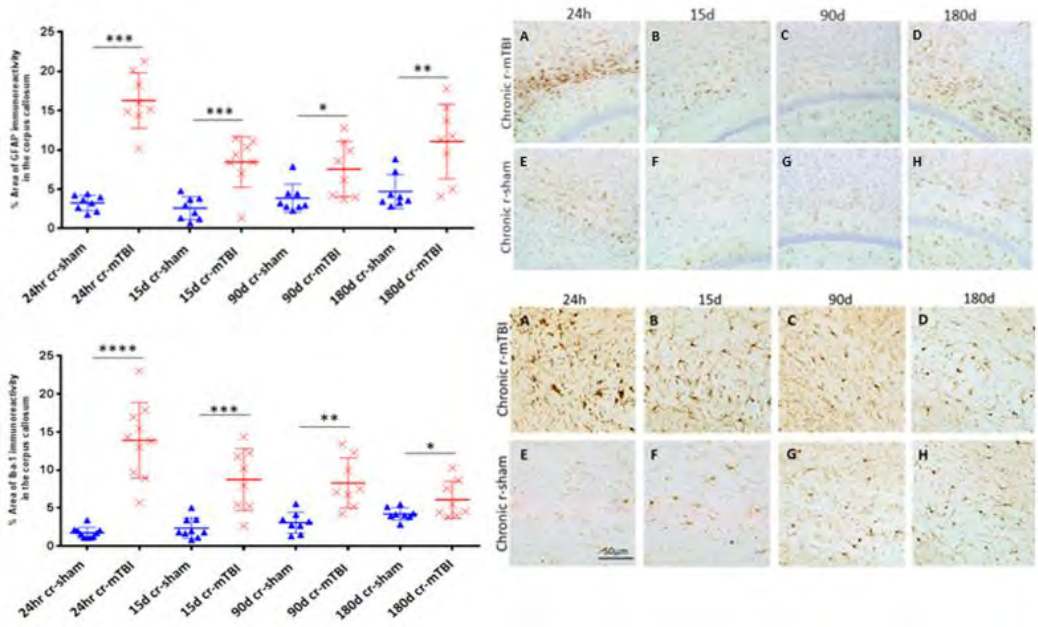
(6) Biochemical Analyses of the 5r-mTBI model: Western Blot analyses of multiple tau antibodies (RZ3 (pTau Thr231) and DA9 (Total tau), normalized to GAPDH) has been carried out on brain homogenates from the 5r-mTBI model at 24hrs post injury suggesting age and gender-dependent responses (Figure 3).

Figure 3: Western blot analyses of tau antibodies (PHF1, CP13 and RZ3) standardized to total tau (DA9) in brain homogenates from 5r-mTBI/sham mice:



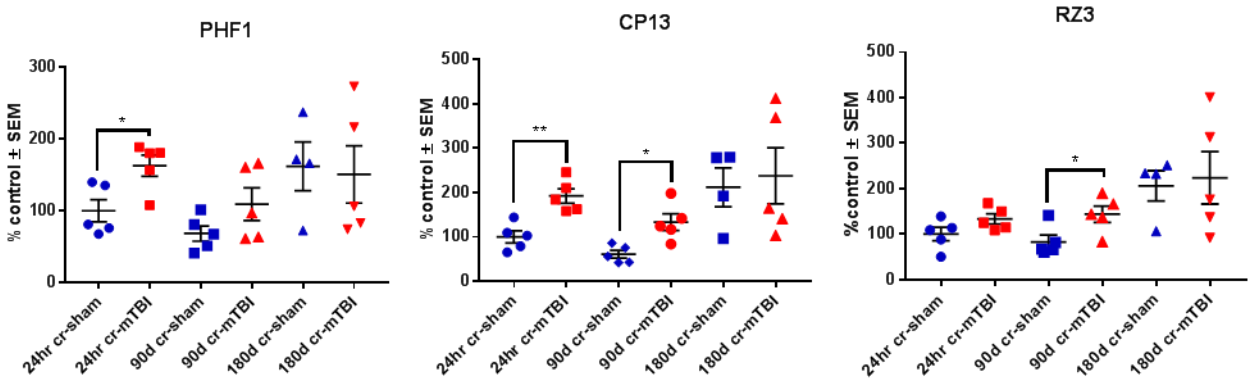
(7) Neuropathological Analyses of the cr-mTBI model: Immunohistochemical analyses for astrogliosis (GFAP) and microgliosis (Iba1) has been carried out for all timepoints though more sections remain to be analyzed. Significant differences between TBI and sham mice are evident at all timepoints for both markers indicate the robust persistence of neuroinflammatory responses in this chronic model (Figure 4).

Figure 4: GFAP and Iba1 immunohistochemistry in the cr-mTBI/sham model at a range of time points post-last injury As with the 5r-mTBI model, neuropathological analyses at other markers is ongoing.



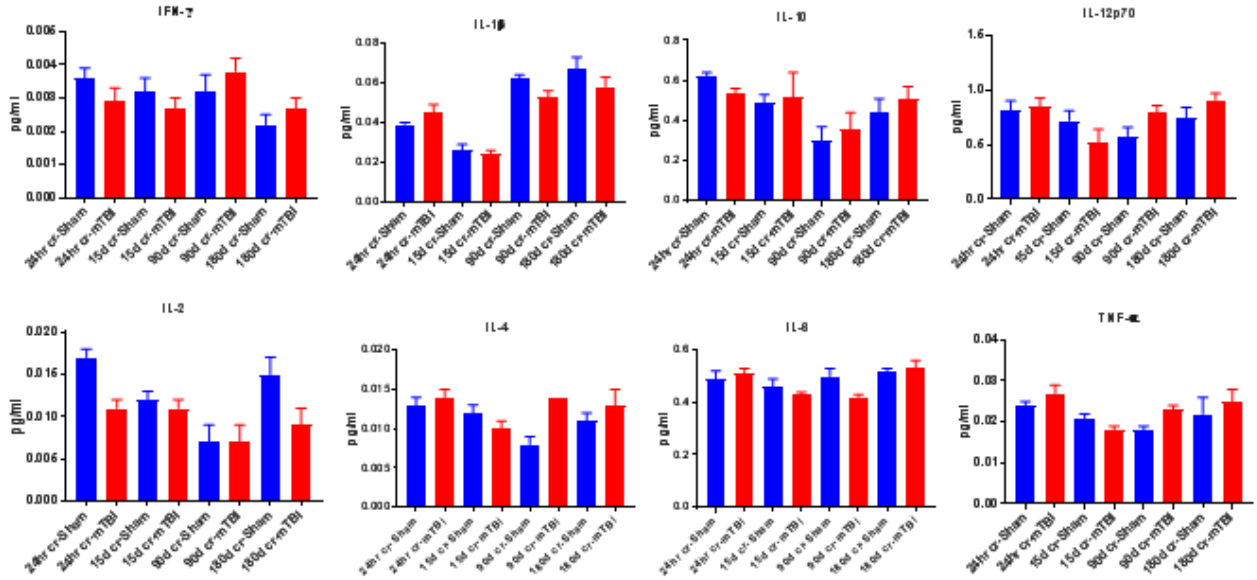
(8) Biochemical Analyses of the cr-mTBI model: Western Blot analyses of multiple tau antibodies (CP13, RZ3, PHF1, DA9, normalized to GAPDH) has been carried out on brain homogenates from the cr-mTBI model, revealing injury and time-dependent responses (Figure 5).

Figure 5: Western blot analyses of tau antibodies (PHF1, CP13 and RZ3) standardized to total tau (DA9) in brain homogenates from cr-mTBI/sham mice:



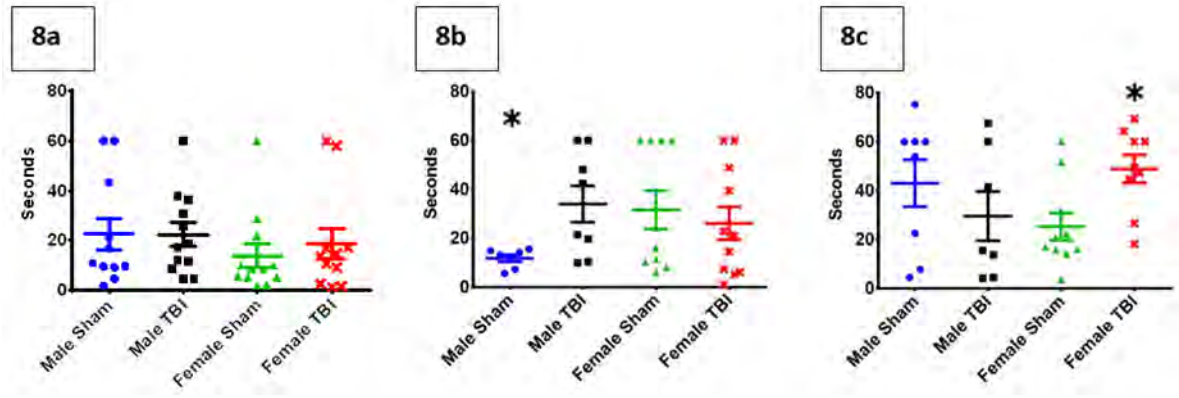
(9) We have also used a multiplex cytokine array (MesoScale Diagnostics) to evaluate brain cytokine responses from the cr-mTBI model; these data revealed some significant differences between injured versus sham animals for IL2 and IL6 at different timepoints; in both cases the cytokine levels were higher in the sham group. The lack of a consistent pro-inflammatory cytokine signal is surprising and we plan to repeat this analysis to confirm the findings (Figure 6).

Figure 6: Analysis of a panel of cytokines in brain homogenates of cr-mTBI/sham mice by multiplex ELISA (MSD). Analysis of plasma markers (GFAP, CIC, Aβ) by ELISA is in progress:



(10) Neurobehavioral Data: As previously reported – we have demonstrated cognitive deficits in the short term after both injury paradigms are delivered, but we subsequently observe different outcomes over the long term. In mice injured at a young age (3 months) we have no evidence for persistence of cognitive deficits, and by 360 days post injury injured and sham, male and female mice are all performing equally (Figure 8a). However, in older mice (12 months at injury) we see gender and aging influences whereby e.g. at the 15 day timepoint the male shams are performing as badly as the injured animals (previously reported, and published in Ferguson et al., 2017), at the 180 day timepoint the female shams are performing at the same level as the TBI mice (Figure 8b), and at the 360day timepoint there appears to again be a gender shift with male sham mice performing poorly (Figure 8c). As these studies were well powered we believe that these aging and gender effects warrant further investigation and correlation with the neuropathological findings, in particular tau and neuroglial pathology.

Figure 8: Performance on the Barnes Maze Probe Trial by a) young 5r-mTBI mice at 360 days post injury; b) aged 5r-mTBI mice at 180 days post injury; c) aged 5r-mTBI mice at 360 days post injury:



(11) The human brain component of project 5 has also investigated the spread of tau pathology within the medial temporal lobe memory circuit. Male caucasian and African-American former professional contact-sport athletes from Stage II (n = 6, age at symptom onset 20–65 y; age at death 25–70 y), Stage III (n = 6, age at symptom onset 24–40 y; age at death 45–67 y), and Stage IV (n = 6, age at symptom onset 30–68 y; age at death 62–80 y) were obtained from the CENC supported Boston University School of Medicine brain bank. Quantitative analysis revealed significantly more pretangle neurons in the CA1 and CA3 hippocampal subfields and the entorhinal cortex (EC) in Stage IV compared to Stage II. The EC and hippocampal subfields also displayed significantly smaller pretangle neuronal area in Stage IV compared to Stage II. Stage III displayed intermediate values for both pretangle neuron count and size, suggesting a transitional pathological stage. In contrast, minimal amyloid beta profiles were mainly seen in the hippocampal-EC complex in Stage IV, suggesting that amyloid is not a necessary recondition for the initiation of tau pathology in CTE. Data suggest that phosphorylated tau protein levels may provide a biomarker and a drug target to slow the progression of CTE.

Figure 9. Hippocampal subfields stained for AT8 showing pretangle pathology across the pathological stages of CTE:

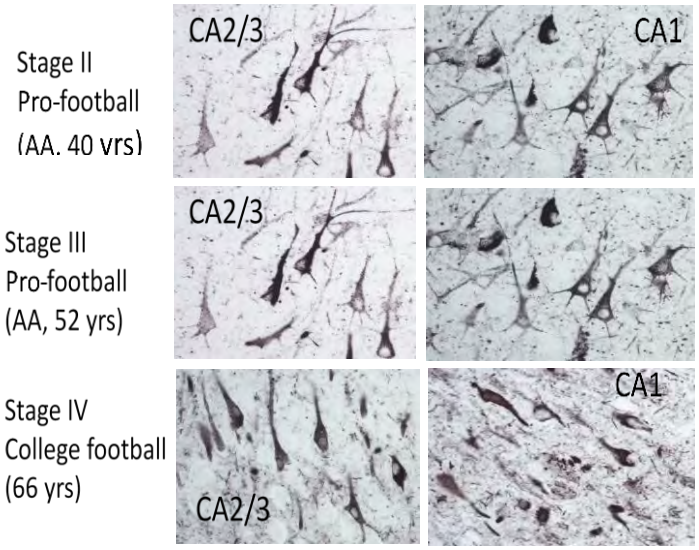
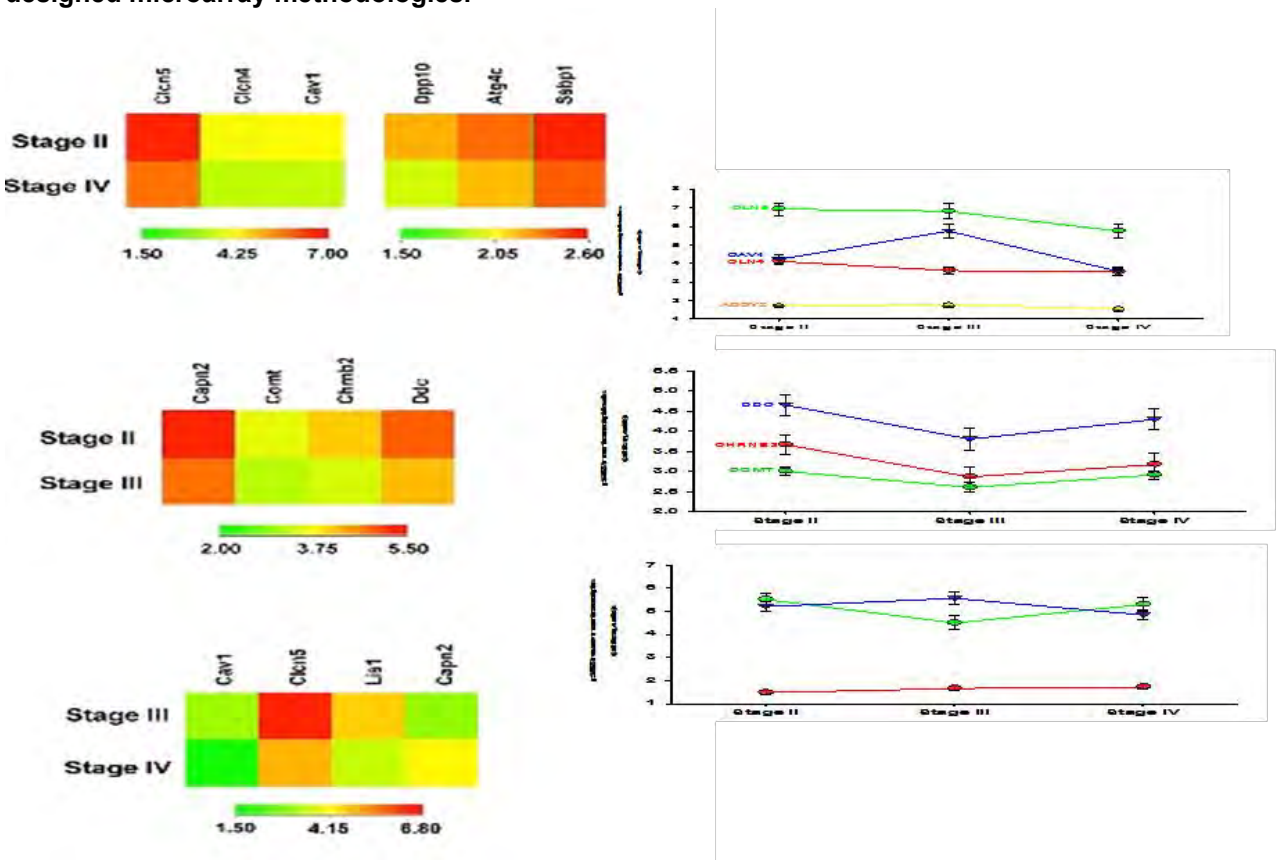


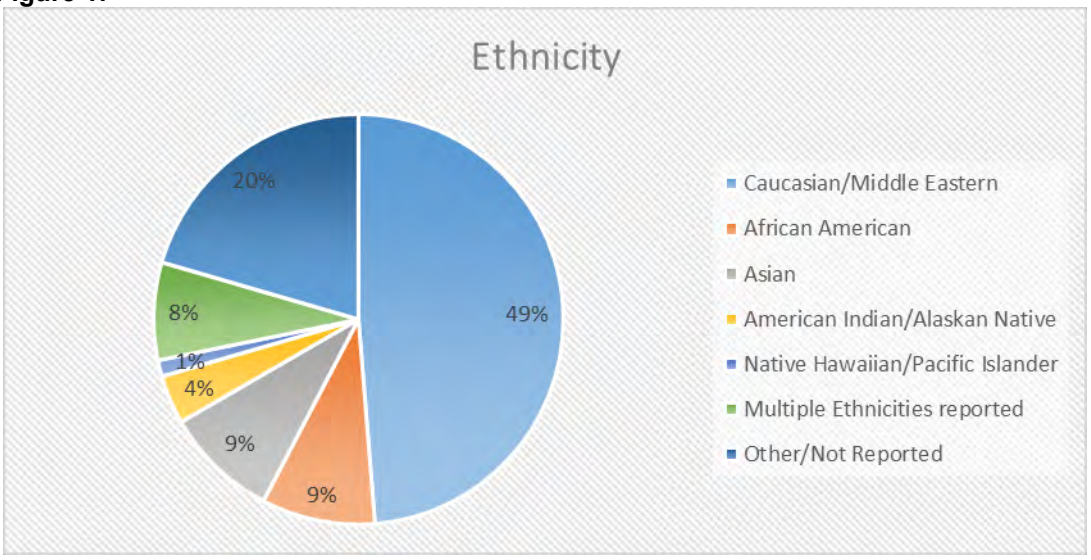
Figure 10: Genetic signature of nbM neurons containing the p-tau pretangle maker pS422 obtained from CTE subjects who came to autopsy and received a neuropathological staging assessment (Stages II, III, and IV) using the methods of laser capture microdissection and custom-designed microarray methodologies.



j. **CENC0020P - Novel White Matter Imaging to Improve Diagnosis of Mild TBI:**
This study will prospectively examine the utility of the mcDESPOT imaging sequence to identify white matter micro-structural damage in otherwise normal appearing white matter in Veterans with a history of mTBI and to better differentiate white matter changes due to mTBI from those due to mental health etiologies. The mcDESPOT sequence will be utilized to specifically calculate myelin volume in vivo in a sample of OEF/OIF/OND Veterans with mTBI, PTSD, or both, as well as controls. If mcDESPOT demonstrates improved sensitivity and specificity over DTI in this population, this approximately 12 minute MRI sequence can serve as deliverable clinical tool for diagnosis and prognosis of mTBI. During this fiscal year, the study has:

(1) Since the beginning of the study, we enrolled 104 subjects total, 24 of those were enrolled in FY18. Of those enrolled in the past year, 6 did not proceed beyond initial assessment: 4 of these were determined ineligible and 2 were not responsive to follow up calls. All recruitment, data collection, and data entry, and data cleaning activities have been completed.
(2) A total of 78 participants have completed the full assessment and imaging protocol. Scoring, double-scoring, data entry, and data cleaning are complete.
(3) All assessment data collection and cleaning has been completed. All processed DTI and structural data has been received from the neuroimaging core and all mcDESPOT data has been processed locally. We have requested resting state data from the imaging core. We are proceeding with analysis of mcDESPOT and other imaging data as well as neuropsychological data and are working on a draft of the main mcDESPOT manuscript.
(4) Participants completing the protocol included 78 combat exposed OEF/OIF/OND Veterans, ages 18-50 years (M = 34.06, SD = 6.31). Participants had either a history of mTBI (n = 23), a current PTSD diagnosis (n = 16), had comorbid mTBI and PTSD (n = 23), or were healthy controls (n = 16). See Figure 1 and table 1 for demographic variables.

Figure 1:



(5) Preliminary results using a subset of our data, revealed no significant MWF differences using a traditional ROI approach once applying FDR correction when comparing Veteran's with and without history of mTBI. However, when using an exploratory analysis applying limited spatial constraints, significantly more clusters of low MWF were found in Veterans with history of mTBI compared to those without (Table 2). Additionally, significant positive correlations were found between MWF and a measure of speeded attention (PASAT) in multiple brain regions, such that higher MWF was related to better performance on the task (Table 3).

Table 1. Descriptives and group differences on demographic, injury, psychiatric, performance validity, and cognitive, measures.

	Total Sample		**mTBI**		**PTSD**		**Comorbid**		**Control**			
Demographics	Mean (SD) or %	n	Mean (SD) or %	n	Mean (SD) or %	n	Mean (SD) or %	n	Mean (SD) or %	n	X or F	*p*-value
Age	34.06 (6.31)	78	34.39 (6.10)	23	36.88 (6.44)	16	32.65 (5.67)	23	32.81 (6.89)	16	1.72	.170
% Male	91.0	78	87.0	23	87.5	16	95.7	23	93.8	16	1.46	.692
Years of education	15.10 (1.65)	78	15.22 (1.45)	23	15.25 (1.39)	16	14.61 (1.90)	23	15.50 (1.75)	16	1.08	.362
% Hispanic	35.5	78	26.1	23	43.8	16	36.4	23	40.0	16	4.01	.675
% Caucasian	56.4	78	73.9	23	43.8	16	52.2	23	50.0	16	4.34	.227
% MDD	29.5	62	8.7	23	62.5	16	47.8	23	---	--	**13.51**	**.001**
% GAD	12.8	62	4.3	23	31.3	16	17.4	23	---	--	5.09	.078
WRAT4 Reading SS	103.49 (10.35)	78	104.78 (12.17)	23	104.13 (10.68)	16	100.26 (6.71)	23	105.63 (11.35)	16	1.12	.347
TBI injury												
% with LOC presence	69.6	46	73.9	23	---	--	65.2	23	---	--	.411	.522
% with PTA presence	78.3	46	73.9	23	---	--	82.6	23	---	--	.511	.475
# of mTBIs	3.46 (3.25)	46	3.26 (3.74)	23	---	--	3.65 (2.74)	23	---	--	.164	.688
% with blast TBI history	47.8	46	34.8	23	---	--	60.9	23	---	--	3.136	.077
Years since last mTBI	7.22 (5.89)	46	7.52 (5.96)	23	---	--	6.92 (5.94)	23	---	--	.116	.735
Psychiatric												
PCL-5	27.21 (18.14)	78	19.65 (15.01)	23	35.81 (12.79)	16	39.48 (16.04)	23	11.81 (12.93)	16	15.44	.000*
PHQ-9	9.33 (6.85)	78	7.43 (5.43)	23	13.25 (7.20)	16	12.48 (5.88)	23	3.63 (4.83)	16	10.49	.000*
Performance Validity												
% TOMM Failure	5.1	78	0.0	23	6.3	16	13.0	23	0.0	16	5.11	.164
% MSVT Failure	6.4	78	8.7	23	0.0	16	13.0	23	0.0	16	4.079	.253

Note: *$p < .05$; TOMM Failure defined as a score below 45 on either trail 2 or retention. MSVT Failure defined as a score of 85% or less on either immediate recall, delayed recall, or consistency. Abbreviations: % = percent; SD = standard deviation; mTBI = mild traumatic brain injury; MDD = major depressive disorder; GAD = generalized anxiety disorder; PTSD = posttraumatic stress disorder; WRAT4 = Wide Range Achievement Test Fourth Edition scaled score; LOC = loss of consciousness; PTA = posttraumatic amnesia; PCL-5 = Posttraumatic Stress Disorder Symptom Checklist for DSM 5; PHQ-9 = Patient Health Questionnaire; TOMM = Test of Memory Malingering Trial 2; MSVT = Medical Symptoms Validity Test.

Table 2. Group differences in MWF potholes by cluster size and z-threshold.

z-threshold	Cluster Size	Total Sample Median (SD)	n	No mTBI history Median (SD)	n	mTBI history Median (SD)	n	*U*	*p*
-2.00	1 mm^3	16.00 (34.18)	51	16.00 (39.71)	27	15.00 (26.61)	24	301.5	.671
-2.00	5 mm^3	1.00 (8.85)	51	1.00 (10.38)	27	1.00 (6.67)	24	295.5	.583
-2.00	10 mm^3	.00 (4.77)	51	.00 (5.99)	27	.50 (2.77)	24	301.5	.645
-2.50	1 mm^3	4.00 (9.60)	51	2.00 (10.42)	27	4.50 (8.78)	24	259.9	.220
-2.50	5 mm^3	.00 (1.98)	51	.00 (2.36)	27	.00 (1.50)	24	273.5	.255
-2.50	10 mm^3	.00 (.999)	51	.00 (1.19)	27	.00 (.761)	24	299.5	.465
-3.00	1 mm^3	1.00 (3.08)	51	.00 (3.01)	27	2.00 (3.01)	24	162.0	.001*
-3.00	5 mm^3	.00 (.717)	51	.00 (.456)	27	.00 (.924)	24	291.5	.332
-3.00	10 mm^3	.00 (.440)	51	.00 (.192)	27	.00 (.612)	24	322.0	.911

Note: *$p < .05$; *U* indicates Mann-Whitney Test values for no mTBI history group versus mTBI history group.
Abbreviations: SD = standard deviation; mTBI = mild traumatic brain injury.

Table 3. Correlations between Myelin Water Fraction in Regions of Interest and Cognitive Measures

	PASAT	Digit Span	Symbol Search	Coding	BVMT-R Delay	CVLT-II LDFR
Genu of CC	.374*	.106	.046	.033	.003	-.133
Body of CC	.351*	.085	-.007	.007	-.054	-.102
Splenium of CC	.343*	.093	-.017	-.005	-.053	-.125
Left Anterior Limb of IC	.346*	.067	-.005	.008	-.019	-.117
Right Anterior Limb of IC	.363*	.080	.004	.024	-.001	-.103
Left Posterior Limb of IC	.342*	.059	-.002	.002	-.066	-.094
Right Posterior Limb of IC	.366*	.093	.005	.016	-.045	-.082
Left Retrolenticular Limb of IC	.331*	.074	-.035	-.035	-.053	-.125
Right Retrolenticular Limb of IC	.337*	.088	.001	.000	-.032	-.100
Right Cingulum (cingulate gyrus)	.363*	.119	.015	.038	-.052	-.103
Left Cingulum (cingulate gyrus)	.340*	.076	.012	.031	-.046	-.116

Note: *$p < .05$; All cognitive measures are raw scores. Abbreviations: CC = corpus callosum; IC = internal capsule; PASAT= Paced Auditory Serial Addition Test 3-second version total correct; CVLT-II = California Verbal Learning Test- Second Edition; LDFR = Long Delay Free Recall; BVMT-R DR = Brief Visuospatial Memory Test- Revised Delayed Recall.

(6) Traditional ROI based analysis may be less effective than a novel, less spatially constrained, exploratory “pothole” analysis for identifying the multifocal, subtle, and diffuse white matter changes that are typical following mTBI. White matter damage after mTI that persists in the post-acute phase following injury may be difficult to detect and characterize, especially using traditional approaches. Additionally, WMF was found to

correlate with an object measure of speeded processing, adding to a growing body of evidence showing myelin integrity to be related to processing speed. (See APPENDIX #XX for more details)

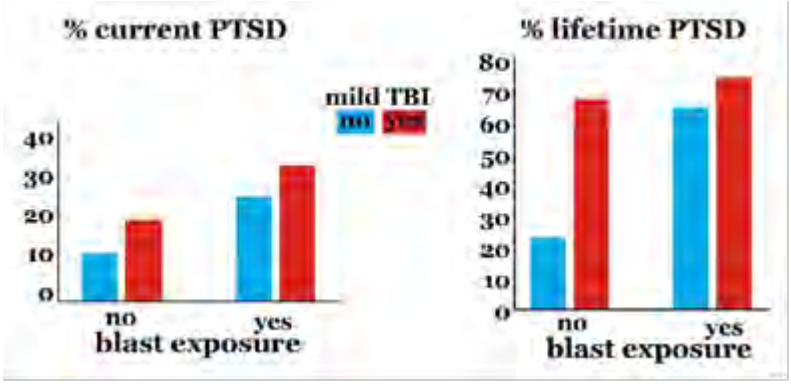
k. **CENC0034P - Structural and Functional Neurobiology of Veterans Exposed to Primary Blast Forces:** The goal of this project is to more fully characterize the neurobiological sequelae of exposure to primary blast forces. We will use multiple advanced neuroimaging techniques to better understand the effect of exposure to primary blast forces alone on brain structure (structural MRI – T1W, FLAIR, SWI, DTI, DKI, MTI) and function (resting state fMRI, resting state and task activated MEG), cognitive function, and symptom presentation compared to TBI from other and/or mixed forces. This study will allow us to further investigate the nature of white matter abnormalities previously observed in Veterans exposed to primary blast forces, providing a better understanding of the possible changes in the brain caused by this exposure. Additionally, we will be able to investigate how these changes may affect brain function by examining alterations in brain networks. We will also examine how exposure to primary blast forces may alter the individual's ability to focus, concentrate, learn, and perform complex tasks. Finally, we will examine symptoms present following exposure to primary blast forces including anxiety, posttraumatic stress, depression, irritability, poor sleep, and overall quality of life. This study will provide a comprehensive investigation of how exposure to primary blast may affect an individual, including whether it differs from other TBI mechanisms:

(1) Participant Recruitment & Data Acquisition – In FY18, 105 participants were consented and completed the assessment visit, and 60 participants also completed the imaging visit. We had achieved 82% of our planned goal of 200 when enrollment was halted May 31 (see Consort Diagram below for details). RTI finalized their dataset and released it to us in July. We received the FreeSurfer volumetric analysis on the first 102 subjects in October 2017 and the full dataset in August. We received the ENIGMA DTI region of interest analysis on the first 138 subjects in April and the full dataset in September. We received the automated fiber-tract quantification DTI analysis on the first 127 subjects in June. We completed segmentation of deep white matter hyperintensities in early September.

(2) Initial analyses have focused on exploring [1] whether exposures to primary blast forces that were not associated with acute TBI symptoms might have detrimental chronic sequelae and [2] whether there are interactions among exposures during deployment and present neuropsychological, neuropsychiatric and neurobiological measures.

A history during deployment of blast exposure is associated with increased rates of both current and lifetime PTSD, whereas a history during deployment of mild TBI is associated with higher rates of lifetime but not current PTSD (Figure 1).

Figure 1. Effect of Blast Exposure & mild TBI on PTSD Rates:

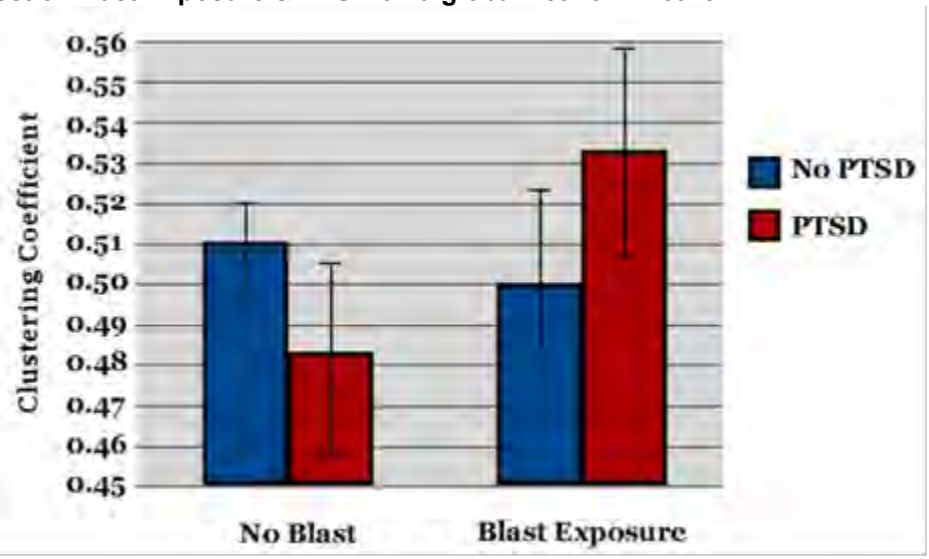


When participants with deployment-acquired TBI were removed from the analysis, blast exposure remained associated only with lifetime PTSD, whereas higher severity blast exposure was associated with both current and lifetime PTSD. These results indicate that blast exposure is associated with increased rates of PTSD independent of mild TBI. Recovery from PTSD, defined as meeting criteria for lifetime but not current PTSD, also differed by blast exposure status. As the severity of blast exposure increased (as defined by the event with the highest pressure rating), the likelihood of recovery from PTSD decreased. As expected, recovery from PTSD was associated with better behavioral health outcomes and quality of life. Significant interaction effects between blast exposure and PTSD recovery were present for alcohol use problems. If the blast exposure was related to the index trauma then alcohol use problems were greater and quality of life was poorer. Hierarchical linear regression adjusting for current PTSD diagnosis and TBI history indicated that blast exposure was not independently associated with cognitive outcomes beyond PTSD and mild TBI. However, a significant interaction effect was seen between deployment TBI and blast exposure on a test of attention (Trail Making Test A). Lower performance was found in Veterans with TBI who also had blast exposure. Thus, Veterans who incur a TBI and have significant blast exposure during deployment may experience persisting difficulties with cognitive functioning due to alterations in basic attention abilities. Blast exposure should be considered in etiology of cognitive complaints in this population.

(3) Preliminary analyses of resting state MEG from a small group (n=40) examining the association between deployment-acquired blast exposure and network metrics did not find differences between participants with and without blast exposure. However, participants with higher-severity blast exposure displayed higher levels on some metrics (clustering coefficient, small worldness). These findings remained when deployment-acquired mild TBI was included in the model, and no interaction between blast exposure and mild TBI was observed. The effects were no longer significant when PTSD was included in the model and no interaction with PTSD was observed. Results support the utility of MEG in identifying changes in brain networks associated with deployment-acquired TBI and blast exposure history, both with and without PTSD; however, these analyses are underpowered to observe interactive effects. These analyses support the

hypothesis that higher severity of blast exposure is related to increased alterations in brain networks. Initial analyses of resting state fMRI (n=115) indicate that higher severity blast exposure and current PTSD interact to alter the topology of functional brain networks across many global metrics (clustering coefficient, local and global efficiency, assortativity, minimum connection strength). In the presence of higher severity blast exposure PTSD, was associated with higher levels of most network metrics (Figure 2), while in the absence of this exposure PTSD was associated with lower levels (the opposite was found for global efficiency). In contrast, mild TBI history was not associated with alterations in these network metrics. This finding mirrors the results of previous studies by our group and raises questions about the etiology of PTSD in the presence versus the absence of blast exposure. The model including lifetime PTSD revealed main effects of higher severity blast exposure, but no significant interaction with PTSD. Similar analyses found no differences in regional brain volumes or ventricular volume associated with blast exposure or TBI history.

Figure 2. Effect of Blast Exposure & PTSD on a global network metric

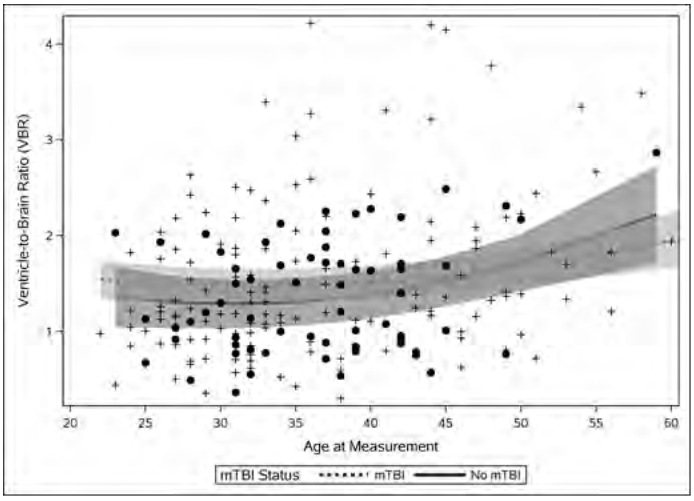


l. **<u>CENC0049P - Clinical and Neuroimaging Correlates of Neurodegeneration in Military mTBI:</u>** The objective of this study is to test several psychological and biological measures for utility as markers of mTBI-related neurodegeneration, and characterize the utility and limitations of self-report measures in the context of mTBI and comorbid psychopathology. During this fiscal year this project has:

(1) Analyses of ventricle-brain ratio (VBR), the first of four potential markers of mTBI-related neurodegeneration originally proposed, have been completed. Specifically, the study tested the hypotheses that (1) mTBI is associated with accelerated increases in VBR, (2) higher symptom burden at baseline predicts greater VBR increases over subsequent years, and (3) the magnitude of VBR change corresponds to changes in other symptom domains. No effect of mTBI history was supported in these analyses (Figure 1); however, the roles of normative aging, education, personality traits, and depression symptoms in VBR changes over time highlight several potential targets for

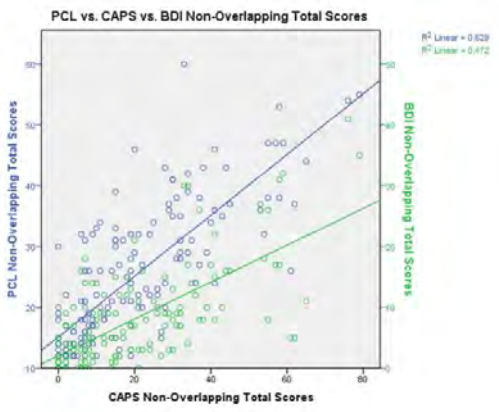
influencing neurodegenerative processes. Similar analyses of the other candidate markers are underway.

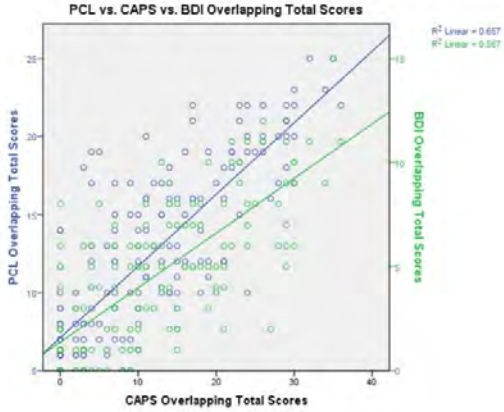
Figure 1. Relationship between age and VBR in those with (stipled line) and without (solid line) history of mTBI:



(2) Initial analyses of measures from the clinical interview and self-report questionnaires indicate that retrospectively reported mental health symptoms for a prior arbitrary time point (i.e., during the legacy study visit) correspond well to levels reported at that time; however, retrospective report is also heavily influenced by current symptom levels, providing support for the possibility that current distress is associated with over-reporting of prior symptoms and experiences. Moreover, self-reported levels of PTSD symptoms (PTSD Checklist) correlate as strongly with self-reported levels of major depression (Beck Depression Inventory; r=.827) as with interview-based ratings of PTSD symptoms (Clinician-Administered PTSD Scale; r=.833), even after accounting for direct overlap (e.g., sleep disruption, concentration problems) (Figures 2a and 2b), demonstrating the difficulty in characterizing mental health in trauma-exposed military.

Figures 2a and 2b. Relationships of PTSD Checklist (PCL) and Beck Depression Inventory (BDI) with Clinician-Administered PTSD Scale (CAPS). Plots are shown for total scores of (a) the 5 items that overlap across measures and (b) the remaining (i.e., non-overlapping) items.





m. **CENC0056P - Visual Sensory Impairments and Progression Following Mild Traumatic Brain Injury:** The objective of this project is to identify the spectrum of visual sensory disturbances after mTBI by utilizing new imaging technology. During this fiscal year this project has:

(1) Enrollment: Since exceeding our original enrollment goal of 100 subjects (50 mild TBI and 50 age-matched control veterans) to reach a total enrollment of 136 subjects (67 mild TBI and 69 age-matched control veterans) in the prior year, Minneapolis VA has been meeting follow up visits, returning every 6 months for repeat testing of all of the visual, neurocognitive and psychiatric measurements. This will amount to a total of 5 visits over 2 years from enrollment.

To date (September 25, 2018), we have completed 498 study visits:
18 participants who have completed 5 visits = 90 visits
62 participants who have completed 4 visits = 248 visits
47 participants who have completed 3 visits = 141 visits
9 participants who have completed 2 visits = 18 visits
1 participant who has completed 1 visit = 1 visit

(2) For the neuroimaging portion of the study (MRI at baseline enrollment and then follow up MRI at the last visit at end of 2 years):
Visit 1 MRI =121 completed; 9 partial MRI's discontinued due to anxiety or pain
Last Visit MRI: 52 completed MRI scans and more are being scheduled

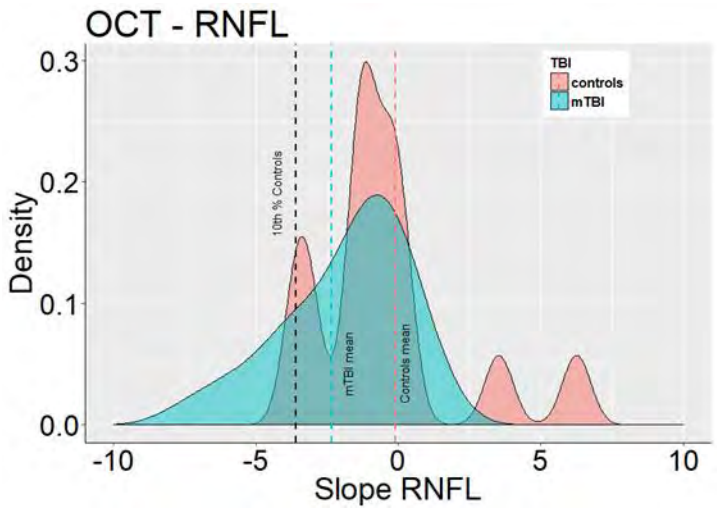
(3) Our retention rate is 97% for visit 1 and 94% for visit 2 (we are still scheduling for visits 3 & 4 & 5). Our overall study retention rate is 96% (we have only 5 participants lost to follow-up; 1 death, 1 prison, 1 moved, and 2 are too busy to make follow up visits).

(4) A subset of the enrolled subjects were recruited from our Neurotrauma study which generated pilot data prior to CENC funding; those subjects are still enrolled in the Neurotrauma study and return for a 3 month visit between the 6 month CENC visits, at which time Optical Coherence Tomography (OCT) imaging of the retinal layer thickness is performed, contrast sensitivity testing is measured and a condensed battery of neurocognitive and psychiatric measurements are performed. These subjects have consented to allow us to use their data from the Neurotrauma study to supplement their CENC data. We are using a statistical model that can account for more time points for this subset in the longitudinal analysis of change over time.

(5) We have performed a limited interim analysis of the longitudinal data to date, but have done so only to search for any unanticipated issues with data collection and analysis. Because ours is a longitudinal study of mild TBI vs age-matched control veterans across a large number of outcome measures of visual and neurologic structure and function, we have been careful not to introduce any bias into the data collection by a premature analysis of the data, since we are still in the midst of completing

longitudinal data collection. We have developed a statistical model for analysis of the longitudinal data which takes into consideration a number of important parameters, including age, time, number of time points, baseline measurement at time of enrollment and variability of each measured outcome measure. We have developed a statistical model for both group analysis comparing mild TBI with age-matched normal veterans and a model for assessing individual subjects in order to identify specific subjects that are showing abnormal deterioration over time, not accounted for by aging.

(6) Assessment of Retinal Layer Thickness (OCT) and Visual Field Sensitivity Testing: In our recent interim analysis of the retinal nerve fiber (RNFL) layer thickness measured by optical coherence tomography (OCT) as a function of time since enrollment in normal subjects and mild TBI subjects, there was no significant group difference between the control and mTBI groups with respect to the baseline RNFL thickness or rate of change (slope). However, when analyzed on an individual basis, 25% of Veterans with an mTBI had a negative slope of RNFL thickness below the 10th percentile of that for controls (see Figure below), indicating significant loss of retinal neurons over time in these veterans. We are also investigating reasons for why some subjects show a positive slope (increasing thickness over time), which could be due to gliosis (replacement of neural elements with glial cells) or axoplasm flow stasis. A similar phenomenon has also been reported in glaucoma which may be an important new finding of injured neurons in TBI.



This figure shows density plots of the distribution of slopes (microns change in retinal nerve fiber layer per year) in both the control group and mild TBI (mTBI) group. 25% of veterans with mTBI had a negative slope below the 10th percentile of that for controls (aqua colored density to the left of the vertical dotted line), indicating a significant loss of retinal neurons over time.

This would be the first objective structural evidence for progressive neural degeneration (in the retina) in mild TBI in living subjects. We will be further investigating if any of the mild TBI subjects enrolled that are showing progressive decline in OCT structure of the retina are also showing a decline in visual function tests (visual acuity, contrast

sensitivity, and visual field sensitivity). We will also be comparing this to the longitudinal analysis of cognitive and psychiatric functional measures as well as white and grey matter volume change over time in MRI studies.

(6) Executive function and functional MRI in mild TBI: We have also been analyzing data on executive function in our cohorts related to functional MRI studies performed at the time of enrollment. Subjects received an fMRI scan at 3T while performing the Color and Word Stroop task to assess executive processing abilities. Severity of mTBI was assessed with the Minnesota Blast Exposure Screening Tool (MN-BEST). A multiple linear regression was performed with fMRI task activation, age, and mTBI severity. Following an ROI-wise permutation analysis (379 ROIs across cortical hemispheres and sub-cortex), the left inferior parietal lobule showed significant interaction effects such that with increasing age and more severe mTBI, greater activation was observed in the left inferior parietal lobule. This analysis reveals that with an increase in age and MN-BEST scores there is an increase in activation within the left inferior parietal lobule, suggesting that older participants with more severe mTBIs required more attentional resources. This may have implications for the clinical course and care of our aging Veteran population with an mTBI.

(7) For baseline enrollment data, there does not appear to be any significant difference between the inner retinal layer thickness (surrogate of number of neurons and axons in the inner retina) comparing the mild TBI group with the normal group. In our interim analysis, we have identified a group of veterans in the mild TBI group (25%) that appear to be showing progressive thinning of the inner retinal layers over time that exceeds the 10th percentile of that seen in the normal aging control group. We will need to see if there are any further subjects identified as we collect more longitudinal data and compare this with their CNS functions and MRI scans over time. We have also found that with an increase in age and severity of mild TBI, more attentional resources were required causing greater activation in the left inferior parietal lobe. We will be assessing similar dysfunction over time with the longitudinal data set, once completed.

4. KEY RESEARCH ACCOMPLISHMENTS:

a. Developed a highly pragmatic national analytic dataset of 1.6 million veterans, including all veterans with TBI, receiving healthcare within the VHA medical system from 2000-2015.

b. Generated the “all sources” TBI severity algorithm resulting in seven distinct and clinically meaningful categories of TBI severity using modified 2012 DVBIC/AFHSB criteria.

c. Study 34’s NIH Toolbox crossover study is the first research study to directly assess the comparability of the two methods of test administration. Our preliminary results indicate a need for caution and further study.

d. Development of the first fully comprehensive, quantitative MRI QA report system that provides an automatically-generated report system including: a) “good to go” dashboard; b) comprehensive match to ground truth metrics; and c) longitudinal data of instrument change. Details of the automated reporting system were presented to the Government Steering Committee. The figure below illustrates some of the features of software development which enabled automated segmentation of fluids and fibers and well as quantitative analysis plots that are included in the report.

5. CONCLUSION: Nothing to report.

6. PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:

a. List all manuscripts submitted for publication during the period covered by this report resulting from this project. Include those in the categories of lay press, peer-reviewed scientific journals, invited articles, and abstracts. Each entry shall include the author(s), article title, journal name, book title, editors(s), publisher, volume number, page number(s), date, DOI, PMID, and/or ISBN.

(1) Lay Press:

Dr. Ann McKee: Times Magazine’s 100 Most Influential People 2018

(2) Peer-Reviewed Scientific Journals:

Barnes DE, Byers AL, Gardner RC, Seal KH, Boscardin WJ, Yaffe K, and the Chronic Effects of Neurotrauma Consortium Study Group. Association of Mild Traumatic Brain Injury With and Without Loss of Consciousness With Dementia in US Military Veterans. JAMA Neurology, 2018, 75(9):1055-1061. DOI:10.1001/jamaneurol.2018.0815

Bertenthal D, Yaffe K, Barnes DE, Byers AL, Gibson CJ, Seal KH, and the Chronic Effects of Neurotrauma Consortium Study Group. Do postconcussive symptoms from traumatic brain injury in combat veterans predict risk for receiving opioid therapy for chronic pain? Brain Injury, 2018, 10: 1188-1196. DOI:10.1080/02699052.2018.1493535

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Kenney, K., Qu, B., Lai, C., Devoto, C., Motamedi, V., & Walker, W. C. (2018). Higher exosomal phosphorylated tau and total tau among veterans with combat-related repetitive chronic mild traumatic brain injury. *Brain Injury*, *32*(10), 1276-1284. doi:10.1080/02699052.2018.1483530

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(3) Abstracts: See below for abstracts related to MHSRS and other conferences

b. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.

Byers A., Li Y., Barnes D., Seal K., Boscardin J., Yaffe K.	Mild Traumatic Brain Injury and Risk of Suicide and Death by Drug Overdose. International Summit on Suicide Research, Henderson, NV., November 2017	Presentation
Crawford, F.	Current research on Traumatic Brain Injury. “Grey Matters” Symposium: Sarasota, FL, September 22, 2017.	Presentation
Ferguson, S.	Assessment of visual dysfunction of the optomotor response in APOE transgenic mice after TBI. Annual Society for Neuroscience (SFN) Meeting: Washington, DC, November 11-15, 2017.	Poster
Algamal, M.	Chronic behavioral deficits, HPA axis abnormalities and altered synaptic plasticity (after 6months) in a mouse model of post-traumatic stress disorder. Annual Society for Neuroscience (SFN) Meeting: Washington, DC, November 11-15, 2017.	Poster
Morin, A.	Nilvadipine ameliorates repetitive mild TBI-induced memory impairment in aged mice. Annual Society for Neuroscience (SFN) Meeting: Washington, DC, November 11-15, 2017.	Poster
Crawford, F.	Burns Court, Sarasota, FL. Presentation on Traumatic Brain Injury. January 2018.	Platform
Crawford, F.	Preclinical Models of Repetitive Mild Traumatic Brain Injury. New Perspectives on Central and Peripheral Inflammation in TBI Meeting at the Tampa Veterans Administration Medical Center: Tampa, FL, May 18, 2018	Platform
Morin, A.	Effect of age on response to treatment with nilvadipine after repetitive mild TBI. Tampa Veterans Administration Research Day: Tampa, FL, May 22, 2018.	Poster
Saltiel, N.	Age-Dependent Neurobehavioral and Neuropathological Effects of Repetitive Mild Traumatic Brain Injury. Tampa Veterans Administration Research Day: Tampa, FL, May 22, 2018.	Poster
Crawford, F.	Chronic outcomes in a mouse model of repeated, unpredictable stress. National Neurotrauma Society (NNS) Annual Meeting: Toronto, ON, August 11-16, 2018.	Platform
Ferguson, S.	Age-Dependent Effects in Response to Repetitive Mild TBI in hTau Transgenic Mice at Latent Time Points. National Neurotrauma Society (NNS) Annual Meeting: Toronto, ON, August 11-16, 2018.	Poster
Eisenbaum, M.	Tau Processing by Mural Cells in Traumatic Brain Injury. National Neurotrauma Society (NNS) Annual Meeting: Toronto, ON, August 11-16, 2018.	Poster
Lynch, C.	Chronic Cerebrovascular Reactivity Impairment and Associated Pathological Abnormalities in a Mouse Model of Repetitive Mild Traumatic Brain Injury. National Neurotrauma Society (NNS) Annual Meeting: Toronto, ON, August 11-16, 2018.	Poster
Morin, A.	Effect of age on response to treatment with nilvadipine after repetitive mild TBI. National Neurotrauma Society (NNS) Annual Meeting: Toronto, ON, August 11-16, 2018.	Poster

Kelley, C.	Hippocampal and entorhinal cortex Alzheimer's disease-like pathology in human chronic traumatic encephalopathy: a chronic effects of neurotrauma consortium study, Neuroscience meeting, 2018	Poster
Kelley, C.	Medial temporal lobe pathology in human chronic traumatic encephalopathy: a chronic effects of neurotrauma consortium study, Military Health System Research Symposium, Florida, 2018	Poster
Mufson, E.	Preliminary expression profiling of tau-positive cholinergic basal forebrain neurons in the nucleus basalis of Meynert in postmortem chronic traumatic encephalopathy brain: A Chronic Effects of Neurotrauma Consortium Study, Neuroscience meeting, 2016	Poster
Perez, S.	Expression profiling of tau-positive cholinergic neurons within the nucleus basalis of Meynert in brains from veterans and athletes with a postmortem diagnosis of chronic traumatic encephalopathy (CTE): A Chronic Effects of Neurotrauma Consortium Study, International Brain Injury Association, New Orleans, 2017.	Poster
Pugh MJ, Swan AA, Delgado RE, Amuan ME, Tate DF, Yaffe K, Wang CP.	Comorbidity phenotypes in Veterans with mild TBI: A Chronic Effects of Neurotrauma Consortium study. Symposiuim conducted at the TBI Federal Interagency Conference, Washington, DC., June 2018	Symposium
Yaffe K	TBI and Dementia: What We Know & What We Don't Know. Head Trauma in Sports and Risk for Dementia, Nobel Forum, Karolinska Institutet. Stockholm, Sweden, May 2018.	Presentation
Gardner R & Yaffe K	Featured Research Symposium on TBI. 2018 Alzheimer's Association International Conference, Chicago, IL, July 2018.	Presentation
Yaffe K	TBI and Dementia: What We Know & What We Don't Know. VA HSR&D Cyberseminar, July 2018.	Presentation
Gullickson J. T., Sponheim S.R., Davenport N.D.	Effects of Cognitive Reserve on Post-DeNeurodegeneration and Symptomatology (216.1). 2017 Society for Neuroscience, Washington, DC.	Poster
Pogoda T.K.,Grey S.F., Fogleman E., Nolen T., Carlson K., Chronic Effects of Neurotrauma Consortium Study 1 Group.	A Causal Analysis of Employment Status in Post-9/11 Combat Veterans with or without Mild TBI. TBI Federal Interagency Conference, Washington, DC., June 2018	Oral presentation
Nayak A.,Wilde E., Taylor B., CENC Neuroimaging Core Investigators, Reyes L, Pierpaoli C.	A Living Phantom Study to Evaluate the Echo Planar Imaging (EPI) Distortion Correction Effects in Reducing Inter-site Variability. International Society for Magnetic Resonance in Medicine, Port de Versailles Paris, France, June 2018	Poster
Agyemang A.	Advances in the study of mild traumatic brain injury among Warfighters: Findings from The Chronic Effects of Neurotrauma Consortium (CENC). 2018 Military Health System Research Symposium, Orlando, FL.	Track session
Dennis E.L.,Wilde E.A, Scheibel R.S., Troyanskaya M.,	Altered White Matter Organization after Military Brain Injury: Preliminary Results from the ENIGMA Military Brain Injury Group. TBI Federal Interagency Conference, Washington, DC, June 2018	Poster

Velez C,...Tate D.T.		
Dennis E.L., Wilde E.A., Newsome M.R., Scheibel R.S., Troyanskaya M.	Meta-Analysis of Diffusion MRI in the ENIGMA Military Brain Injury Group: Preliminary Results. 2018 Organization for Human Brain Mapping Annual Meeting.	Poster
Shura R., Rowland, Martindale, Spengler, & Taber K.	Preliminary Results from a Novel Method for Evaluating Blast Exposure. 2018 American Academy of Clinical Neuropsychology Annual Meeting in San Diego, CA, June 2018.	Poster
Pugh MJ, Swan AA, Delgado RE, Amuan ME, Tate DF, Yaffe K, Wang CP	*Comorbidity Phenotypes in Veterans with Mild TBI: A Chronic Effects of Neurotrauma Consortium Study, 4th Interagency TBI Conference, Washington DC, June 2018	Presentation
Norman R.S., Wang C.P., Amuan M., Pugh M.J.	Phenotypes of Comorbidity among Women Veterans and Service Members after Mild Traumatic Brain Injury. 2018 TBI Federal Interagency Conference, Washington, DC.	Poster
Pugh MJ	*Trajectories of Comorbidity among Male and Female Veterans and Service Members After TBI; NINDS Workshop: Understanding Traumatic Brain Injury in Women, Bethesda MD, December 2017	Presentation
Delgado RE, McConnell K, Pugh MJ	Health-Related Characteristics in a Cohort of Military Caregivers: Caring for Wounded, Ill and Injured Veterans, Military Health System Research Symposium, Kissimmee FL August, 2018	Presentation
Pugh MJ, Song K, McGeary D, McGeary C, Jaramillo CA, Eapen BC, Potter JS, Wang CP	Five Year Trajectories of Pain and Pain Treatment in Post-9/11 Veterans with mTBI, Military Health System Research Symposium, Kissimmee FL August, 2018	Poster
Pugh MJ	TBI and Epilespy: What We Know and What We Don't Know; Red Cross Military Caregiver Network, September 2018 (Webinar)	Presentation
Jak, A.J.	Assessment and treatment of persistent post-concussive symptoms in Veterans: rethinking the role of concussion. Annual Meeting of the International Neuropsychological Society, Washington, D.C.	Presentation
Hoffman S.N., Herbert M.S., Crocker L.D., DeFordN.E., Keller A.V., Jurick S.M.,Sanderson-Cimino M. & Jak A.J.	The role of pain catastrophizing in cognitive functioning among veterans with history of mild traumatic brain injury. Submitted to Journal of Head Trauma.	Poster
Vasudevan, R. S., Herbert, M. S., Jurick, S. M., DeFord, N. E., Keller, A. V., Hoffman, S. N.,	Examination of symptom over-reporting and self-reported pain and depression in Iraq and Afghanistan Veterans with mild traumatic brain injury. Poster presented at the 46th annual International Neuropsychological Society Conference in Washington, D.C.	Poster

Lee, M., Sanderson-Cimino, M., & Jak, A. J.		
Dismuke-Greer C.E., Gebregziabher M., Hunt K., Taber D., Axon N., Egede L.E.	Association of Clinically Diagnosed Depression With Total, Inpatient, Outpatient and Pharmacy VA Costs in Veterans Diagnosed with Traumatic Brain Injury. Military Health System Research Symposium, Orlando, FL, August 2018.	Poster
Dismuke-Greer CE Gebregziabher M, Byers AL, Taber D, Axon N, Yaffe K, Egede LE	*Comorbid TBI-Depression Costs in Veterans: A Chronic Effects of Neurotrauma Consortium (CENC). 2018 Military Health System Research Symposium, August 20-23, 2018.	Presentation
Hoot M.R., Levin H.S., Smith A.N., Goldberg G., Wilde E.A., Walker W.C., Nolen T., Pugh N.L.	Pain and Chronic Mild Traumatic Brain Injury in the US Military Population: a Chronic Effects of Neurotrauma Consortium Study. Military Health System Research Symposium, Orlando, FL, August 2018.	Poster
William W.C., Nowak K., Kenney K., Manning-Franke L., Eapen B.C., Skop K., Levin H.S., Agyemang A., Tate D., Wilde E.A., Hinds S., Hirsch S., Nolen T.	The Relationship between Repetitive Mild Traumatic Brain Injury and Balance Performance; A Chronic Effects of Neurotrauma Consortium (CENC) Multi-Center Observational Study Interim Analysis. Military Health System Research Symposium, Orlando, FL, August 2018	Poster
Walker W.C., Hirsch S., Cifu D.X., Hines S., Williams R., Vanderploeg R., Belanger H., Temkin N., Carne W.	Diagnosing Mild Traumatic Brain Injury: Description and findings of methods used in the Chronic Effects of Neurotrauma Consortium (CENC) multicenter observational study. Military Health System Research Symposium, Orlando, FL, August 2018.	Poster
Kenney K., Qu B.X., Lai C., Devoto C., Motamedi V., Walker W,C., Levin H., Nolen T., Wilde E.A., Diaz-Arrastia R., Gill J.	Elevated Exosomal Total and Phosphorylated Tau Among Veterans with Chronic Repetitive Mild Traumatic Brain Injury. Military Health System Research Symposium, Orlando, FL., August 2018	Poster
Kiernan P.T., Abdolmohammadi B.A., Goldstein L.E., Huber B.R., Alvarez V.A., Stein T.D., Alosco M.L., Mez J., Mahar I., Cherry J.D., Kowall N.W., Katz D.,	Clinical and Neuropathological Features in a Case Series of 15 Operation Enduring Freedom/Operation Iraqi Freedom Veterans exposed to Civilian and Military-Related Traumatic Brain Injury. Military Health System Research Symposium, Orlando, FL, August 2018.	Poster

Dwyer B., Stern R.A., McKee A.C.		
Akin, F.	Otolith Dysfunction and Postural Stability. Military Health System Research Symposium, Orlando, FL., August 2018	Poster
Pogoda T., Belanger H.G., Carlson K.F., Levin H., Nolen T.L., Nowak K.J., O'Neil M.E., Tate D., Wilde EA, Walker W.C.	The Relationship Between Mild Traumatic Brain Injury and Neurobehavioral Symptoms Among Those Who Served In OEF/OIF/OND Combat: A Chronic Effects of Neurotrauma Consortium study. Military Health System Research Symposium, Orlando, FL., August 2018.	Poster
Garcia A., Nakase-Richarson R., Vanderploeg R., Wilde L., Levin H., Dikmen S.,...Pastorek N.	Obstructive Sleep Apnea Risk is Associated with Cognitive Impairment After Controlling for TBI: A Chronic Effects of Neurotrauma Consortium Study. Military Health System Research Symposium, Orlando, FL., August 2018	Poster
Pugh M.J., Swan A., Delgado R., Amuan M.,Tate D. Yaffe K., Wang C.	Comorbidity Phenotypes in Afghanistan and Iraq War Veterans with mild and no TBI: A Chronic Effects of Neurotrauma Consortium Study. American Academy of Neurology Conference in Los Angeles, CA., April 2018.	Poster
Taber K.H., Rowland J.A., Epstein E., Martindale S.L., Miskey H.M., Shura R.D.	Influence of Primary Blast Exposure on Development of PTSD Following Deployment. Society for Neuroscience 48th Annual Meeting, San Diego, CA., November 2018	Poster
Davenport, N.D.	Longitudinal changes in cortical thickness associated with military mTBI: A CENC study. Presented at Military Health System Research Symposium, August 2018. Kissimmee, FL.	Poster
Fleming, C.L.	Correspondence of Self-Report vs. Clinician-Administered Ratings of PTSD Symptoms Among Deployed Veterans. Presented at Society for Research in Psychopathology, September 2018. Indianapolis, IN.	Poster
Ferguson S., Mouzon B., Hahn-Townsend C., Lungmus C., Mullan M., Crawford F.	Age-Dependent Effects in Response to Repetitive Mild TBI in hTau Transgenic Mice at Latent Time Point. Submitted to NeuroTrauma Conference 2018, Toronto, CN, August 2018	Poster
Kardon, R.	"Ocular Biomarkers of Traumatic Brain Injury" and "New Aspects of Ocular Blood Flow in Health and Disease", University of South Florida, Department of Ophthalmology, Tampa, Florida, February 15, 2018.	Presentation
Kardon, R.	"New Insights into Causes and Treatment of Photosensitivity", Roskamp Research Institute, Sarasota, Florid, February 16, 2018.	Invited Talk
Kardon, R.	"Ocular Manifestations of Traumatic Brain Injury", University of Oregon and Casey Eye Institute, Portland, OR, May 10-12, 2018.	Invited Talk
Kardon, R.	"Ocular Biomarkers of Traumatic Brain Injury", United Kingdom Blind Veterans Association, Manchester, England, May 23, 2018.	Invited Talk

Hall C.D., Akin F.W., Murnane O.D., Sears J., Atlee R.	Impact of Otolith Dysfunction on Postural Stability and Quality of Life: A Chronic Effects of Neurotrauma Consortium Study.	Abstract
Erin D. Bigler, Tracy J. Abildskov , Barry Eggleston , Brian A. Taylor, David F. Tate , Mary R. Newsome, Randall S. Scheibel, Harvey Levin, William C. Walker, Naomi Goodrich-Hunsaker, Nick J. Tustison, James R. Stone,Andrew R. Mayer, Timothy D. Duncan, Gerry E. York, Elisabeth A. Wilde	Structural Neuroimaging in Mild Traumatic Brain Injury: A Chronic Effects of Neurotrauma Consortium Study. Submitted to Brain Injury	Abstract

7. INVENTIONS, PATENTS AND LICENSES: Nothing to report.

8. REPORTABLE OUTCOMES:

Below is a list of grant applications that are a result of CENC funding. These were submitted with the GSC directed aim of establishing CENC beyond current governmental funding:

a. Grant Applications:

(1) VA: BLR&D Collaborative Merit Review Award for Traumatic Brain Injury (TBI) Research: Linked Merit Grant: Chronic Traumatic Brain Injury Tauopathy in Mice and Human: Neurodegeneration after Repetitive Neurotrauma: Mechanisms and Biomarker Discovery, 04/01/2019- 03/31/2023, (PI: McKee, A. submitted)

(2) CDMRP W811XWH-18-JWMRP, “CENC: Serum and Clinical Biomarkers for Predicting and Novel Intervention for Preventing Neurodegeneration”, submitted AUG 2018 (PI: David Cifu; Biomarker project PI: Kimbra Kenney: pending).

(3) “Efficacy of Augmented Cognitive Rehabilitation Therapy Using Individual Profiles of Injury to Guide tDCS to Treat Mild TBI in Veterans With Persistent Symptoms” Letter of Intent/pre-application submitted to JPC-8/CRMRP CTRR; submitted September 2018 (PIs: Tate, Wilde, and Bouix; status: under review).

(4) “ENIGMA TBI Working Group: Big Data Statistical Approaches to Identify Clinically Meaningful Imaging Biomarkers” submitted June 2018 (PIs: David Tate and Elisabeth Wilde, status: resubmission planned).

(5) “A Longitudinal Study of Chronic TBI in OEF/OIF/OND Veterans and Service Members (Renewal)”; submitted June 2018 (PI: Randall Scheibel: status: under revision).

(6) “Leveraging Data within the Federal Interagency Traumatic Brain Injury Research (FITBIR) Informatics System to Identify Actionable Insights for the Diagnosis, Management and Treatment of TBI” Response to Request for Information (RFI): W81XWH-18-DSM6810; submitted 2018 (PIs: Tate and Wilde).

(7) “VA Program Project in Health Services and Rehabilitation Research Improving Sleep Apnea Management After TBI (I-SAM-TBI)” (PI: Risa Richardson) Component Project: “Undetected Sleep Apnea and Associated Risk for Poor Health and Economic Outcomes in Veterans with TBI”, submitted 2018 (PI: Mary Jo Pugh; Co-PI: Libby Dismuke).

(8) “Longitudinal Assessment of Neurodegeneration Following TBI”, Merit Review grant to the VA RR&D, Submitted August 2018 and will be resubmitted in December 2018, (PI: Randy Kardon).

(9) “Influence of APOE Genotype on the neurodegenerative sequelae of repetitive mild TBI in an hTau mouse model”. NIH R01 application submitted 1st time June 2018 not reviewed; submitted 2nd time October 2018. Awaiting Reviewer comments. (PI: Crawford).

(10) “Astroglia pathobiology in the neurodegenerative sequelae of Repetitive Mild Traumatic Brain Injury”. CDMRP PRARP application submitted October 2018. (PI: Dr. Crawford, Co-PI: Dr. Ojo, Sub-award Investigator: Dr. Elliott Mufson).

(11) “Effects of Opioid and Other Psychotropic Drug Exposures on Long-term Outcomes of TBI: Developing Measurement Best Practices.” Veterans Affairs, Rehab R&D application submitted in September 2018. (PI: Kathleen Carlson).

(12) “RCT of Traditional Cognitive Rehabilitation Augmented by Repetitive Transcranial Magnetic Stimulation (rTMS) in TBI With Cognitive Problems and Chronic Pain.” Dept of Defense, CDMRP, Psychological Health/Traumatic Brain Injury Research Program, Complex Traumatic Brain Injury Rehabilitation Research, Clinical Trial Award Funding Opportunity Number: W81XWH-18-CTRR-CTA. Pre-application submitted September 2018. (PI: William C. Walker).

b. Funded:

(1) “Shared Equipment Evaluation Program (ShEEP) grant proposal to upgrade the Michael E. DeBakey VA Medical Scanner from a Siemens Trio to a Siemens Prisma”; submitted Sept 2017 (PI: Randall Scheibel: status: awarded in 2018).

(2) “Cognitive control-related brain activation in veterans and service members with PTSD”; submitted March 2018 (PI: Randall Scheibel: status: awarded in 2018).

(3) “Genetic, comorbidities, and ethnicity: Effects of TBI on dementia” FY17 Congressional Directed Medical Research Program (CDMRP) Peer-Reviewed Alzheimer’s Research Program Research Partnership Award. W81XWH-18-1-0692 (PI: Kristine Yaffe).

(4) “A Novel Visually Graded CT Biomarker of Preinjury Brain Structure to Improve Prediction of Cognitive Decline after Mild Traumatic Brain Injury”, FY17 Congressional Directed Medical Research Program (CDMRP) Peer-Reviewed Alzheimer’s Research Program Research Partnership Award. W81XWH-18-1-0514. (PI: Raquel C. Gardner).

(5) “A Neuroscience-Based Cognitive Intervention to Improve Brain Health in Older Veterans with Traumatic Brain Injury”, FY17 Congressional Directed Medical Research Program (CDMRP) Peer-Reviewed Alzheimer’s Research Program Research Partnership Award. W81XWH-18-1-0286 (PI: Allison Kaup).

(6) “Trajectories of Pain and Pain Treatment in Veterans with Mild Traumatic Brain Injury (mTBI)”, NIH/NICHD Eunice Kennedy Shriver National Institute of Child Health and Human Development, 1R21HD089098-01, (PI: Mary Jo Pugh).

(7) “Phenotypes of comorbidity in epilepsy: Variation by TBI severity and deployment status”, FY17 CDMRP Epilepsy Research Program (ERP) Idea Development Award, W81XWH1810247, (PI: Mary Jo Pugh).

(8) “Epidemiological Characterization and Prognostic Models for PTE: A Collaborative TBI-MS and VHA Study”, FY17 CDMRP Epilepsy Research Program (ERP) Idea Development Award, W81XWH1810, (PI: Amy Wagner).

(9) “Personal Biology & Comorbidity Impact on Post-TBI Cognitive Dysfunction & Neurodegenerative Disease”, FY17 CDMRP Psychological Health/Traumatic Brain Injury Research Program Complex Traumatic Brain Injury Rehabilitation Research Clinical Research Award, PT170100, (PI: Amy Wagner).

(10) “The UCD-DGMC TBI Precision Medicine Network for Complex Trauma”, Peer Reviewed Medical Research Program Discovery Award, W81XWH-18-2-0071, (PI: Tina Palmieri).

(11) “Development of neural stem cell mediated therapy for repetitive mild TBI”. NIH R03 application submitted March 2018. (PI: Mouzon, Consultant - Crawford).

(12) “Identifying APOE related lipid biomarkers for diagnosing chronic neurocognitive deficits in TBI patients”. VA RR&D application submitted December 2017 Not funded; Resubmitted June 2018 (PI: Abdullah, Multiple PI- Crawford). This project will access the CENC biorepository.

(13) “Pilot Study: Mechanisms of Comorbidity of Posttraumatic Stress and Alcohol Use Disorder in Veterans with PTSD.” Wake Forest Translational Alcohol Research Center (WF-TARC, Weiner) P50 AA026117 01 (Co-PIs: Rowland & Godwin, status: funded 2/1/2018 – 1/31/2020).

c. Not Funded:

(1) “Efficacy of Individual Profiles of Injury to Guide Transcranial Direct Current Stimulation to Treat Mild TBI in Veterans with Persistent Symptoms” submitted to the Department of Defense (PIs: David Tate and Elisabeth Wilde, status: scored 1.6, but not funded)..

(2) Neural Imaging of Blast-Exposed Veterans Who Exhibit Auditory and Cognitive Deficits” submitted to VA RR&D submitted late fall 2015 (PI: Folmer, status: not funded).

(3) “The Role of Deployment-Acquired Mild Traumatic Brain Injury, Blast Exposure, and Functional Brain Networks in the Development and Resolution of Posttraumatic Stress Disorder.” VA RR&D (PI: Rowland, status: scored; resubmitting Cycle I - Winter).

(4) “Factors Related to Invalid Neuropsychological Testing in Post-9/11 Veterans with a History of mild Traumatic Brain Injury.” (PI: Shura, status: unscored; resubmitting Cycle Cycle III – Summer).

(5) “Effects of Sleep on Cognition in OEF/OIF/OND Veterans with Alcohol Use Disorder.” (PI: Martindale, status: scored; resubmitting Cycle III – Summer).

(6) “Structural and Functional Neurobiology of Veterans Exposed to Primary Blast Forces.” VA RR&D (PI: Taber, status: scored; resubmitting Cycle I - Winter)

9. OTHER ACHIEVEMENTS:

10. REFERENCES: List all references pertinent to the report using a standard journal format (i.e., format used in *Science*, *Military Medicine*, etc.).

11. APPENDICES: See Appendices 1-52.

QUAD CHARTS: See Attachments

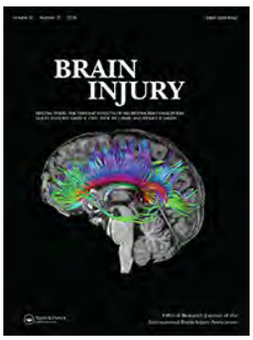
CENC

Chronic Effects of Neurotrauma Consortium

Appendices for 2018

Appendix 1

Chronic Effects of Neurotrauma Consortium: a combined comparative analysis of six studies Introduction to Special edition of Brain Injury



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Chronic Effects of Neurotrauma Consortium: a combined comparative analysis of six studies
Introduction to Special edition of Brain Injury

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KEYWORDS Traumatic brain injury; concussion; military; veteran
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Concussions, or mild traumatic brain injuries (mTBI), are the most common, potentially clinically debilitating, neurological injury associated with military combat, sports, vehicular accidents and domestic trauma (1). Awareness efforts surrounding the identification and management of concussions have existed for decades, but, given the recent Gulf Wars and concerns regarding repeated concussions in sports, there has been increasing attention focused on them. Research efforts to systematically and conclusively categorize and understand the diagnosis, short-term management and late effects of mTBIs remain nascent. There are a number of studies (2) supporting the incidence of concussive injuries from the Afghanistan (Operation Enduring Freedom [OEF]), Iraq (Operation Iraqi Freedom [OIF]) and subsequent worldwide War on Terror (Operation New Dawn [OND]) wars. The incidence of concussions from these conflicts ranges from 6% to 20% among all U.S. Service members (SMs) (3,4). Approximately 40% of OEF–OIF–OND concussed Veterans seeking care at Veterans Affairs Medical Centers (VAMCs), which represents nearly 8% of all those deployed in these conflicts, report persistent neurosensory (headache, hearing, tinnitus, vision), somatic (balance, coordination, sleep), cognitive (executive function, memory) and behavioural symptoms (irritability, anxiety) (5). Additionally, secondary co-morbidities that may be associated with the traumatic episode but are not directly physically related to the actual brain trauma, such as post-traumatic stress disorder (PTSD), depression, substance abuse or low back or joint pain, may be seen in more than three-quarters of these Veterans with combat-associated concussions, adding to the diagnostic and management complexity (5).

In 2013, as a response to the National Research Action Plan (6), the Departments of Veterans Affairs and Defense jointly-funded the Chronic Effects of Neurotrauma Consortium (CENC) (www.cenc.rti.org) (7). Consisting of more than 50 leading clinical, translational, epidemiologic and basic scientists from more than 30 academic universities, 15 VAMCs and 12 military treatment facilities (see Figure 1), CENC is a nationwide consortium focused on identifying and characterizing the anatomic, molecular and physiological mechanisms of combat-associated mTBI, evaluating how co-morbidities are associated with and exacerbated by combat-associated mTBI and studying treatment and rehabilitation strategies for the short- and long-term effects of combat-associated mTBI. To date, CENC has initiated 10 major clinical, animal and epidemiologic studies that are supported by five centralized, research and administrative infrastructure cores. This report examines the findings to date of the six clinical projects, describes the growing cohort of Veterans and SMs and identifies emerging cross-study similarities and differences.

Whereas this report provides a cross-sectional, broad stroke comparison of six of the CENC clinical studies, this special issue also contains 14 other papers that present more nuanced findings on individual CENC studies. There are a number of papers reporting on various aspects of a smaller sample of the currently 1450+ participants enrolled in CENC's longitudinal study. These include the association of mTBI with pain, functional brain connectivity and cortical thickness, balance performance, Department of Veterans Affairs (VA) -defined service-connected disability and with the biomarker tau, as well as a description of its highly successful recruitment strategies and the factor structure of the battery of neuropsychological assessments used in the sample. Other papers in this issue describe findings on the longitudinal changes in neuroimaging and neuropsychiatric status of post-deployment Veterans, sensory dysfunction in the context of TBI and the association of mTBI with ventricular volume changes and characterize those individuals receiving opioid therapy for chronic pain. Of additional interest, there are also two papers describing advances in mTBI methodology, including an assessment of quantitative magnetic resonance imaging metrics in the brain through the use of a novel phantom and a description of a novel white matter imaging technique. Finally, there is a paper evaluating the impact of age on acute post-TBI neuropathology findings using CENC's standardized mouse model for repetitive mTBI.

Methods

Beginning in October 2013, six clinical studies, after each being reviewed and competitively scored by a peer review

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Figure 1. Map of CENC sites.

panel of subject matter experts, were initiated across the CENC research network in geographically diverse settings, utilizing standardized subject recruitment and assessment approaches. For each of these six separate investigations, the research approaches were developed and finalized, submitted for institutional review board and federal regulatory approval and then initiated following final approvals. While each of these studies had unique hypotheses, aims and specialized assessment approaches needed to address their focused areas of investigation (e.g., differing types of advanced neuroimaging, innovative or experimental neurophysiologic tools), the uniform use of the TBI common data elements and the centralized quality oversight of data collection and entry from all the studies allow for the use of an overall data set that combines all six studies.

Studies

Data for the current paper came from six CENC clinical studies with differing research objectives, but the common overarching goal of enhancing understanding of the nature of and effects of mTBI: (1) Study 1, which is an ongoing Longitudinal Study (target recruitment $n = 1100$) that is prospectively monitoring subjects for potential long-term changes in their physical and mental health; (2) Study 8, (target recruitment $n = 121$) which aimed to study the effects of mTBI-related vestibular dysfunction on balance, gait and quality of life among Veterans; (3) Study 20 (target recruitment $n = 82$), which aimed to test a new approach for assessing myelin abnormalities, multicomponent-driven equilibrium single-pulse observation of T1 and T2 (McDESPOT), to calculate myelin volume in Veterans with a history of mTBI and/or PTSD; (4) Study 34 (target recruitment $n = 180$), which aimed to study the natural and functional effects of TBI-related white matter abnormalities; (5) Study 49 (target recruitment $n = 180$), which aimed to test the utility of psychological and biological measures as markers for mTBI-related neurodegeneration; and (6) Study 56 (target recruitment $n = 140$), which aimed to identify mTBI-related visual sensory disturbances using a case-control methodology.

Participants

Although each of the six studies has specific participant recruitment goals, all participants were U.S. Veterans and SMs who served on active duty in the OEF–OIF–OND conflicts between the years 2000 and 2014. The current paper describes the demographic, clinical and cognitive characteristics of participants (total $n = 1,643$) who had completed baseline assessments through 15 September 2017 for Study 1 ($n = 1024$), Study 8 ($n = 121$), Study 20 ($n = 62$), Study 34 ($n = 168$), Study 49 ($n = 129$) and Study 56 ($n = 139$). Of this cohort, 74% had sustained one or more concussive events, while the remainder served as controls.

Measures

Data measures from the six clinical studies for this analysis included demographic, mTBI exposure and clinical variables.

Demographic variables

These were self-reported gender, race, ethnicity, age, education, marriage status and military status.

mTBI exposure variables

To determine mTBI exposure status in Study 1 and Study 20, a modified version of the Ohio State University TBI Identification screening instrument (8) was used to identify any lifetime potential concussive event (PCE) (9). Each PCE was further investigated using a detailed structured interview, the Virginia Commonwealth

University Retrospective Concussion Diagnostic Interview (VCU rCDI) (9), which contains an embedded algorithmic preliminary diagnosis based on the Department of Defense (DoD)/VA common definition of mTBI (10). For each Veteran or SM, mTBI was classified as present/absent. Study 8 simply asked if the subject has 'history of head injury (mTBI/concussion)'. Study 34 used a structured TBI Interview from the VA Mid-Atlantic Mental Illness Research Education and Clinical Center (MIRECC) (11), as well as the Salisbury Blast Exposure Interview, which is administered by a clinician to evaluate lifetime blast exposure. Study 49 and Study 56 used the Minnesota Blast Exposure Screening Tool (MN-BEST) (12).

Clinical variables

A number of clinical measures were included in the current analyses.

Symptom Validity – Symptom exaggeration was measured on the Mild Brain Injury Atypical Symptoms (mBIAS) scale (13), designed for use with the Neurobehavioral Symptom Inventory (NSI) (14), and is commonly used to measure symptom validity in mTBI populations. The NSI is a self-report measure of the severity of post-concussive symptoms that was used to capture participants' TBI-related symptoms. The NSI also has a Validity scale built in to identify symptom exaggeration. The Medical Symptom Validity Test (MSVT) was used to evaluate respondents' effort at completing cognitive tasks (15). The MSVT categorizes respondents into three groups based on consistency between their verbal memory and responses—pass; fail due to poor or inadequate effort; and fail due to severe cognitive impairment similar to dementia.

Patient Health Questionnniare-9 (PHQ-9) – The PHQ-9 is a well-validated and widely used nine-item self-report measure of current depressive symptoms that uses items derived from DSM-IV and DSM-5 criteria for depressive disorders (16).

Deployment Exposure Risk and Resilience Inventory, Version 2 (DRRI-2) – The Combat Experiences scale of the DRRI-2 was used to assess exposure to different combat situations, with higher scores indicating greater combat experience (17). Study 1 uses a 16-item version with six response options (maximum score = 96). Study 20 and Study 34 used the 17-item version with six response options (maximum score = 102). Study 49 used a 16-item version with five response options (maximum score is 80).

Symptoms of PTSD – Symptoms of PTSD were measured on the Posttraumatic Stress Disorder Checklist for DSM 5 (PCL-5) for Studies 1, 20 and 34. The PCL-5 is a well-validated and commonly used self-report measure of PTSD symptomatology (18). The military versions of the PCL (PCL-M) (19) were used in Study 49 and the civilian version (PCL-C) (20) was used in Study 56.

Sleep Dysfunction – Sleep disturbance was evaluated with the Pittsburgh Sleep Questionnaire Inventory (PSQI), a psychometrically sound measure of sleep quality that has been validated in military study populations (21). Items included in the current analyses were sleep onset latency or the number of minutes it takes an individual to fall asleep; total hours of sleep per night; past month sleep quality; and past month sleep aid use.

Cognitive Dysfunction – There were several overlapping cognitive measures included in the current analyses. Subtests from the Wechsler Adult Intelligence Scale-4th Edition (WAIS-IV) (22) were used to measure working memory (Digit Span [DS]) and processing speed (Coding [CD] and Symbol Search [SS]) in most of the studies. Study 49 used the WAIS-III (23). The Trail Making Test Parts A and B (TMT-A, TMT-B), which are complementary parts of a test commonly used in standard neuropsychological batteries to assess for cognitive impairment (24), were also used in most studies. Finally, the California Verbal Learning Test-Second Edition (CVLT-II), which measures learning and memory (25) and has been widely used to assess for learning and memory deficits in TBI populations (26), was used across most studies.

Data analysis

For this analysis, data tables from the six studies were compared for all data collected through 15 September 2017. No attempt was made to impute missing data; missing data or data reflecting 'refused/don't know' responses were excluded from analysis. Where a study did not collect certain data, the comparison tables report 'NC' for not collected. Variables presented in the comparison tables represent those that were similar in definition to allow for cross-study comparisons. While some studies collected detailed information on present or former military service, for the purposes of this paper, an SM is defined as 'a person who is still in the military whether they are Active Duty/National Guard/Reserve/Active Guard Reserve/Ready Reserve. The person still wears the uniform in some capacity whether it is one weekend a month or on a daily basis'. Detailed analyses across variables were not performed at this time due to the ongoing nature of most of the studies with additional subject enrolment underway.

Results

The six studies were compared on demographic, clinical and cognitive characteristics.

Demographic characteristics

Findings from the comparison of demographic variables are presented in Table 1. Overall, the sample was predominantly White (72%) and male (88%), with the remainder being primarily African-American (19%). Studies 1, 34 and 56 each had proportions of females greater than 10%, and Study 34 exhibited the greatest proportion of African-Americans (37%). The mean age varied across studies, with Study 20 having the youngest cohort (mean = 33.6 years) and Study 8 having the oldest cohort (mean = 56.5), due to its focus on Veterans. Among the five studies that enrolled both Veterans and SMs, the majority of the sample were Veterans (83%), though there was also an appreciable representation of current SMs, ranging from approximately 6% in Study 20 to 12% in Study 1. Consistent with CENC objectives of studying the effects of mTBI, mTBI exposure ranged from 82% in Study 1 to 27% in Study 8.

Clinical characteristics

Across the four studies that administered the mBIAS, almost all participants (99–100%) produced valid responses, indicating that there is little concern about symptom exaggeration (see Table 2). Similarly, the NSI validity scale showed valid responses in nearly 100% of respondents. The fail rate on the MSVT ranged from

Table 1. Demographic differences by CENC study.

Characteristics[a]	CENC study					
	Study 01 (*N* = 1024)	Study 08 (*N* = 121)	Study 20 (*N* = 62)	Study 34 (*N* = 168)	Study 49 (*N* = 129)	Study 56 (*N* = 139)
Gender						
Male	886 (86.5%)	120 (99.2%)	57 (91.9%)	146 (86.9%)	125 (96.9%)	117 (84.2%)
Female	138 (13.5%)	1 (0.8%)	5 (8.1%)	22 (13.1%)	4 (3.1%)	22 (15.8%)
Race[b]						
White	714 (70.5%)	108 (91.5%)	36 (58.1%)	96 (57.5%)	110 (89.4%)	119 (85.6%)
African-American	220 (21.7%)	7 (5.9%)	4 (6.5%)	62 (37.1%)	2 (1.6%)	14 (10.1%)
Other	79 (7.8%)	3 (2.5%)	22 (35.5%)	9 (5.4%)	11 (8.9%)	6 (4.3%)
Ethnicity[b]						
Not Hispanic or Latino	793 (78.4%)	99 (98.0%)	38 (64.4%)	158 (94.6%)	NC	NC
Hispanic or Latino	219 (21.6%)	2 (2.0%)	21 (35.6%)	9 (5.4%)	NC	NC
Age						
N	1024	121	62	168	129	139
Mean (StdDev)	39.5 (9.8)	56.5 (16.5)	33.6 (6.0)	41.4 (9.8)	39.3 (8.1)	49.9 (11.1)
Min, Max	22, 70	25, 84	25, 47	26, 68	26, 60	23, 65
Education[c]						
College graduate	413 (40.3%)	41 (33.9%)	28 (45.2%)	71 (42.3%)	51 (41.8%)	70 (51.5%)
Some college	433 (42.3%)	52 (43.0%)	32 (51.6%)	81 (48.2%)	62 (50.8%)	46 (33.8%)
High school graduate	175 (17.1%)	25 (20.7%)	2 (3.2%)	16 (9.5%)	9 (7.4%)	20 (14.7%)
Less than high school	3 (0.3%)	3 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Marriage						
Married	599 (58.5%)	NC	32 (51.6%)	106 (63.1%)	65 (52.8%)	NC
Not married	425 (41.5%)	NC	30 (48.4%)	62 (36.9%)	58 (47.2%)	NC
Military status[d]						
Service member	120 (12.0%)	0 (0.0%)	2 (5.9%)	10 (9.9%)	13 (10.2%)	NC
Veteran	882 (88.0%)	121 (100.0%)	32 (94.1%)	91 (90.1%)	115 (89.8%)	NC
mTBI exposure[e]						
Unexposed	186 (18.2%)	88 (72.7%)	17 (27.4%)	29 (17.3%)	43 (33.3%)	71 (51.1%)
mTBI	838 (81.8%)	33 (27.3%)	45 (72.6%)	139 (82.7%)	86 (66.7%)	68 (48.9%)

NC = not collected.
[a]Count and percentages for all demographic characteristics exclude missing and do not know responses.
[b]For Studies 49 and 56, Hispanic ethnicity was included as a race option. Ethnicity was not collected separately from race. The 'Other' race category includes all races except White and African-American.
[c]College graduate includes those with a B.A., Masters or Doctorate. Some college includes technical degree, associate's degree or some bachelor's classes.
[d]Study 56 differs in military status identification from the other studies and is not reported in this table. For all other studies, a service member is defined as: 'A Service Member is a person who is still in the military whether they are Active Duty/National Guard/Reserve/Active Guard Reserve/Ready Reserve. The person still wears the uniform in some capacity whether it is one weekend a month or on a daily basis'. Military status for Studies 20 and 34 was added after study initiation, thus the higher percent of missing data.
[e]Although study group classification varies across studies, for purposes of this analysis, mTBI is defined as a participant experiencing any lifetime blast or blunt mTBI.

approximately 16% (Study 34) to 8% (Study 20). Among those that failed the MSVT, 46.4% from Study 1 failed due to 'True memory impairment' compared to 34.6% from Study 34 and 20% from Study 20.

Participants across all studies, with the exception of Study 49, completed the NSI. The total mean scores across these studies ranged from 12.7 (Study 56) to 27.7 (Study 1), with these scores corresponding to the 10th–50th percentile bands. Importantly, this is comparable to a published sample of deployed National Guard personnel with deployment-related mTBI (27), suggesting that the levels of post-concussive symptomatology in CENC samples were representative. When compared to the same National Guard sample, mean scores on the four domains of the NSI fell within similar percentile bands—Somatic (10–50th); Affective (25–50th); Cognition (10 to ≥50th); and Vestibular (10–50th) (27).

Measures of psychological symptoms indicated generally subclinical levels of psychological distress across studies. Mean scores on the PHQ-9 ranged from 8.8 for Study 1 to 9.6 for Study 20, which fell within the mild depression range. Mean scores on the PCL, ranging from 9.2 on Study 56 to 31.6 on Study 34, similarly fell below the clinical cut-off score. In contrast, participants reported significantly disturbed sleep on several sleep quality indices. The mean sleep onset latency ranged from 39.8 minutes in Study 1 to 44.7 minutes in Study 20, and the mean total hours of sleep per night ranged from 5.3 to 5.4 hours. In comparison, in a clinical insomnia sample, the mean sleep onset latency was 20.6 minutes, and the mean total hours of sleep per night was 6.5 hours (28). Approximately one-quarter (22.6–29.2%) of CENC participants reported using sleep aids three or more times a week and more than one-half (51.2–72.6%) rated their sleep over the previous month as 'Fairly bad' or 'Very bad'.

Means scores on the Combat Experiences scale of the DRRI-2 ranged from 31.9 (Study 49) to 40.5 (Study 20). Although there are no published clinical norms, the mean scores across CENC studies were similar to the mean score reported for a sample of male combat-exposed veterans (31.0) (29) but lower than the mean reported in the same study among combat-exposed veterans with PTSD (53.1).

Cognitive functioning

Mean scaled scores on WAIS-IV subtests ranged from 9.2 to 10.5 for Digit Span, 10.3 to 10.5 for Symbol Search and 9.1 to 9.7 for Coding in CENC samples (see Table 2). These scores correspond to the 37–50th percentile or the average range for working memory and processing speed. The mean T-scores for TMT-A ranged from 47.5 to 55.0 and from 48.4 to 51.0 for TMT-B, which similarly correspond to the Average range of attention and executive functioning, respectively. Learning, as measured by the mean CVLT-II Trial 1–5 Total raw scores, ranged from

Table 2. Clinical outcome differences by CENC study.

Clinical measure[a]	CENC study					
	Study 01 (*N* = 1024)	Study 08 (*N* = 121)	Study 20 (*N* = 62)	Study 34 (*N* = 168)	Study 49 (*N* = 129)	Study 56 (*N* = 139)
Medical Symptom Validity Test (MSVT)[b]						
Pass	806 (88.0%)	NC	55 (91.7%)	141 (84.4%)	NC	NC
Fail	110 (12.0%)	NC	5 (8.3%)	26 (15.6%)	NC	NC
Reason fail MSVT[c]						
Effort validity failure	59 (53.6%)	NC	4 (80.0%)	17 (65.4%)	NC	NC
True memory impairment	51 (46.4%)	NC	1 (20.0%)	9 (34.6%)	NC	NC
Neurobehavioral Symptom Inventory (NSI) validity[d]						
Valid	905 (95.9%)	116 (96.7%)	60 (96.8%)	162 (96.4%)	NC	136 (100.0%)
Invalid	39 (4.1%)	4 (3.3%)	2 (3.2%)	6 (3.6%)	NC	0 (0.0%)
NSI total						
N	944	120	62	168	NC	136
Mean (StdDev)	27.7 (16.5)	23.0 (16.6)	27.1 (16.5)	25.8 (17.0)	NC	12.7 (12.5)
Min, Max	0, 80	0, 75	0, 65	0, 78	NC	0, 55
NSI somatosensory						
N	948	120	62	168	NC	137
Mean (StdDev)	7.2 (5.1)	6.5 (5.5)	6.6 (5.3)	6.3 (5.3)	NC	3.2 (3.8)
Min, Max	0, 25	0, 25	0, 21	0, 25	NC	0, 17
NSI affective						
N	949	120	62	168	NC	137
Mean (StdDev)	10.2 (5.8)	8.1 (6.3)	9.6 (5.9)	9.8 (6.2)	NC	5.1 (5.0)
Min, Max	0, 24	0, 24	0, 23	0, 24	NC	0, 23
NSI cognition						
N	950	120	62	168	NC	136
Mean (StdDev)	5.8 (4.0)	4.8 (4.2)	6.0 (3.6)	5.8 (4.2)	NC	2.6 (3.0)
Min, Max	0, 16	0, 16	0, 15	0, 16	NC	0, 15
NSI vestibular						
N	950	120	62	168	NC	137
Mean (StdDev)	2.4 (2.3)	3.7 (2.6)	2.7 (2.4)	1.8 (2.0)	NC	0.9 (1.5)
Min, Max	0, 12	0, 11	0, 8	0, 9	NC	0, 7
mBIAS validity[e]						
Valid	942 (99.1%)	NC	62 (100.0%)	167 (99.4%)	NC	137 (100.0%)
Invalid	9 (0.9%)	NC	0 (0.0%)	1 (0.6%)	NC	0 (0.0%)
mBIAS total						
N	951	NC	62	168	NC	137
Median (IQR)	0.0 (0.0, 1.0)	NC	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	NC	0.0 (0.0, 0.0)
Min, Max	0, 14	NC	0, 6	0, 8	NC	0, 7
WAIS digit span[f]						
N	931	NC	62	166	122	NC
Mean (StdDev)	9.2 (2.7)	NC	9.7 (3.2)	9.8 (2.7)	10.5 (2.7)	NC
Min, Max	2, 19	NC	4, 19	5, 19	5, 18	NC
WAIS symbol search[f]						
N	931	NC	61	166	NC	NC
Mean (StdDev)	10.4 (2.9)	NC	10.5 (3.4)	10.3 (3.1)	NC	NC
Min, Max	2, 19	NC	2, 18	2, 19	NC	NC
WAIS coding[f]						
N	931	NC	61	166	122	NC
Mean (StdDev)	9.5 (2.6)	NC	9.6 (2.6)	9.1 (2.6)	9.7 (2.9)	NC
Min, Max	2, 19	NC	4, 19	1, 16	4, 19	NC
Trail Making Test A						
N	933	NC	NC	167	121	NC
Mean (StdDev)	47.5 (11.5)	NC	NC	47.5 (11.5)	55.0 (11.1)	NC
Min, Max	0, 85	NC	NC	7, 86	29, 84	NC
Trail Making Test B						
N	933	NC	NC	167	120	NC
Mean (StdDev)	48.4 (11.1)	NC	NC	48.5 (11.4)	51.0 (10.5)	NC
Min, Max	15, 84	NC	NC	5, 75	16, 81	NC
CVLT-II Trial 1–5 total						
N	919	NC	61	NC	120	NC
Mean (StdDev)	47.0 (10.5)	NC	50.9 (10.0)	NC	48.4 (9.2)	NC
Min, Max	13, 79	NC	30, 78	NC	21, 75	NC
CVLT-II Short Delay Free Recall						
N	919	NC	60	NC	120	NC
Mean (StdDev)	10.0 (3.3)	NC	11.2 (2.9)	NC	10.4 (3.0)	NC
Min, Max	0, 16	NC	5, 16	NC	2, 16	NC
CVLT-II Short Delay Cued Recall						
N	919	NC	60	NC	120	NC
Mean (StdDev)	10.9 (3.1)	NC	12.0 (2.6)	NC	11.7 (2.7)	NC
Min, Max	1, 16	NC	5, 16	NC	3, 16	NC
CVLT-II Long Delay Free Recall						
N	919	NC	60	NC	120	NC
Mean (StdDev)	10.1 (3.6)	NC	11.4 (2.8)	NC	10.6 (3.0)	NC
Min, Max	0, 16	NC	5, 16	NC	2, 16	NC
CVLT-II Long Delay Cued Recall						
N	919	NC	60	NC	120	NC
Mean (StdDev)	10.8 (3.3)	NC	12.0 (2.8)	NC	11.6 (2.8)	NC
Min, Max	0, 16	NC	4, 16	NC	3, 16	NC

(*Continued*)

Table 2. (Continued).

Clinical measure[a]	CENC study					
	Study 01 (*N* = 1024)	Study 08 (*N* = 121)	Study 20 (*N* = 62)	Study 34 (*N* = 168)	Study 49 (*N* = 129)	Study 56 (*N* = 139)
Combat Exposure Development Risk and Resilience Inventory (DRRI-2)[g]						
N	1,023	NC	61	168	118	NC
Mean (StdDev)	39.2 (15.9)	NC	40.5 (17.0)	37.7 (17.8)	31.9 (9.9)	NC
Min, Max	16, 93	NC	17, 92	17, 96	16, 57	NC
PTSD Checklist (PCL)[h]						
N	949	NC	62	168	119	137
Mean (StdDev)	29.0 (19.5)	NC	29.8 (18.1)	31.6 (19.7)	19.8 (16.0)	9.2 (11.7)
Min, Max	0, 80	NC	0, 76	0, 77	0, 68	0, 46
Patient Health Questionnaire-9 (PHQ-9)[i]						
N	948	NC	61	168	NC	NC
Mean (StdDev)	8.8 (6.2)	NC	9.6 (6.4)	9.3 (6.3)	NC	NC
Min, Max	0, 27	NC	0, 24	0, 27	NC	NC
Minutes take to Fall Asleep (PSQI)						
N	947	NC	62	168	NC	NC
Mean (StdDev)	39.8 (33.6)	NC	44.7 (44.5)	44.1 (41.3)	NC	NC
Min, Max	0, 420	NC	2, 210	1, 320	NC	NC
Hours of sleep per night (PSQI)						
N	950	NC	62	168	NC	NC
Mean (StdDev)	5.4 (2.0)	NC	5.4 (1.4)	5.3 (1.3)	NC	NC
Min, Max	0, 45	NC	2, 9	3, 8	NC	NC
During past month, how often take medicine to help you sleep (PSQI)?						
Not during the last month	499 (52.5%)	NC	32 (51.6%)	96 (57.1%)	NC	NC
Less than once a week	73 (7.7%)	NC	6 (9.7%)	13 (7.7%)	NC	NC
Once or twice a week	97 (10.2%)	NC	10 (16.1%)	10 (6.0%)	NC	NC
Three or more times a week	281 (29.6%)	NC	14 (22.6%)	49 (29.2%)	NC	NC
During past month, how would you rate your sleep quality (PSQI)?						
Very good	56 (5.9%)	NC	1 (1.6%)	6 (3.6%)	NC	NC
Fairly good	315 (33.2%)	NC	16 (25.8%)	76 (45.2%)	NC	NC
Fairly bad	341 (35.9%)	NC	29 (46.8%)	65 (38.7%)	NC	NC
Very bad	238 (25.1%)	NC	16 (25.8%)	21 (12.5%)	NC	NC

NC = not collected

[a]Counts and percentages exclude missing responses.

[b]To pass the MSVT validity test, scores must be greater than 85% on Immediate Recall (IR), Delayed Recall (DR) and Consistency (CNS) (as recommended by Green's Publishing).

[c]Among those that failed the MSVT. Effort failure is defined as having a mean on the IR, DR or CNS that is 20 points less than the mean on the Paired Associate (PA) and Free Recall (FR) subtests. Effort failure can also occur if there is an order violation (either IR or DR or CNS < either PA or FR).

[d]NSI validity based on the NSI Validity-10 scale published by Vanderploeg et al. (2014). Score >22 suggestive of symptom aggrandizement.

[e]Score >7 suggestive of invalid symptom reporting.

[f]Study 49 used the 3rd edition of the Wechsler Adult Intelligence Scale (WAIS), while Studies 01, 20 and 34 used the 4th edition.

[g]Studies 20 and 34 use a 17-item questionnaire with six response options (max. score is 102). Study 01 uses a 16-item questionnaire with six response options (max. score is 96). Study 49 uses a 16-item questionnaire with five response options (max. score is 80). Higher scores indicate greater combat experience.

[h]Studies 01, 20 and 34 administer the PCL-5 version (max. score is 80). Study 49 administers the PCL-M (Military) version and Study 56 administers the PCL-C (Civilian) version (max. score is 68). Higher scores indicate greater PTSD severity.

[i]Total score is derived by summing all item response options (max. score is 27). Higher scores indicate greater depression severity.

47.0 to 50.9, which was similar to the mean Total raw score reported for a sample of individuals with mTBIs three months to one-year post-injury (48.9–54.5) (30). For memory, mean scores for Short Delay Free Recall ranged from 10.0 to 11.2 and for Long Delay Free Recall, from 10.1 to 11.4, which were also similar to mean scores in the same sample of individuals with mTBIs (11.1–12.3) (30).

Discussion

This paper reports on a comparative analysis of the demographic, clinical and cognitive characteristics of more than 1600 OIE/OEF/OND Veterans and SMs with and without mTBI exposure enrolled across six CENC studies. Results from these analyses provide an important snapshot of the psychological and cognitive functioning of a diverse group of Veterans and SMs exposed to combat during the wars in Iraq and Afghanistan. These findings indicate mild depressive symptoms overall and PTSD symptoms slightly below the clinical threshold. Poor sleep was more prevalent across studies, with participants reporting taking approximately 40–45 minutes to fall asleep and concomitant regular sleep aid use among 22–29% of participants. Generally, measures of cognitive functioning across studies showed average working memory, processing speed and attention and learning and memory comparable to other published samples of individuals with mTBIs. Notably, the response patterns of respondents overwhelmingly indicate valid responding, supporting that the level of symptomatology described in this paper is an accurate reflection of the true level of distress and limited cognition difficulties in this sample.

Along with this paper, CENC findings presented in this special issue capture the complex and varying associations between mTBI and psychological, clinical and cognitive functioning. While these cross-sectional findings denote an important step towards expanding our understanding of the impact of mTBI on our Veterans and SMs, further longitudinal study is critical. CENC's Study 1 has just recently begun to amass a sufficient pool of subjects who have a series of longitudinal follow-up data that will allow researchers to begin exploring the longer-term effects of mTBI.

Declaration of interest

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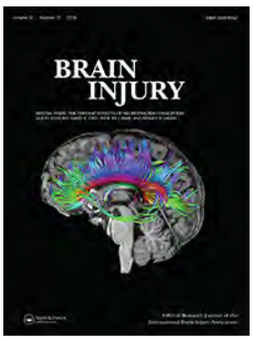
Appendix 2

Longitudinal evaluation of ventricular volume changes associated with mild traumatic brain injury in military service members



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Longitudinal evaluation of ventricular volume changes associated with mild traumatic brain injury in military service members

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ABSTRACT

Primary objective: To investigate differences in longitudinal trajectories of ventricle-brain ratio (VBR), a general measure of brain atrophy, between Veterans with and without history of mild traumatic brain injury (mTBI).

Research design: Structural magnetic resonance imaging (MRI) was used to calculate VBR in 70 Veterans with a history of mTBI and 34 Veterans without such history at two time points approximately 3 and 8 years after a combat deployment.

Main outcomes and results: Both groups demonstrated a quadratic relationship between VBR and age that is consistent with normal developmental trajectories. Veterans with history of mTBI had larger total brain volume, but no interaction between mTBI and age was observed for brain volume, ventricular volume, or VBR.

Conclusions: In our longitudinal sample of deployed Veterans, mTBI was not associated with gross brain atrophy as reflected by abnormally high VBR or abnormal increases in VBR over time.

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Concussion; mild brain injury; military; neurodegeneration; MRI

Introduction

Traumatic brain injury (TBI), especially mild TBI (mTBI), is common among military Servicemembers returning from recent combat deployments (1–4). Over 375,000 military TBI diagnoses were made between 2001 and 2017, and 82% of these were classified as mild, defined by the Department of Defense as loss of consciousness up to 30 min or confusion, disorientation, or memory loss up to 24 h (5). Many military personnel also report a history of mTBI prior to combat deployment (6,7) from either civilian or non-combat military sources (e.g., training). As in civilian mTBI, the symptoms associated with military mTBI, including headache, dizziness, irritability, and attention problems, typically resolve within days or weeks (4,8,9) but can persist beyond 3 months in a subset of individuals (10–12). Furthermore, the experience of mTBI events during deployment is associated with an increased risk of post-traumatic stress disorder (PTSD) (12,13) and depression (14) after deployment, and may increase risk of neurodegenerative disorders, such as chronic traumatic encephalopathy, later in life (15–17).

The observation of long-term disruptions to psychological health following mTBI raises the possibility of lasting, and possibly progressive, neural damage. This hypothesis is consistent with the well-established observation of progressive neurodegeneration associated with moderate and severe TBI (18–20), which can lead to progressive gray matter and white matter volume loss for months or even years following the injury (21,22). The loss of brain tissue is accompanied by an increase in cerebrospinal fluid (CSF) volume, primarily manifested as ventricular expansion. The ratio of ventricular volume to total brain volume (TBV), termed the ventricle-brain ratio (VBR), has been demonstrated to be a sensitive indicator of global brain atrophy (23,24). Several studies have used structural neuroimaging techniques, particularly computed tomography (CT) and magnetic resonance imaging (MRI), to quantify the degree and course of volume loss following moderate or severe TBI (25–28). Despite variation in the timing of the initial measurement (relative to the injury) and the longitudinal delay, each of these studies has observed a greater rate of brain volume decrease (26–28) or CSF volume increase (25) among people with TBI than among healthy people of a similar age, gender, and education.

It is less clear whether mTBI is associated with a similar neurodegenerative course in the brain. Several studies have found both regional and global brain volume changes following mTBI (29–31), while some have found no evidence of volume loss (32,33), and others have reported evidence of progressive neurodegeneration after mTBI, but included cases of moderate TBI (34) in their samples, making it difficult to determine the specificity of effects. However, the applicability of these prior studies to the presence or absence of long-term degeneration may be limited by several features. First, investigations into mTBI-related neurodegeneration have typically acquired baseline data within the first few months after injury (e.g., (29–31,33)) when acute post-injury structural changes (e.g., due to edema and inflammatory

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responses) may still be present (35,36) and may particularly affect ventricular volume (37), possibly leading to over-estimation of atrophic brain volume loss. Second, longitudinal data are collected after a delay of months, usually 1 year or less. While changes in brain volume over such a brief time period would certainly be relevant to characterizing the short-term course of mTBI, they provide little information about long-term neural effects. Indeed, the magnitude of changes over the course of a single year may be insufficient for statistical detection; a longer delay would allow for more stable measurement of volumetric changes. Finally, there are changes in brain and ventricle volumes that occur during the course of normal development, and these changes are nonlinear over the age ranges typically studied (e.g., 20–60 years of age) (38–42). Such age-related volumetric trajectories must be accounted for in longitudinal investigations in order for effects of non-age-related variables (i.e., mTBI) to be determined.

In the present study, we examined whether mTBI in military Servicemembers and Veterans is associated with an accelerated rate of ventricular expansion or brain atrophy several years after the injury. Using longitudinal data, we implemented a statistical model explicitly accounting for linear and quadratic relationships of age on measurements of VBR. The overall hypothesis was that mTBI is associated with greater rate of increase in VBR.

Methods

Participants

We conducted a longitudinal follow-up of two cohorts of American military Veterans and Servicemembers whose baseline characteristics have been previously described (43,44). Cohort 1 was recruited from community flyers, Veterans Affairs (VA) patient records, and prior research studies of Minnesota Army National Guard Soldiers based on presence or absence of mTBI and PTSD history, regardless of whether treatment was sought. Cohort 2 was recruited from records of Veterans who reported a potential mTBI event during deployment on the VA TBI Screening Tool, also referred to as the VA TBI Clinical Reminder. Although all participants in both cohorts had been deployed as part of Operations Enduring Freedom or Iraqi Freedom (OEF/OIF), the time between last deployment and study participation ranged from less than 1 month to 11 years. Likewise, because the longitudinal follow-up was conducted over a shorter time period than the baseline studies, delay between time points ranged from 38 months to 99 months. Of the 276 individuals enrolled in one of the two baseline studies, complete longitudinal data were available for 106 participants. All participants completed an informed consent procedure, and the protocol was approved by the Institutional Review Boards of the Minneapolis VA Health Care System and University of Minnesota.

TBI diagnosis and comorbidities

Participants completed a battery of clinical interviews, neuropsychological assessments, and self-report measures at both baseline and follow-up visits. Demographic characteristics were obtained at both visits by self-report, including gender, age at visit, race and ethnicity, years of education, and income. Information about deployments, including dates, location, role (e.g., combat vs. support), and military occupational specialty (MOS), was collected at both visits. Potential mTBI events were assessed using the Minnesota Blast Exposure Screening Tool (MN-BEST)(45). Up to three events involving exposure to explosive blast and up to three with only non-blast sources were assessed, for a maximum of six total events per person. Information was collected for each event about mechanism of injury, context (i.e., deployed, non-deployment military, or civilian), protective equipment, alteration or loss of consciousness, post-traumatic amnesia, acute symptoms, and any medical treatment that was provided or sought. Each event was reviewed by a team of doctoral-level neuropsychologists with expertise in mTBI assessment and was given a consensus rating of severity and likelihood. Only those participants reporting events determined to be consistent with mTBI, defined by Ruff and Richardson (46) as alteration or loss of consciousness less than 30 min accompanied by at least one neurological symptom (e.g., headache, sensitivity to light or noise) and post-traumatic amnesia less than 24 h, with a confidence level of 'probable' or 'definite' were included in the mTBI group. Participants who did not report a head injury event meeting criteria for mTBI, or who reported only events that were determined to be 'possible' but not 'probable', were assigned to the no mTBI group. For secondary analyses, individual events were classified as 'blast mTBI' if the person reported feeling the blast wave and attributed subsequent mTBI symptoms to its effects, though secondary (e.g., hit by debris) and tertiary (e.g., thrown against the ground) blast injury components were allowed. Events that did not involve an explosion, or in which the blast wave did not directly contribute to the injury, were classified as 'impact mTBI'.

The level of post-concussive symptomatology (PCS) was quantified at both visits by the presence or absence of eight symptoms commonly reported in the chronic phase of mTBI: headache, sensitivity to noise, sensitivity to light, irritability, balance problems, memory problems, insomnia, and tinnitus. A total score was derived by summing the total number of PCS present, ranging from 0 to 8. Subjective ratings of PTSD symptoms were collected using the PTSD Checklist - Military Version (PCL-M; (47)), a self-report measure assessing each of the 17 PTSD symptoms from the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR; (48)) on a five-point scale for possible total scores ranging from 17 to 85.

Image acquisition and processing

All MRI data were collected on the same Siemens 3T scanner (Erlangen, Germany); however, due to a hardware upgrade between time points, baseline data were collected on Tim Trio hardware, and follow-up data were collected on Prisma Fit hardware. As part of larger MRI protocols, we acquired T1-weighted 3D Magnetization-Prepared Rapid Acquisition Gradient Echo (MP-RAGE) images at baseline and at follow-up. Parameters for the imaging protocols are summarized

in Table 1. The MP-RAGE was always the first scan collected after the initial localizer and immediately checked for evidence of motion or other artifacts. In the event of poor contrast between cortical gray and white matter due to movement, a second MP-RAGE was collected either immediately or at the end of the scan session. In all cases, only the higher quality MP-RAGE was used for subsequent processing and analysis.

To reduce sequence-related differences in orientation and resolution between time points, all MP-RAGE volumes were first processed through the co-registration step of the FMRIB Software Library (FSL) tool SIENA (49,50), which performs constrained registration between baseline and follow-up images and resamples each image to the common space halfway between the two. The resulting images were segmented and parcellated using the automated Freesurfer (51,52) longitudinal pipeline (53) (version 5.3.0). Output images were visually inspected to ensure accurate brain and ventricle segmentation. Regional volume estimates provided automatically by Freesurfer were used to calculate TBV and total ventricular volume (TVV). Specifically, TBV was defined as the supratentorial portion of the brain (i.e., cerebrum), not including the ventricles (i.e., SupraTentorialVolNotVent label in Freesurfer's aseg.stats output), and TVV was defined as the difference between the total supratentorial volume (i.e., SupraTentorialVol label) and TBV. The region labelled as '4th ventricle' was also subtracted from TVV since it is located outside the cerebrum. VBR was defined as TVV divided by TBV, and multiplied by 100 to convert to percentage units (54, Figure 1 displays the average segmentation for TVV and TBV.

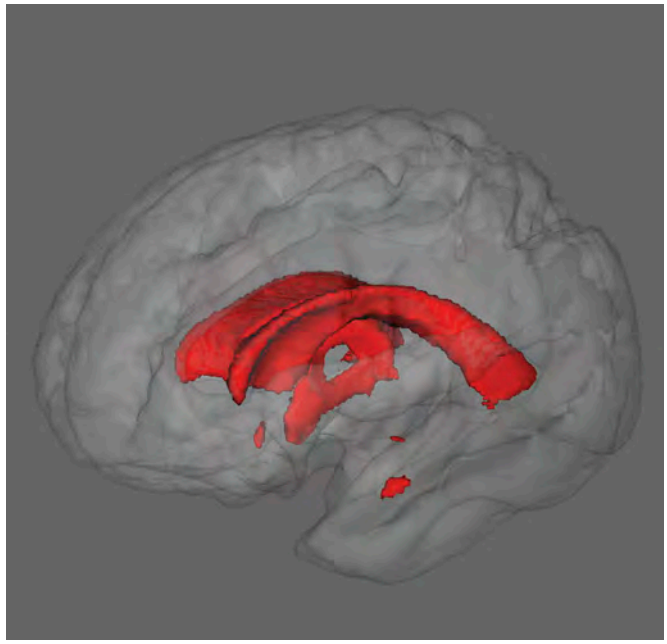

Figure 1. Rendering of total brain volume (TBV) and total ventricle volume (TVV). Example brain (glass) and ventricle (opaque red) volumes used in calculation of ventricle brain ratio (VBR) are shown from a front-left perspective. Volumes represent the average of all subjects.

Statistical analysis

Characteristics of the cohort, stratified by mTBI exposure, were summarized by mean and standard deviation for normally distributed continuous variables, median and minimum/maximum for non-normally distributed continuous variables, and with frequency and percentage for categorical variables. Unadjusted differences in VBR, TVV, and TBV between the mTBI and no mTBI study groups at each study visit were tested via the Student's T-Test (TBV) and Wilcoxon Test (VBR and TVV).

To measure longitudinal change in VBR, we calculated age at the time of each MRI and then computed the elapsed time, in months, from the end of last combat deployment to each study visit MRI date. The time since last deployment serves as a proxy for time since injury, which is undefined for those without mTBI and thus cannot be included in a combined model. As the timing of the MRIs varied substantially across subjects, the generalized least squares (GLS) technique was used to model the change in VBR from the baseline visit to the follow-up visit. In GLS, also known as a general linear model with correlated errors, the correlation between measurements on the same participant (repeated measurements) is accounted for by specifying a residual covariance structure for within subject's error 55. Compound symmetry, which assumes a single covariance between measures and that the variance of measures is the same for all subjects, was employed as there were only two measures of VBR for each subject and variances across them differed minimally (56). Covariates considered in the model included time since most recent deployment, age, sex, and years of education. To model nonlinear (i.e., quadratic) change, the covariates time since deployment and age were centered, and a second squared version of each variable was created. The analysis first modeled VBR in the 36 subjects without history of mTBI to generate a baseline model of how covariates impacted VBR using the a priori GLS model presented below:

$$Y_{ij} = \alpha + \beta_1 time_{ij} + \beta_2 time_{ij}^2 + \beta_3 age_{ij} + \beta_4 age_{ij}^2 + \beta_5 sex_i + \beta_6 education_i + \beta_7 (time \times age)_{ij} + \epsilon_{ij},$$

where Y_{ij} is the jth measure of VBR in subject i, α is the intercept, β_1 through β_7 are coefficients, and ϵ_{ij} is the residual error term. To simplify this model, covariates with small, non-significant coefficients were removed and reduced models were run, then compared to the full model with likelihood ratio tests and two model fit indices: Akaike information criterion (AIC) and Bayesian information criterion (BIC) (52). Influence diagnostics, including predicted residual error sum of squares (PRESS) and likelihood distance, were

Table 1. MPRAGE sequence parameters for the baseline and follow-up time points.

	Baseline	Follow up
Orientation	Coronal	Sagittal
TR/TE/TI (ms)	2530/3.65/1100	2400/2.24/1060
Slices	240 (Cohort 1) 224 (Cohort 2)	208
FOV (mm)	256	256
Voxel size (mm^3)	1.0 x 1.0 x 1.0	0.8 x 0.8 x 0.8

MPRAGE = magnetization prepared rapid acquisition gradient echo, FOV = field of view, TE = echo time, TR = repetition time, TI = inversion time

used to identify cases that exerted undue influence on the regression (e.g., outliers). When the baseline model was established, a model with mTBI as a covariate and interaction terms with all other covariates was run on all subjects (mTBI and no mTBI) to determine the effect of mTBI on each covariate's relationship with VBR. Small, non-significant interactions were removed and the reduced models were compared to the fuller model with likelihood ratio tests to create a final parsimonious model. Based on a priori hypotheses, mTBI and its two-way interaction with age were included in the final model regardless of significance. To explore relative contributions of ventricular expansion versus brain atrophy to observed VBR patterns, models for TVV and TBV were analyzed using the same steps outlined above. To determine whether the mechanism of injury (i.e., blast vs. impact) influenced effects on VBR, the GLS model for VBR was rerun with the mTBI covariate replaced by a four-group factor (no mTBI, blast mTBI only, impact mTBI only, blast and impact mTBI) and its interactions with age and age (2). Finally, to test the hypothesis that history of mTBI is associated with progressive worsening of PCS, the GLS model described above was also conducted with number of PCS items reported as the outcome measure. In addition, this model included VBR as an independent variable to determine if increases in VBR predict increase in symptomatology reporting. All data manipulation and analysis was conducted with SAS Version 9.3 (Cary, NC).

Results

Influence metrics

During development of the initial GLS model, two subjects in the no mTBI group were found to be influential outliers that substantially changed the effects observed. Both cases had extremely high VBR values at both time points, were older (ages 48 and 54 years at baseline), had extreme PCS scores (0 and 7 at baseline), and had a relatively short time since deployment compared to other participants. Moreover, both reported very limited combat exposure and low total deployment duration (10 and 19 months) despite lengthy military careers. Given concerns about whether these cases are representative of the rest of the cohort, combined with strong impact on the GLS models, both were excluded from further analyses.

Demographic, military experience, and comorbidities

Sample characteristics are summarized in Table 2. A total of 70 participants (67.3%) reported experiencing either a blast or impact mTBI, while 34 participants (32.7%) did not report an event meeting criteria for mTBI. For the mTBI group, the average number of lifetime mTBI events was 1.8 (range 1–5) and the median time between last combat deployment and the baseline visit was 33.5 months, compared to 37.0 months for those without a history of mTBI. Overall, demographic characteristics were statistically similar between the mTBI and no mTBI cohorts during the follow-up visit. Most participants in both groups were male, white, married, and lived with a spouse, family, or partner. Age (mTBI 39.4 years vs. no mTBI 38.9 years), years of education (15 vs. 16 years), and PCL-M scores (37.4 vs. 34.4) were also similar. Participants with history of mTBI endorsed significantly more PCS items (4.6 vs. 3.6; $p = 0.03$) than those without mTBI history, though the full range of scores was reflected in both groups.

Table 2. Baseline Demographic Profile.

Characteristic	mTBI Exposure: mTBI ($N = 70$)	mTBI Exposure: No mTBI ($N = 34$)	*P*-value
Gender[FE]			
Male	67 (95.7%)	33 (97.1%)	1.0000
Female	3 (4.3%)	1 (2.9%)	
Race[FE]			
White	63 (90.0%)	30 (88.2%)	0.6914
Hispanic	1 (1.4%)	1 (2.9%)	
African-American	2 (2.9%)	0 (0.0%)	
Other	4 (5.7%)	3 (8.8%)	
Age (at follow-up visit)[T]			
Mean (StdDev)	39.4 (8.8)	38.9 (7.0)	0.8038
Min, Max	28, 63	26, 59	
Total years of education[KW]			
Median	15	16	0.3706
Min, Max	12, 22	12, 24	
Marriage[FE]			
Married	48 (68.6%)	25 (73.5%)	0.6543
Not married	22 (31.4%)	9 (26.5%)	
Living Status[FE]			
Alone	5 (7.1%)	3 (8.8%)	0.9029
Spouse/Family/Partner	61 (87.1%)	29 (85.3%)	
Parent/Sibling/Friend	4 (5.7%)	2 (5.9%)	
Income[W]			
< $31K	8 (11.4%)	1 (2.9%)	0.8338
$31K – $51K	12 (17.1%)	9 (26.5%)	
$51K – $95K	32 (45.7%)	15 (44.1%)	
≥ $95K	18 (25.7%)	9 (26.5%)	
Experienced blast mTBI	37 (52.9%)		–
Experienced impact mTBI	54 (77.1%)		–
Total number of mTBIs			
Mean (StdDev)	1.8 (1.1)		–
Min, Max	1, 5		
Total PCS score[T]			
Mean (StdDev)	4.6 (2.1)	3.6 (2.4)	0.0316
Min, Max	0, 8	0, 8	
Total PCL-M score[T]			
Mean (StdDev)	37.4 (14.2)	34.4 (18.4)	0.3598
Min, Max	17, 69	17, 85	
Months since last combat Deployment (at baseline visit)[KW]			
Median	33.5	37.0	0.8980
Min, Max	0, 131	6, 131	
Age at last combat deployment[KW]			
Median	26.6	28.8	0.5466
Min, Max	19, 58	21, 51	

Abbreviations: FE = Fisher Exact; T = T-Test; W = Wilcoxon; KW = Kruskal Wallis

VBR changes by age

There was no significant difference in VBR between groups at either the baseline ($p = 0.410$) or the follow-up study visit ($p = 0.496$). For the baseline visit, the VBR median and interquartile range (IQR) for the mTBI study group was 1.25 (0.96) compared to 1.25 (0.86) for the no mTBI study group. Similarly, for the follow-up visit, the VBR median and IQR for the mTBI study group was 1.32 (0.95) compared to 1.27 (0.99) for the no mTBI study group. Similar results were observed for TVV. However, the mTBI group had a significantly higher

average TBV compared to the no mTBI group at both baseline (1,081,604 vs. 1,040,904 mm^3, respectively; $p = 0.031$) and follow-up visits (1,039,458 vs. 996,580 mm^3, respectively; $p = 0.012$).

Table 3 shows results of the GLS models of VBR. In the initial model for subjects with no mTBI, only the quadratic age parameter showed a statistically significant impact on VBR. None of the other covariates were found to significantly impact VBR and were removed from the model. Comparing the reduced model to the initial model, the likelihood ratio test was not significantly different between the two models (χ^3 statistic = 5.64, df = 7, p-value = 0.582), but AIC and BIC values were substantially lower for the reduced model, indicating better efficiency. When subjects with mTBI were included in the analysis, and effects of mTBI and its interactions with linear and quadratic age were modeled, none of the additional parameters was statistically significant. The additional covariates of time since most recent deployment, PCL-M, sex, and education did not improve model fit and were discarded. As seen in Figure 2, VBR varied in a quadratic manner with age, and this relationship was not significantly different between the mTBI groups.

When the mTBI parameter was redefined as a four-level factor based on injury mechanism (i.e., no mTBI, blast mTBI only, impact mTBI only, blast and impact mTBI), neither this grouping variable ($F_{3,96} = 1.25$, $p = 0.30$) nor its interactions with age ($F_{3,91} = 0.73$, $p = 0.53$) and quadratic age ($F_{3,91} = 1.56$, $p = 0.21$) demonstrated a significant effect, indicating that none of the three mTBI groups differed from the no mTBI group. Estimated VBR trajectories for the four groups are shown in Figure 3.

Model results for TBV and TVV are provided in Tables 4 and 5, respectively. Final parsimonious models demonstrated that TBV steadily decreased with age (reduction of 5,952 mm^3 for each year increase in age; $p \leq 0.001$) and TVV varied quadratically with age ($p \leq 0.001$), and these relationships did not differ by mTBI history. Additionally, mTBI was associated with higher TBV (those with mTBI had an average TBV that was 40,770 mm^3 greater than those without mTBI; $p \leq 0.05$). Overall, we did not observe sufficient evidence to support the hypotheses that mTBI is associated with accelerated ventricular expansion or loss of brain volume.

Postconcussive symptoms

Table 6 displays model results for PCS. Neither age nor time since deployment was associated with level of PCS in the initial GLS model, indicating that reports of these symptoms did not systematically change over time. Similarly, VBR was not associated with PCS reporting and was dropped from model consideration. In the final model ($F_{1,81} = 5.27$, $p = 0.0243$), higher years of education was associated with fewer PCS items reported (Figure 4), and this relationship did not differ by mTBI history, as indicated by the nonsignificant interaction term between mTBI and education in the full model ($F_{1,81} = 2.21$, $p = 0.142$).

Discussion

We conducted a longitudinal comparison of structural neuroimaging measures within 104 Servicemembers and Veterans to test the hypothesis that a history of mTBI is associated with accelerated ventricular expansion and/or brain atrophy. Because brain and ventricular volumes are known to change considerably and nonlinearly during normal development across the age range of our sample, we explicitly modeled the effects of age and time since deployment to improve sensitivity to non-normative changes. In the full model, VBR demonstrated a quadratic relationship with age that did not differ by mTBI history. Moreover, participants with a history of mTBI had somewhat larger brain volumes, but similar changes in brain and ventricle volume across age, compared to those without such a history. Taken together, these patterns provide evidence that when normal age-related changes in VBR are considered, history of mTBI is not associated with the generalized, progressive neurodegeneration reported in more severe forms of TBI.

Table 3. Generalized least squares model results of ventricle to brain ratio (VBR).

		No MTBI participants only		All participants	
	Parameter	Initial model	Final model	Initial model	Final model
Fixed effects	Intercept	1.286** (0.273)	1.3295*** (0.0967)	1.3315*** (0.1269)	1.3558*** (0.1253)
	Age	0.0207 (0.014)	0.0145** (0.0048)	0.0142* (0.0055)	0.0146** (0.0055)
	Age$^{(2)}$	0.0030* (0.001)	0.0012** (0.0004)	0.0012* (0.0005)	0.0007*** (0.0002)
	Time	−0.0007 (0.001)	- -	- -	- -
	Time$^{(2)}$	0.0000 (0.0000)	- -	- -	- -
	Female sex	0.1713 (0.550)	- -	- -	- -
	Education	−0.0017 (0.016)	- -	- -	- -
	Age*Time	−0.0003 (0.0002)	- -	- -	- -
	mTBI	- -	- -	0.1583 (0.1547)	0.1261 (0.1523)
	Age* mTBI	- -	- -	−0.0084 (0.0064)	−0.0087 (0.0064)
	Age$^{(2)}$* mTBI	- -	- -	−0.0006 (0.0005)	- -
Variance/Covariance	Within-subject covariance	0.285*** (0.071)	0.2981*** (0.0740)	0.5214*** (0.0736)	0.5238*** (0.0739)
	Measurement variance	0.009*** (0.002)	0.0094*** (0.0024)	0.0120*** (0.0017)	0.0121*** (0.0017)
Fit indices	−2 Log Likelihood	16.8130	20.8100	140.2042	141.4551
	AIC	36.8130	30.8100	156.2042	155.4551
	BIC	52.0767	38.4418	177.3594	173.9658
	N	34	34	104	104

Notes: All parameters presented as: estimates (standard error). AIC: Akaike information criterion.
BIC: Bayesian information criterion.
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

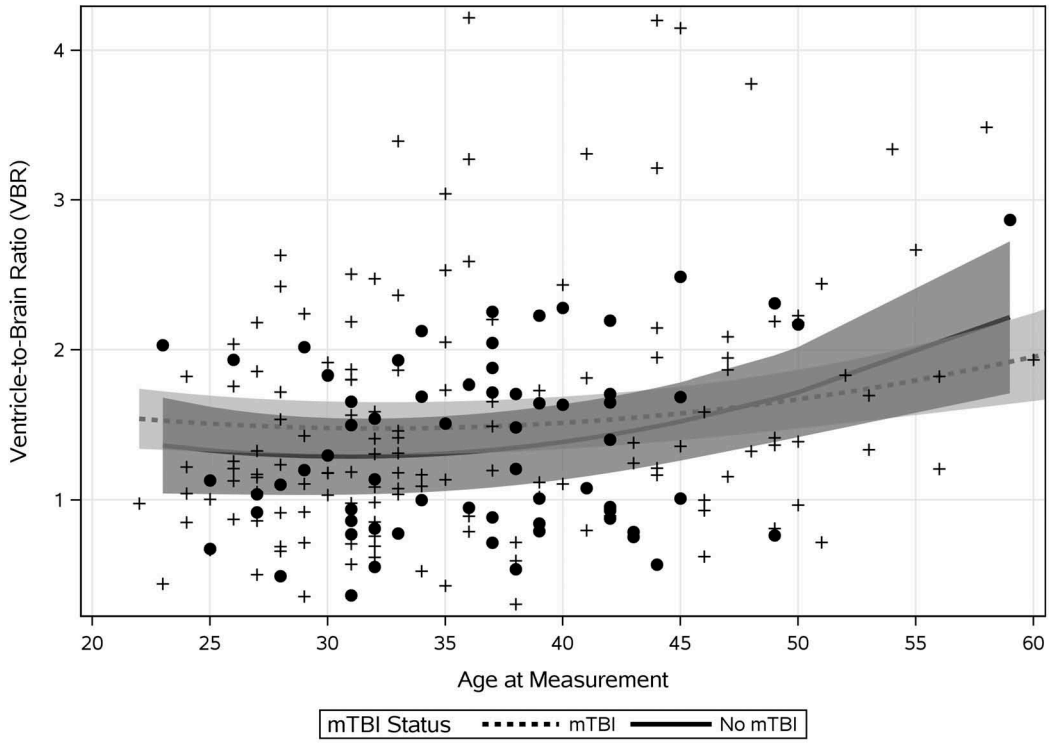

Figure 2. Changes in VBR by mTBI Group and Age. Individual data points, trend lines, and confidence intervals depict the relationships between ventricle-brain ratio (VBR) and age for subjects with (crosses, stippled line, light shading) and without (filled circles, solid line, dark shading) history of mild traumatic brain injury (mTBI).

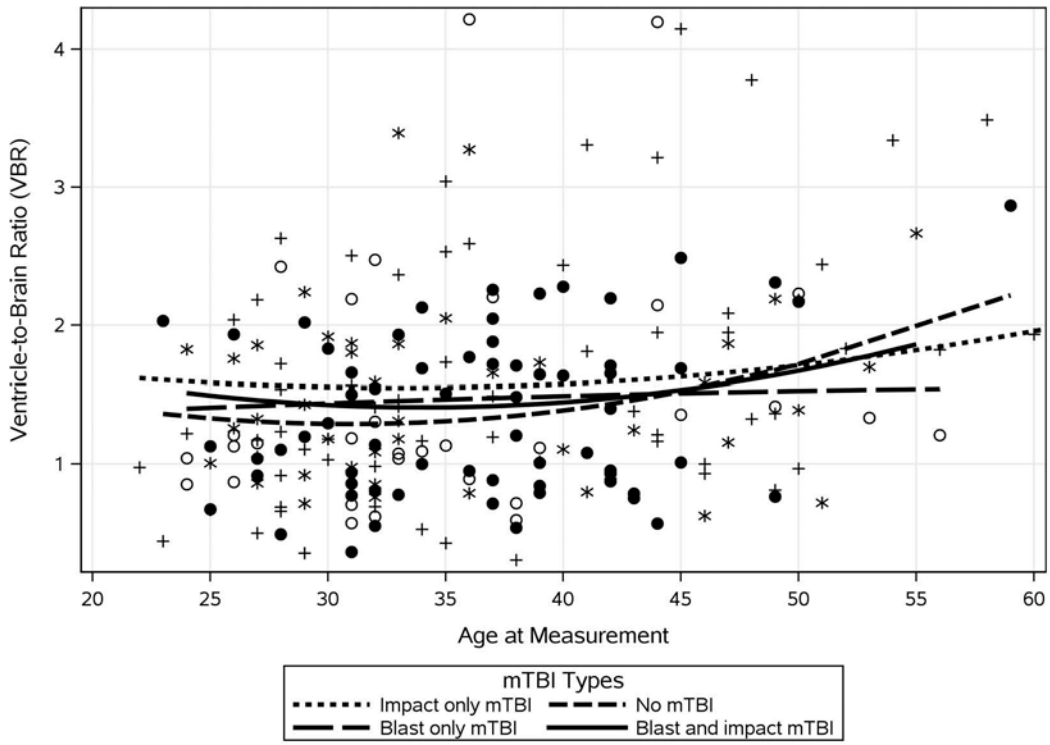

Figure 3. Effect of mTBI injury mechanism on age-related changes in VBR. Individual data points and trend lines depict the relationships between ventricle-brain ratio (VBR) and age for subjects with history of impact mTBI (crosses, stippled line), blast mTBI (empty circles, long dashes), both (filled circles, short dashes), or neither (asterisks, solid line). mTBI = mild traumatic brain injury.

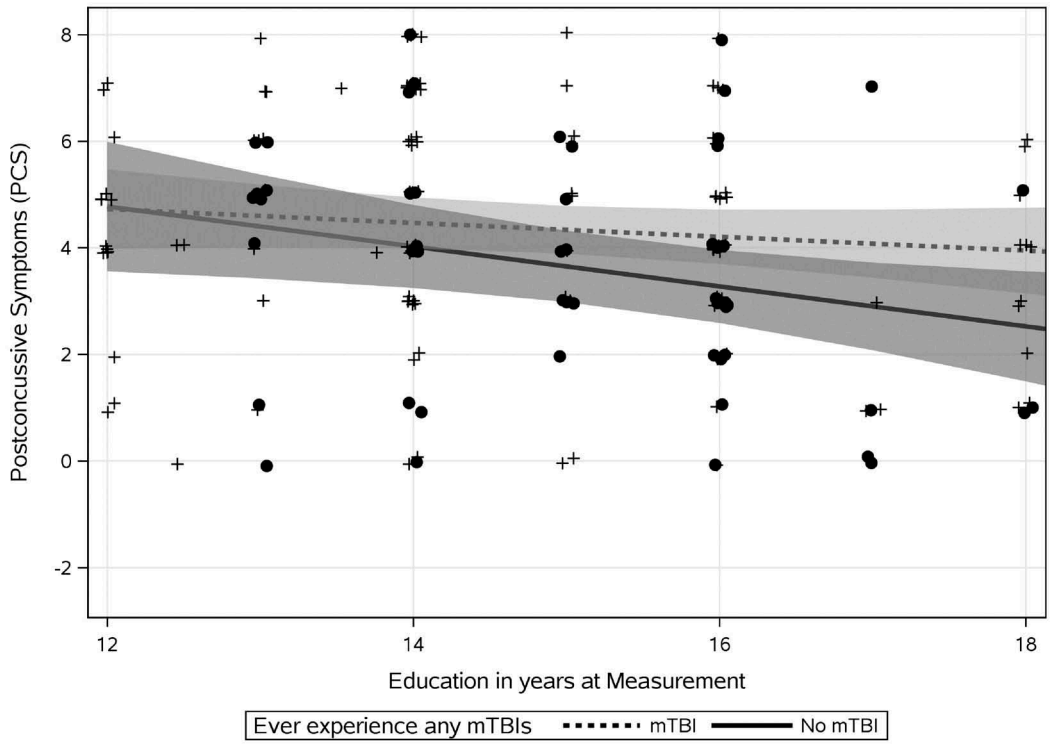

Figure 4. Effect of education on PCS reporting. Individual data points, trend lines, and confidence intervals depict the relationships between number of postconcussive symptoms (PCS) reported and years of education for subjects with (crosses, stippled line, light shading) and without (filled circles, solid line, dark shading) history of mild traumatic brain injury (mTBI).

Table 4. Generalized least squares model results of total brain volume (TBV).

		No MTBI participants only		All participants	
	Parameter	Initial model	Final model	Initial model	Final model
Fixed effects	Intercept	1074608*** (50370.00)	1009449*** (14724.38)	1009807*** (15886.94)	1013478*** (15328.83)
	Age	−3314.61 (2153.280)	−7647.09*** (926.5384)	−7514.80*** (1069.120)	−5952.05*** (533.9283)
	$Age^{(2)}$	−174.996 (210.1120)	134.1496 (76.6661)	127.5726 (88.4729)	59.8018 (37.3612)
	Time	−392.477 (195.1277)	- -	- -	- -
	$Time^{(2)}$	−2.4576 (2.4839)	- -	- -	- -
	Female sex	76457.34 (80041.82)	- -	- -	- -
	Education	−3283.26 (3004.109)	- -	- -	- -
	Age*Time	50.4797 (38.2165)	- -	- -	- -
	mTBI	- -	- -	45683.89* (19407.88)	40769.99* (18571.62)
	Age* mTBI	- -	- -	2004.582 (1229.835)	- -
	$Age^{(2)}$* mTBI	- -	- -	−80.4989 (97.3409)	- -
Variance/ Covariance	Within-subject	$5.9608 \cdot 10^{(9)}$***	$6.6213 \cdot 10^{(9)}$***	$7.5736 \cdot 10^{(9)}$***	$7.5664 \cdot 10^{(9)}$***
	covariance	$(1.5035 \cdot 10^{(9)})$	$(1.6912 \cdot 10^{(9)})$	$(1.1523 \cdot 10^{(2)})$	$(1.1437 \cdot 10^{(9)})$
	Measurement variance	$3.4802 \cdot 10^{(8)}$*** (89107924)	$3.812 \cdot 10^{(8)}$*** (98883162)	$5.2585 \cdot 10^{(8)}$*** (78990155)	$5.4221 \cdot 10^{(8)}$*** (80819779)
Fit indices	−2 Log Likelihood	1582.001	1588.382	5002.182	5005.232
	AIC	1602.001	1598.382	5018.182	5017.232
	BIC	1617.264	1606.014	5018.924	5017.661
	N	34	34	104	104

Notes: All parameters presented as: estimates (standard error). AIC: Akaike information criterion.
BIC: Bayesian information criterion.
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Prior investigations of volumetric changes following mTBI have been inconsistent, with some reporting greater brain volume loss relative to matched controls (29,30,34) and others reporting no significant differences in volumetric changes (32,33). All have focused on civilian mTBI and most have been limited to the first year after injury, complicating comparisons to our military sample in which both measurements occurred in the chronic phase and were separated by 3–8 years. In this context, it is important to properly characterize what is represented by the current observations. In particular, because all participants had served a recent combat deployment and were recruited based on exposure to potential mTBI events and/or reports of post-deployment mental health symptoms, many of the measures that are typically more common among individuals with mTBI history (e.g., PCS, PTSD symptoms) were present at similar levels among those without mTBI, allowing statistical consideration. Consequently, the primary contrast of mTBI history reflects the narrow distinction of whether at least one event exceeded the symptomatic threshold used to define mTBI. It is possible that an alternative threshold (e.g., requiring loss of

Table 5. Generalized least squares model results of total ventricular volume (TVV).

		No MTBI participants only		All participants	
	Parameter	Initial model	Final model	Initial model	Final model
Fixed effects	Intercept	14303.02*** (2705.770)	13468.11*** (1011.745)	13481.22*** (1357.728)	13752.62*** (1338.271)
	Age	163.3451 (151.3830)	35.0693 (47.5853)	31.0162 (56.0262)	−19.8930 (28.4775)
	Age$^{(2)}$	25.6217 (14.5796)	12.3414** (3.9383)	12.1054* (4.6378)	6.8223*** (1.9080)
	Time	−12.2804 (13.1462)			
	Time$^{(2)}$	0.0218 (0.1413)			
	Female sex	2751.013 (5836.792)			
	Education	−86.1240 (152.4174)			
	Age*Time	−2.6676 (2.5392)			
	mTBI	- -	- -	2367.425 (1655.569)	1999.761 (1627.816)
	Age* mTBI	- -	- -	−71.9199 (64.7714)	
	Age$^{(2)}$* mTBI	- -	- -	−6.4878 (5.0745)	
Variance/Covariance	Within-subject covariance	32242915*** (8033995)	32870069*** (8138565)	60011790*** (8486516)	59866379*** (8465038)
	Measurement variance	816123.3*** (210233.5)	910579.3*** (232664.8)	1229286*** (176329.9)	1269252*** (181956.3)
Fit indices	−2 Log Likelihood	1216.216	1220.309	3896.639	3899.592
	AIC	1236.216	1230.309	3912.639	3911.592
	BIC	1251.479	1237.941	3913.381	3912.021
	N	34	34	104	104

Notes: All parameters presented as: estimates (standard error). AIC: Akaike information criterion.
BIC: Bayesian information criterion.
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table 6. Generalized least squares model results of postconcussive symptoms (PCS).

		No MTBI participants only		All participants	
	Parameter	Initial model	Final model	Initial model	Final model
Fixed effects	Intercept	9.3623** (2.4882)	9.7143*** (2.4972)	10.3142*** (2.5827)	6.8984*** (1.4979)
	Age	−0.0417 (0.0571)	−0.0022 (0.0442)	−0.0146 (0.0454)	0.0030 (0.0226)
	Age$^{(2)}$	−0.0098 (0.0061)	−0.0043 (0.0038)	−0.0050 (0.0040)	−0.0016 (0.0018)
	Time	0.0092 (0.0071)	- -	- -	- -
	Time$^{(2)}$	−0.0001 (0.0002)	- -	- -	- -
	Female sex	0.3941 (1.9870)	- -	- -	- -
	Education	−0.4304* (0.1575)	−0.3908* (0.1558)	−0.4268* (0.1617)	−0.2150* (0.0937)
	VBR	0.8715 (0.6297)	- -	- -	- -
	Age*Time	0.0016 (0.0014)	- -	- -	- -
	mTBI	- -	- -	−3.8867 (3.1173)	0.7979 (0.4149)
	Age*mTBI			0.0183 (0.0522)	- -
	Education* mTBI	- -	- -	0.2946 (0.1984)	- -
Variance/Covariance	Within-subject covariance	3.1535** (1.0399)	3.2460** (1.1215)	2.2156*** (0.5552)	2.3697*** (0.5662)
	Measurement variance	1.1921*** (0.3624)	1.3626*** (0.4219)	2.2806*** (0.3644)	2.2565*** (0.3574)
Fit indices	−2 Log Likelihood	227.5526	232.4020	784.3602	787.4886
	AIC	249.5526	244.4020	804.3602	801.4886
	BIC	266.3426	253.5602	830.8041	819.9993
	N	34	34	104	104

Notes: All parameters presented as: estimates (standard error). AIC: Akaike information criterion.
BIC: Bayesian information criterion.
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

consciousness or including subconcussive exposures) or a dimensional quantification of mTBI history would produce a different pattern of results. In the current data, when the mTBI group was further broken down by mechanism of injury, the age-related trajectories of VBR continued to be similar, providing evidence that the observed patterns are stable across at least one alternative definition of mTBI. Similarly, VBR is a very general measure that captures both ventricular expansion and brain volume atrophy regardless of anatomical location; however, more localized volumetric changes may be missed. Therefore, due to the scarcity of longitudinal volumetric data in the chronic phase of mTBI, especially among military samples, the primary goal of the current investigation was to determine whether the experience of a substantial head injury (i.e., mTBI) is systematically associated with evidence of gross brain atrophy, and interpretations of results should be limited accordingly.

Our GLS model accounted for effects of age and timing more thoroughly than prior studies, allowing us to explicitly characterize volumetric trajectories over time. The age-related patterns of VBR, TVV, and TBV observed in the current sample align well with published norms in healthy adults (e.g., (38)), including a linear decrease in TBV with age and nonlinear patterns (i.e., larger increases at older ages) in TVV and VBR. In particular, the observation of decreasing VBR with age in younger participants and increasing VBR with age in older participants (Figure 2) illustrates the importance of accounting for age when comparing volumetric changes. Two prior longitudinal studies of volumetric changes following mTBI (29,30) entered age as a linear covariate into analysis of variance (ANOVA) designs, and while this approach may be effective in regions with linear dependency like we observed for TBV, it would be ineffective for the nonlinear patterns of TVV and VBR. Further longitudinal investigations

will be essential to characterizing the long-term effects of mTBI and other deployment experiences (e.g., blast exposure) on brain anatomy, and appropriate consideration of normal aging will be of increasing importance.

The only significant predictor of PCS was years of education, manifest as fewer PCS reported by participants with more education. This relationship likely reflects an underlying association between PCS reporting and a correlate of educational attainment, including differences in insight, reporting threshold, cognitive reserve, nature of combat exposure, or job satisfaction, which may be useful considerations to understanding the role of PCS in post-deployment outcomes. The absence of relationships among PCS, mTBI, and VBR suggests that symptomatology is largely unrelated to underlying brain volumetrics. Specifically, having high PCS was not associated with higher VBR, accelerated ventricular expansion, or history of mTBI. Moreover, none of the measures of time (i.e., age, time since deployment and their squares) or their interactions with mTBI had a significant impact on PCS reporting, suggesting that symptoms are stable over time regardless of mTBI history. This pattern of results is further evidence of the non-specificity of PCS to mTBI, especially in deployed military samples in which PTSD and depression are also associated with elevated PCS (3,12,13,57,58). Identification of phenotypic markers that are specific to mTBI will be beneficial to further characterizing the relationship between clinical sequelae and structural brain alterations.

In summary, this is the first large, longitudinal study of deployed Servicemembers and Veterans to investigate the influence of mTBI history on age-related changes in VBR. We did not find evidence that a history of mTBI is associated with disruption of the normal VBR trajectory, even when considering mechanism of injury (i.e., blast vs. impact). Reporting of PCS did not vary across age, with time since deployment, or by mTBI history, demonstrating neither worsening of symptoms nor improvement. The major strengths of the study were its inclusion of longitudinal data from a large number of deployed Servicemembers and Veterans, with both time points at clinically meaningful stages in the putative course of brain changes, and the explicit modeling of time with both linear and quadratic terms. These considerations provide a more comprehensive perspective on volumetric changes over the life course following mTBI than has been possible previously.

Limitations and future directions

Our sample varied substantially in age at deployment, age at baseline measurement, and longitudinal delay. While our model was chosen to account for this variation, future studies that can better standardize these, perhaps by following a single cohort of service members from a common deployment over a consistent time period (i.e., only variation in age), may be better able to characterize sources of variation in VBR. However, because this type of design is difficult in practice, the type of model described here may be valuable for other studies to consider.

The specific MRI sequence acquired was not consistent across time points. Because the volumetric estimations are based on contrast across tissue types rather than raw intensity values, this is unlikely to have substantially affected quantification. We attempted to minimize the effect of sequence differences by equalizing the resolution between images using FSL's SIENA. Moreover, because VBR is a normalized measure, it is less susceptible to global differences in quantification. Nonetheless, it would be preferred to collect the same sequence across time points.

As previously observed, the mTBI events varied considerably in terms of symptoms (e.g., loss vs. alteration of consciousness), context (e.g., combat, non-combat military, civilian), and mechanism (e.g., blast vs. impact) across individuals. Moreover, because the majority of individuals in the mTBI group had multiple events, these features often varied within individuals as well. Because the inclusion of timing variables in the GLS model required a consistent index event, it would be impractical to account for these features within a single model (e.g., 'age at most recent blast mTBI' is not meaningful to the contrast of 'impact mTBI'), and because the index events (and, therefore, the timing variables) would vary across contrasts, models testing the effect of each mTBI feature individually could not be directly compared. However, the importance of these features to differences in functional outcome and neural substrates has been previously established, so future studies would likely benefit from their inclusion when practically possible.

Finally, a limitation of nearly all studies of military mTBI is the heavy dependence on retrospective self-report for determination of mTBI. For a variety of reasons, mTBI events that occur during deployment are much less likely to be reported, assessed, and documented in the acute stages than civilian mTBI events. And although the military has made efforts to improve the level of assessment and documentation at the time of the injury, as well as the early identification of potential mTBI history when entering VA care, it remains the norm that mTBI diagnoses are based primarily on the description of events and symptoms recalled by the Veteran months or years later. While this may increase generalizability of the current results to clinical settings, it also raises the possibility that some effects may be influenced by personality traits or mental health conditions affecting reporting style. We have used a structured interview and a consensus review process to reduce this potential influence.

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Declaration of Interest

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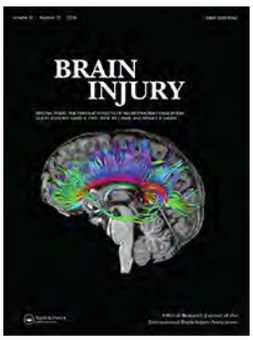
Appendix 3

Understanding the impact of mild traumatic brain injury on veteran service-connected disability: results from Chronic Effects of Neurotrauma Consortium



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Understanding the impact of mild traumatic brain injury on veteran service-connected disability: results from Chronic Effects of Neurotrauma Consortium

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ABSTRACT

Objectives: Disability evaluation is complex. The association between mild traumatic brain injury (mTBI) history and VA service-connected disability (SCD) ratings can have implications for disability processes in the civilian population. We examined the association of VA SCD ratings with lifetime mTBI exposure in three models: any mTBI, total mTBI number, and blast-related mTBI.

Methods: Participants were 492 Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn veterans from four US VA Medical Centers enrolled in the Chronic Effects of Neurotrauma Consortium study between January 2015 and August 2016. Analyses entailed standard covariate-adjusted linear regression models, accounting for demographic, military, and health-related confounders and covariates.

Results: Unadjusted and adjusted results indicated lifetime mTBI was significantly associated with increased SCD, with the largest effect observed for blast-related mTBI. Every unit increase in mTBI was associated with an increase in 3.6 points of percent SCD. However, hazardous alcohol use was associated with lower SCD.

Conclusions: mTBI, especially blast related, is associated with higher VA SCD ratings, with each additional mTBI increasing percent SCD. The association of hazardous alcohol use with SCD should be investigated as it may impact veteran health services access and health outcomes. These findings have implications for civilian disability processes.

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Concussion; traumatic brain injury; military veterans; disability evaluation; veterans disability claims

Introduction

Mild traumatic brain injury (mTBI) in US military service members can be associated with considerable functional limitations, including reduced work productivity and social functioning [(1)]. Exposure to blasts/explosions, common among modern-day combatants, may also contribute to poor functional outcomes. Blast-related mTBI in US military service members has been found to be associated with moderate to severe disability 5 years post-injury (2). A Department of Veterans Affairs (VA) service-connected disability (SCD) is defined as a disability from a disease or injury that arose in, was aggravated by, or otherwise is causally related to military service (3). The VA provided $64.71 billion in compensation to approximately 4.4 million veterans for SCDs during the 2016 fiscal year (3). Brain disease due to trauma, including mTBI, is one of the most prevalent neurological SCDs for which the VA provides compensation, affecting 73 165 (9.56%) Global War on Terror (GWOT) veterans receiving compensation (3). This paper examines the association of total VA SCD percent rating with mTBI exposure measured in three diverse ways: any lifetime mTBI, multiple lifetime mTBIs, and any lifetime blast-related mTBI exposure, while adjusting for other combat and non-combat related confounders and covariates. The potential effects of mTBI history and multiple mTBIs are still largely unknown. Though focused on the military and veteran population, this study can also provide important information regarding the potential association of mTBI history and number of mTBIs with disability in the civilian population.

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The Veterans Benefits Administration (VBA) focuses on disability and is distinct from the Veterans Health Administration (VHA), which provides health services to those veterans who qualify for VA health services. To qualify for disability in VBA, a physical or mental injury must have been experienced or made worse during military service. A compensation and pension examination by a VBA qualified medical professional is necessary for assignment of percent SCD. Thus, medical providers assigning percent SCD are separate and distinct from medical providers giving care to veterans (4).

VA SCD compensation is based on the severity of medically evaluated disability conditions as well as the veteran's number of dependents (5). A combined disability rating consists of all SCD conditions and ranges from 0% for the least to 100% for the most disabling and compensated (5). While a veteran may receive a 0% disability rating, entitling the veteran to VA health services benefits for the condition, only combined ratings that are ≥ 10% will provide the veteran with monetary compensation (5).

SCD contributes to VA veteran health services utilization (6–8). Though little evidence exists yet regarding the impact of mTBI on SCD, there is some evidence regarding the impact of posttraumatic stress disorder (PTSD) disability claims on VA health services utilization. Veterans who filed for PTSD disability claims used more outpatient mental health and medical services after they applied for VA disability benefits compared to prior to applying for benefits (6). Moreover, veterans whose PTSD disability claims were awarded were more likely to have used VA mental health services in the previous year than those whose claims were denied (7).

Approximately 76% of veterans with a 100% SCD rating have used VA health services (7). Veterans who have less than 50% combined SCD are required to make co-payments for VA health services, unless they meet other income and military circumstance conditions (8). A significant increase in specialty visit co-payments has been found to reduce specialty expenditures among veterans obtaining medications at the VA medical centers (9). Therefore, veterans receiving less than 50% combined SCD may be financially vulnerable and utilize fewer VA health services than veterans with similar conditions who received a 50% or more combined SCD rating.

Studies have examined crucial factors that contribute to and may result from the VA SCD process (5,10). Veterans who are denied VA disability compensation may be more likely to experience low socio-economic status, social isolation, and unmet medical and psychiatric health care needs (5). Denied veterans may also experience significant health challenges exacerbated by poverty, which makes them more vulnerable to substance abuse and homelessness (5). Combat exposure, unemployment, and mental and physical impairment have been found to be the strongest predictors of whether veterans are granted disability benefits (10).

It is important to distinguish between a VA SCD award for TBI and a diagnosis of TBI. It is possible that a veteran receives a TBI diagnosis and treatment in the VA, yet not have a VA SCD compensation award for TBI. Veterans must undergo a VBA examination for TBI to determine whether they qualify for SCD for TBI. The evaluation includes a review of medical records consisting of dates and nature of the injury, severity rating of the TBI at the time of injury, whether the condition has stabilized, self-reported symptoms and the extent to which they interfere with work, instrumental activities of daily living and close relationships, along with a physical examination, diagnostic and clinical tests. Military service-related TBI status, severity, and total number of TBIs are documented. The rater also determines the capacity of the veteran to manage financial affairs. Finally, the rater is required to state whether co-morbid mental health conditions exist, which signs and symptoms are attributed to them, and which represent residuals of TBI (11).

In 2015, there were approximately 100 000 veterans receiving SCD compensation for TBI from the VBA, and approximately 80% of these veterans were diagnosed with mTBI (12). Therefore, it is important to expand our understanding of the association of VA SCD ratings with mTBI exposure history and number of mTBIs. Addressing this question is also important because a high proportion of combat injuries among GWOT veterans are attributed to blast exposure, and increasing numbers of veterans are reporting cognitive symptoms related to these injuries (13). Finally, findings regarding mTBI history, number of mTBIs, and disability in the military population can help inform the association of mTBI history and number of mTBIs with disability in the civilian population.

Methods

Participants

This Chronic Effects of Neurotrauma Consortium (CENC) study enrolled veterans who had served in support of the GWOT's Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn (OEF/OIF/OND). Enrolment occurred at four large US Veterans Affairs Medical Centers (VAMCs) located in Houston, TX; Richmond, VA; San Antonio, TX; and Tampa, FL. At each site, potentially eligible participants were identified by phone contact from persons responding to letters or flyers, referral, or in-person contact at veteran or military clinics. Inclusion criteria were: (1) history of deployment in OEF/OIF/OND or related follow-on conflicts, (2) history of combat exposure defined by the Deployment Risk and Resiliency Inventory Section D (DRRI-2-D) (14), and (3) >18 years of age. Exclusion criteria were: any lifetime moderate or severe TBI or history of a major neurologic or psychiatric disorder resulting in significant decrement in functional status or loss of independent living capacity. A more detailed description of this cohort has been described previously (15).

This interim analysis included 492 veterans enrolled between January 2015 and August 2016. For this analysis, participants were excluded if they were active duty military (n = 36) (i.e., likely not yet eligible for VA SCD), indicated likely symptom magnification or endorsed unusual symptoms as per the Neurobehavioral Symptom Inventory/Mild Brain Injury Atypical Symptoms (NSI/mBIAS) (n = 24) (16–18) (i.e., indicating potentially unreliable self-report symptoms) or reported illicit drug use for non-medical reasons (n = 73). In preliminary analyses, illicit drug users with mTBI exposure

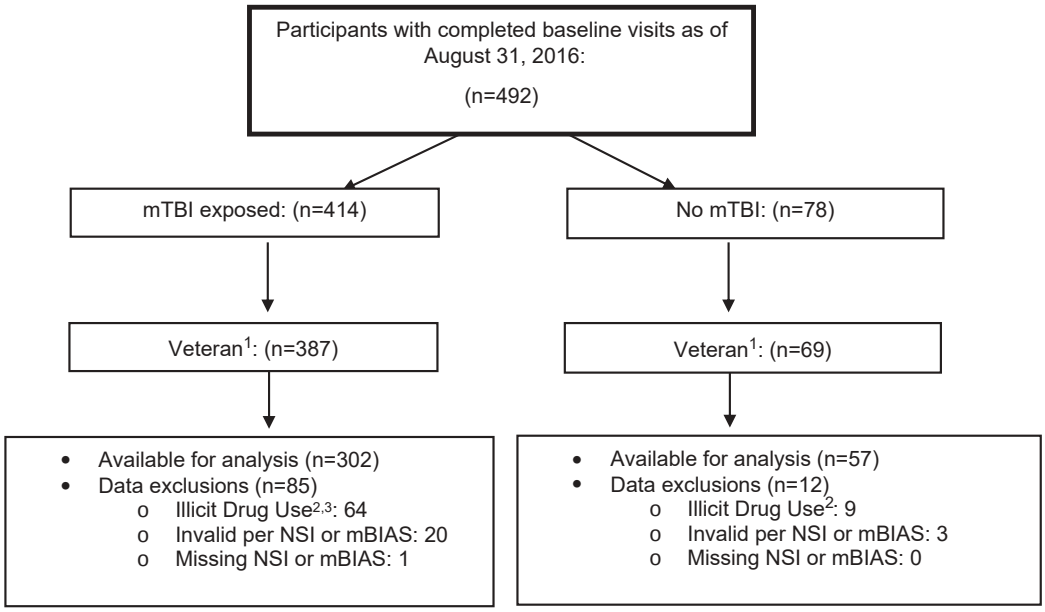

Figure 1. Study CONSORT diagram.

[1]SCD only applies to non-active-duty service members, as such this analysis is subset to veterans only.

[2]Those endorsing illicit drug use were excluded.

[3]Ten subjects in the mTBI Exposed group met more than one exclusion criterion: one subject was excluded for endorsing illicit drug use, having a missing NSI/mBIAS score, and having an unreliable assessment per the assessment reliability codes; two subjects were excluded for endorsing illicit drug use and having missing NSI/mBIAS; seven subjects were excluded for endorsing illicit drug use and having invalid NSI/mBIAS.

were observed to have lower SCD than the mTBI exposed without illicit drug use. Given the small size of this subgroup (n = 10), illicit drug users were removed from analysis since the sample size is not sufficiently large enough to understand the effects of this condition. Consistent with the study's goal to enrol 80% with mTBI exposure and 20% unexposed to any lifetime mTBI, the final sample included 359 participants, 302 with mTBI exposure and 57 without any lifetime mTBI (Figure 1).

Measures

For all assessments possible, the study captures data using published, validated assessments. Additionally, any deviations from intended implementation are documented in the database. No such deviations were noted for the data used in this analysis.

mTBI exposure

A modified version of the Ohio State University TBI Identification screening instrument was employed to identify any lifetime potential concussive event (PCE) (19). Each PCE identified was then investigated via a detailed structured interview, the Virginia Commonwealth University Retrospective Concussion Diagnostic Interview (20), which contains an embedded algorithmic preliminary diagnosis based on the Department of Defense (DoD)/VA common definition of mTBI (21). For each veteran, mTBI was classified as present/absent, the total number of diagnosed mTBI(s) was derived, and the mechanism of mTBI (none/impact only/any blast related) was documented. Additional information regarding total number of controlled (e.g., controlled detonation) and uncontrolled blasts (e.g., improvised explosive device [IED]) and total number of PCE(s) was obtained. An index date was assigned to each veteran, based on the following, in order of priority and applicability: date of the worst combat-related mTBI, date of first mTBI after combat deployment, date of worst combat PCE for veterans without a mTBI diagnosis, or the mid-point date of combat deployment (for veterans without both a mTBI diagnosis and a combat PCE).

Outcome of service-connected disability

Veteran's SCD rating was abstracted from electronic VA medical records and entered into study case report forms. Total percent SCD was derived by summing the percent disabled listed for each identified injury, with a maximum of 100%. Because the VA percent SCD methodology is not uniformly additive when multiple disabilities are present (22), for this analysis we have used a sum of individual disability percent SCD, so the sum is uniform within our cohort. In our study, 76.9% of veterans reported more than 1 SCD (276 out of 359), with the total number of reported SCDs per veteran ranging from 1 to 32, and a median of 5 SCDs per veteran. There were 61 veterans who did not have any abstracted disabilities and were assigned a total percent SCD of 0.

Symptom validity

The NSI (16,17) is a 22-item assessment of post-concussive symptoms in which individuals report the extent to which they have been affected by each symptom within the past 2 weeks, on a scale of 0 (none) to 4 (very severe). Psychometric assessment of the NSI found that 10 of its items are infrequently endorsed as being problematic, and therefore high endorsement of these symptoms (referred to as the Validity-10) may be indicative of

exaggeration. The mBIAS (18) is a five-item measure of unlikely symptoms (e.g., temporary complete deafness) that was developed as a symptom validity test for use with patients following a TBI, and was embedded within the NSI in this study. Veterans who scored below the standard recommended cut-off scores on the NSI Validity-10 (16,17) (≥23) and mBIAS (18) (≥8) were excluded.

Covariate, confounders, and participant characteristics

Demographics. Each veteran completed a standard questionnaire to obtain information including age, gender, race, ethnicity, education, and marital status.

Combat exposure. The DRRI-2-D (14) is a 17-item self-administered questionnaire that measures exposure to combat-related circumstances such as firing a weapon, being attacked by the enemy, or disarming potential combatants. Higher total scores on this tool are indicative of greater combat exposure.

Military history. The Military Status & Mental Health Defense and Veterans Brain Injury Center (23) form is a comprehensive, self-report questionnaire that collects information regarding current housing status, current military status, military history (including combat deployment and non-deployment), veteran status, and mental health and rehabilitation treatment in the past 6 months.

Alcohol abuse. The Alcohol Use Disorder Identification Test (AUDIT-C) (24) is a three-item alcohol screening tool that can identify persons who are hazardous drinkers or have active alcohol use disorders. Men with an AUDIT-C score ≥ 4 and women with an AUDIT-C score ≥3 were considered positive for hazardous alcohol behaviours.

Drug abuse. The Drug Abuse Screening Test (DAST-10) (25) is a 10-item self-administered questionnaire that assesses drug use, not including alcohol or tobacco use, in the past 12 months. Participants indicating drug use other than those required for medical reasons were excluded from the study.

Depression. The Patient Health Questionnaire Depression Scale (PHQ-9) (26) is a nine-item self-administered tool that consists of the criteria upon which the diagnosis of DSM-IV depressive disorders is based. This assesses overall depression severity and status of specific symptoms. PHQ-9 scores range from 0 to 27; scores ≥ 10 are considered positive for depression (moderate, moderately severe, or severe depression).

Posttraumatic stress disorder (PTSD). The Mini-International Neuropsychiatric Interview (M.I.N.I.) (27) is a structured interview, developed jointly by psychiatrists and clinicians in the USA and Europe, for clinical diagnosis of psychiatric disorders, including PTSD. Only the PTSD portion of the interview was collected for this study and was scored using DSM-V criteria.

Pre-injury health questionnaire. To determine prior learning disabilities, participants self-reported if they were diagnosed with any of the following learning disabilities during school: attention deficit (hyperactivity) disability, dyslexia, autism, or other disability. Endorsement of any of these diagnoses was classified as a prior learning disability (yes/no).

Data analysis

Characteristics of the sample stratified by mTBI exposure were summarized by mean and standard deviation for continuous variables, median and interquartile range for non-normally distributed continuous variables, and frequency and percentage for categorical variables.

Standard covariate-adjusted linear regression models were used to analyse the relationship between mTBI exposure and percent SCD, accounting for confounders and covariates. Multiple regression models were built by treating mTBI exposure in three ways: (1) any lifetime mTBI (yes/no), (2) lifetime mTBI total count, and (3) lifetime blast-related mTBI (none/impact only/any blast related). Confounders included research site, service branch, service rank, total combat exposure, total months of combat deployment, total number of uncontrolled blast and non-blast PCEs (including those resulting in mTBI), and total number of controlled blast exposures. Covariates included time since index date, age, gender, hazardous alcohol use, education, and prior learning disability. PTSD and depression, conditions for which a percent SCD can also be awarded, were considered but excluded as covariates, due to the likelihood that these factors are influenced by mTBI and therefore on the causal pathway between mTBI and SCD (and, therefore, not theoretical confounders) (28–30).

First, preliminary analyses were completed to identify which variables and interactions should be considered in the full covariate-adjusted model building process. A study site-adjusted analysis between percent SCD and each independent variable was run. Study site adjustment allows for adjustment for variation in percent SCD processes by site. Variables associated with SCD with p-values <0.10 were retained for further analysis. Additionally, a site-adjusted model was fit for each potential covariate that also included the mTBI exposure variable of interest and the interaction between the two. Interaction terms with p-values <0.10 were retained for further analysis. Interactions between mTBI exposure and confounders were not considered.

Next, a full covariate-adjusted regression model was fit for each mTBI exposure subtype, including covariates, confounders, and mTBI exposure-covariate interactions that were identified in the preliminary analyses. The full covariate-adjusted regression models were then reduced to only include significant interaction terms and main effects ($p < 0.05$). Model reductions were applied consistently across the exposure models with insignificant interactions removed first, followed by insignificant main effects. The final model included research site, service branch, total combat exposure, total number of PCEs (excluding controlled blast), time since index date, age, gender, and hazardous alcohol use. Site, age, and gender were determined a priori to be retained regardless of significance. All data manipulation and analyses were performed using SAS Version 9.3 (Cary, NC).

Table 1. Baseline demographics by mTBI exposure.

Characteristic	Study group: mTBI (*N* = 302)	Study group: No mTBI (*N* = 57)	*P*-value
Age at baseline[W]			
Median	38.0	38.0	0.6658
Min, Max	22, 69	23, 68	
Gender[C]			
Male	264 (87.4%)	46 (80.7%)	0.1756
Female	38 (12.6%)	11 (19.3%)	
Race[C]			
White	201 (67.7%)	41 (71.9%)	0.6295
Black or African American	69 (23.2%)	10 (17.5%)	
Other	27 (9.1%)	6 (10.5%)	
Ethnicity[C]			
Hispanic or Latino	69 (23.0%)	17 (29.8%)	0.2694
Not Hispanic or Latino	231 (77.0%)	40 (70.2%)	
Service branch[C,1]			
Army	206 (68.4%)	37 (64.9%)	0.7749
Marines	43 (14.3%)	7 (12.3%)	
Air Force	30 (10.0%)	8 (14.0%)	
Navy	22 (7.3%)	5 (8.8%)	
Service rank[C]			
Enlisted	267 (88.7%)	46 (80.7%)	0.0947
Officer	34 (11.3%)	11 (19.3%)	
Education[C,2]			
College graduate	114 (37.7%)	22 (38.6%)	0.6127
Some college or technical school	141 (46.7%)	26 (45.6%)	
High school graduate	46 (15.2%)	8 (14.0%)	
Some high school	1 (0.3%)	1 (1.8%)	
Years since index date[W]			
Median	9.3	9.1	0.8077
Min, Max	1, 47	1, 19	
Total combat exposure (DRRI-2-D)[W]			
Median	37.0	26.0	<0.0001
Min, Max	17, 89	16, 71	
Total Number of months combat deployment[N,3]			
Median	15.0	12.0	0.0891
Min, Max	0, 102	0, 51	
Total number of PCEs[N,4]			
Median	3.0	1.0	<0.0001
Min, Max	1, 15	0, 5	
Total number of controlled blast exposures[N,5]			
Median	3.0	0.0	0.2806
Min, Max	0, 99	0, 99	
PTSD (M.I.N.I.)[C]			
Yes	100 (33.2%)	3 (5.5%)	<0.0001
No	201 (66.8%)	52 (94.5%)	
Depression (PHQ-9)[C]			
Yes	131 (43.7%)	15 (26.8%)	0.0184
No	169 (56.3%)	41 (73.2%)	
Hazardous alcohol use (AUDIT-C)[C]			
Yes	96 (31.8%)	15 (26.3%)	0.4123
No	206 (68.2%)	42 (73.7%)	
Prior learning disability[C]			
Yes	33 (10.9%)	2 (3.6%)	0.0887
No	269 (89.1%)	54 (96.4%)	

C: chi-square test; T: T-Test; N: Negative Binomial Regression; P: Poisson; W: Wilcoxon Rank-Sum Test

Note: Due to exclusion of missing data, the number of mTBI cases and no mTBI cases within each variable may not add up to the full number of mTBI and No mTBI cases.

[1]For analyses, Air Force and Navy were collapsed into one level due to small sample sizes. Note that no subjects in this dataset have identified as Coast Guard and Special Operatives status is unknown.

[2]For analyses, education levels were collapsed into any high school, but no college vs. any college.

[3]Nine subjects reported no combat deployment.

[4]Does not include controlled blast exposures.

[5]Only considers controlled blasts during deployment.

Results

Demographic, medical history, military characteristics, combat exposure, and other study data are presented in Table 1, stratified by mTBI exposure. Overall, veterans with lifetime mTBI experienced significantly greater combat exposure ($p < 0.001$), more total PCEs ($p < 0.001$), and a higher frequency of PTSD ($p < 0.001$) and depression ($p = 0.018$). There were no other significant differences in demographic or other characteristics across mTBI exposure.

Unadjusted analysis between each of the three mTBI exposure categories and percent SCD suggest higher SCD compensation with more mTBI exposure. Individuals who

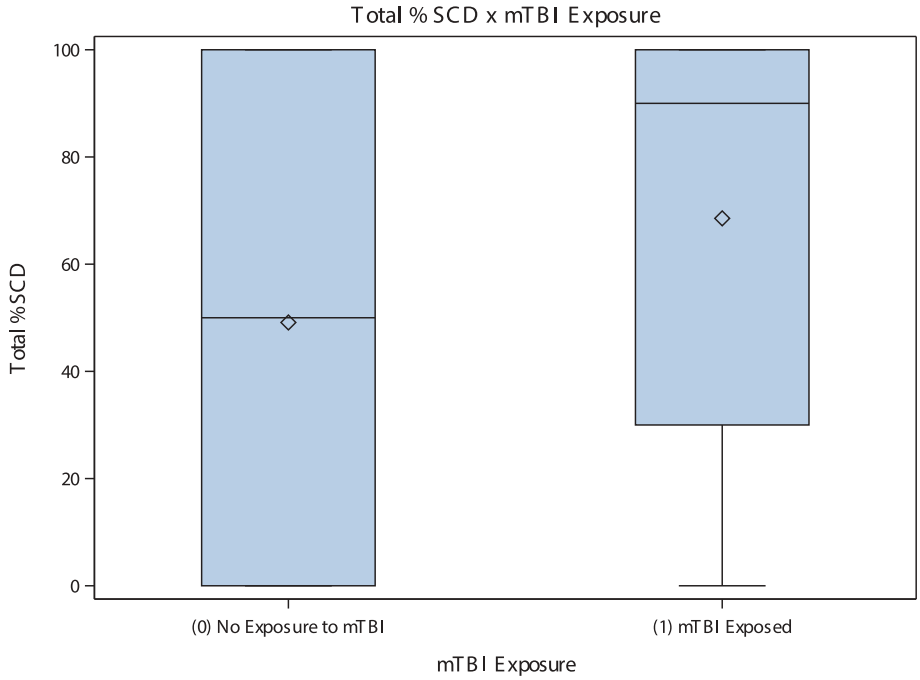

Figure 2. Percent SCD by dichotomized mTBI exposure.
Note: Within each bar, the diamond represents the mean while the horizontal bar represents the median.

experienced at least one lifetime mTBI had an average SCD of 68.5% compared to 49.1% among those without mTBI (Figure 2). There is a general positive, linear correlation between the total number of mTBI(s) and the total percent SCD (Figure 3). Those who experienced at least one blast-related mTBI had a 74.3% average SCD; those with at least one impact mTBI but no blast-related mTBI had a 62.3% average SCD; those without blast-related or impact mTBI had a 49.1% average SCD (Figure 4).

In the preliminary analyses, the variables identified for inclusion in the full covariate-adjusted model building process were age, hazardous alcohol use, service branch, combat exposure, and total number of PCEs. Likewise, the interaction effect between mTBI exposure and hazardous alcohol

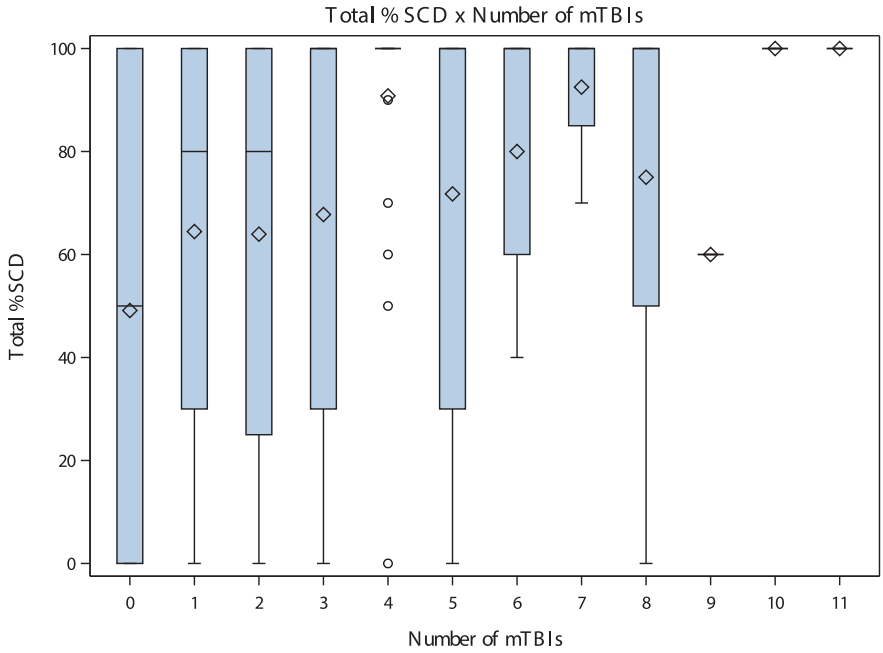

Figure 3. Percent SCD by total mTBI exposure.
Note: Within each bar, the diamond represents the mean while the horizontal bar represents the median. Where median line is not present, the median and 75th percentile both equal 100%.

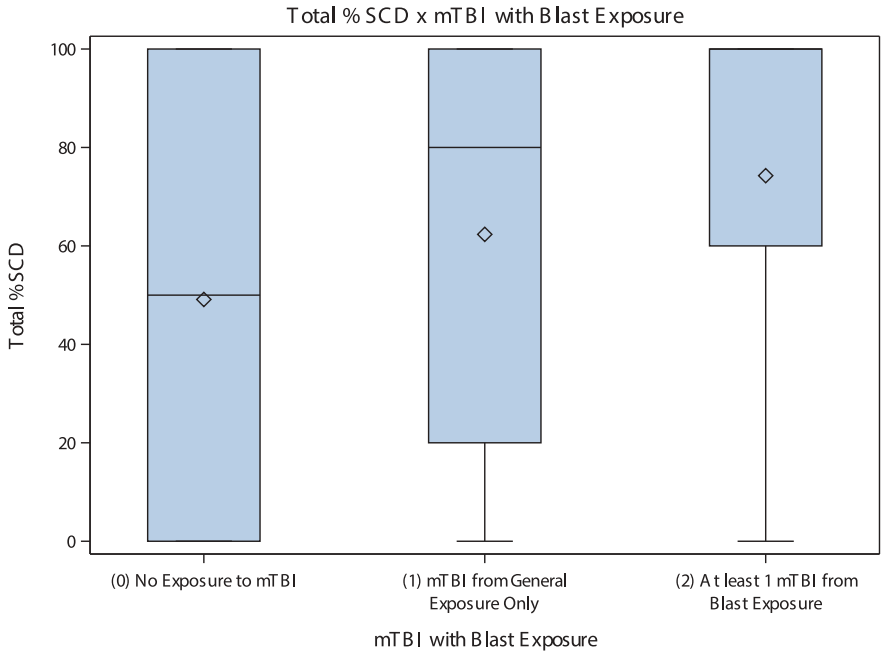

Figure 4. Percent SCD by blast-related mTBI exposure.

Note: Within each bar, the diamond represents the mean while the horizontal bar represents the median. Where median line is not present, the median and 75th percentile both equal 100%.

Table 2. Final covariate-adjusted regression model(s) for percent SCD.

Parameter	mTBI vs. no mTBI (main effects only)		mTBI vs. no mTBI (w/interaction)		Continuous repetitive mTBI		Blast-related mTBI	
	Est.	*p*	Est.	*p*	Est.	*p*	Est.	*p*
mTBI:								
mTBI vs. no mTBI	13.50	0.02	6.78	0.31	–	–	–	–
mTBI continuous	–	–	–	–	3.60	0.04	–	–
General mTBI only (vs. no mTBI)	–	–	–	–	–	–	10.03	0.10
At least one blast-related mTBI (vs. no mTBI)	–	–	–	–	–	–	20.55	<0.01
Years since index date[1]	0.12	0.79	−2.34	0.07	0.10	0.83	0.06	0.89
Age[1]	0.76	<0.01	0.76	<0.001	0.71	<0.01	0.81	<0.001
Hazardous alcohol use (Yes)	−9.83	0.03	−30.47	0.01	−9.17	0.04	−8.35	0.06
Gender (Female)	3.56	0.55	3.78	0.53	2.84	0.64	4.47	0.45
Service branch:								
Marines vs. Army	−4.51	0.45	−3.34	0.575	−4.96	0.41	−4.99	0.40
Air Force/Navy vs. Army	−10.35	0.05	−9.93	0.06	−10.56	0.05	−9.72	0.07
Combat exposure[1]	0.28	0.05	0.28	0.05	0.32	0.03	0.16	0.31
Total number of PCE(s)	1.03	0.26	1.06	0.25	−0.38	0.78	0.79	0.39
Interaction mTBI (yes) with hazardous alcohol use (yes)	–	–	24.34	0.04	–	–	–	–
Interaction mTBI (yes) with Years since index date	–	–	2.78	0.04	–	–	–	–

Models also controlled for site with the *p*-value for site ranging from 0.0101 to 0.0272 across models.
[1]Variable have been centred based on averages from the full CENC population that was eligible for analysis

use, time since index date, and education were also identified for inclusion. Initial multivariable models were fit for all three mTBI exposure subtypes, including main effects for all covariates, confounders, and the identified interaction terms. The final multivariate model(s) only included main effects and interaction terms that were significant at $p = 0.05$ (Table 2).

Only the model using the mTBI vs. No mTBI exposure category retained two significant interaction terms with mTBI: hazardous alcohol use and time since index date. A main effects model without these interaction terms is provided for comparison purposes. In the main effects model, the mTBI exposed group had 13.5 points higher percent SCD rating compared to the non-mTBI group. However, as observed in the interactions model, this association was most marked in hazardous alcohol users and those assessed farther out from injury or combat deployment. Specifically, among those with hazardous alcohol use, SCD was twofold higher among those with mTBI (62.3%) compared to those without TBI (30.5%). The trend was similar although not as strong among those without hazardous alcohol use (68.4% for mTBI vs. 60.9% for no mTBI). For years since index date,

percent SCD increased slightly for every year since index date in the mTBI exposed group; however, it decreased for every year since index date among the mTBI exposed group. For example, the estimated average percent SCD at the 0 centred time since index date (i.e. 9 years since index date) was 46% for non-mTBI exposed and 65% for mTBI exposed. At 5 additional years since index date, the estimated percent SCD is 34% for non-mTBI exposed and 67% for mTBI exposed.

The continuous repetitive mTBI and blast-related mTBI subcategories also suggest more VA SCD with greater mTBI exposure. Every unit increase in mTBI was associated with an increase in 3.6 points of percent SCD. Although there was no statistically significant difference in SCD among those with no mTBI compared to those with strictly impact mTBI ($p = 0.098$), those with blast-related mTBI had almost 21 points greater SCD compared to those without mTBI ($p = 0.002$).

Overall, results were relatively consistent across all three mTBI lifetime exposure classifications. With respect to other factors in the models, increased age and combat exposure were associated with higher percent SCD in all models. Hazardous alcohol use was associated with reduced percent SCD across all models.

Discussion

This study examined the association of the sum of VA percent SCD ratings with three different classifications of TBI exposure: any lifetime mTBI, multiple lifetime mTBIs, and any lifetime blast-related mTBI. Compared to veterans without TBI, a higher average percent SCD rating was associated with veterans who: (1) experienced at least one lifetime mTBI, (2) experienced at least one blast-related mTBI, or (3) had at least one mTBI but no blast-related TBI. In sum, the unadjusted results indicated that exposure to at least one lifetime blast-related mTBI was associated with the highest percent SCD rating relative to no lifetime TBI. Unadjusted results also showed there was a general, positive linear association between percent SCD and the total number of lifetime mTBI(s). This could be due to conditions secondary to TBI which have been approved for SCD that can occur after the initial TBI. These conditions include depression if manifest within 12 months of mild TBI (30).

This is consistent with previous literature that combat exposure (10), especially blast (13), is a major determinant of SCD awards.

Adjusted results confirmed that mTBI was associated with higher percent SCD by various definitions, and these findings suggest that blast-related mTBI had the strongest marginal impact on percent SCD rating. This is consistent with a previous study that found blast-related mTBI was associated with moderate to severe disability (2), which may reflect the increased exposure to blast-related weapons (IEDs, mortars, and rocket-propelled grenades) in the recent conflicts in Iraq and Afghanistan (12,31). Blast-related TBI appears to be distinct from non-blast-related TBI in pathophysiology (32) and may be associated with increased psychiatric sequelae (33) and protracted recovery trajectories (34).

The mTBI and no-TBI groups differed significantly on several factors. Relative to the no mTBI group, the mTBI group had significantly higher: (1) total combat exposure based on the DRRI-2-D, (2) total number of PCEs, (3) prevalence of PTSD based on the M.I.N.I., and (4) prevalence of depression based on the PHQ-9. In addition to independently affecting SCD, PTSD and depression may also mediate the mTBI effect on SCD (28–30). Therefore, controlling for them in the existing covariate-adjusted regression models would be inappropriate. Future analyses employing mediation models would be useful in further exploring the mTBI and SCD relationship.

The multiple analyses based on different classifications of mTBI consistently found that mTBI was associated with higher percent SCD. The importance that mTBI increases total SCD can affect utilization both via reduced co-pays once total SCD surpasses 50% and VA providers may more readily recognize and manage mTBI if it has been identified as a SCD.

These findings are reinforced by excluding veterans who exceeded designated cut points on the NSI Validity-10 (16,17) and mBIAS (18) measures of symptom validity. Previous studies estimated that between 32% and 52% of veterans receiving SCD compensation for mTBI may have exaggerated cognitive deficits based on two tests that assess symptom exaggeration and possibly misattribution by raters, which could cost as much as $136–$235 million per year (12).

Attributing symptoms and functional status to a specific diagnosis, especially among veterans with co-occurring disorders, can be a complicated process (35). In this study, there was a significant interaction effect of hazardous alcohol use with any mTBI, and an independent negative association of hazardous alcohol use with SCD in all models. It is unknown whether the hazardous alcohol use occurred prior to or after the mTBI. Nevertheless, raters of SCD may have difficulty determining whether reported cognitive difficulties are due to mTBI sequelae or hazardous alcohol use (36,37). Such misattribution could potentially explain the observed reduced SCD rating. Regardless of aetiology, it is important that VA health care providers are aware of the potential for hazardous alcohol use among veterans with mTBI and recommend available treatment options (38).

Outside of VA, it is also important to understand the association of lifetime mTBI for civilian disability medicolegal evaluations for social security disability application, personal injury litigation, worker's compensation claims, disability insurance policy applications, other health insurance policy coverage issues, and the determination of competence to work, handle finances, or fulfil other important life functions (39). The VA SCD and civilian processes for assessing impairment and disability are different and complex, thus understanding the underlying disease process and associated injuries are extremely important for optimal evaluation. Analysing the association of number of mTBIs and VA SCD in veterans may provide valuable information on the potential association of number of mTBIs with civilian disability.

Several study limitations should be considered. Most importantly, the CENC longitudinal study involves a selective sample of participants willing and able to enrol in the study, undergo a comprehensive assessment routine, and agree to

annual follow-up activities. Participants may not be representative of all OEF/OIF/OND veterans eligible to receive VA SCD benefits. However, a strength of this study is its enrolment of veterans from different geographic sites. Enrolment is ongoing and additional sites have been added since the initial four upon which these analyses are based. Future analyses examining associations between mTBI and SCD status in a larger, more representative sample may increase generalizability of results. Another potential limitation is that the statistical models included the total number of PCEs as a confounder, rather than only including the number of PCEs not diagnosed as mTBI, thus potentially decreasing effect estimates of mTBI by reducing the absolute value, and increasing the variability, of the coefficient. However, the cumulative effects of PCEs, regardless of whether they resulted in mTBI, may make an individual vulnerable to impairment and disability (40), including the total count of PCEs allowed us to explore this relationship with SCD. A third limitation is that we used a sum of individual SCD ratings rather than the VA's combined rating. However, the sum of the ratings may better reflect disability without reducing the importance of any disability for the veteran with multiple disabilities.

Conclusions

There was a significant and positive association between lifetime mTBI and SCD rating for OEF/OIF/OND veterans. This finding remained robust with three different classifications of lifetime mTBI exposure: any, continuous/repetitive, and blast related. Blast-related mTBI had the greatest independent association with SCD of all measures. This is consistent with the literature regarding the importance of combat exposure, especially blast (2), in SCD awards. One finding that warrants further exploration is that across all models, hazardous alcohol use was found to have a large and significant downward effect on SCD. While it is unknown whether the alcohol abuse was present at the time of the SCD evaluation or subsequent to it, lower percent SCD ratings can possibly lead to poor health outcomes, social isolation, and homelessness, as with denied SCD claims (5,41). Our findings show that there is a very important and significant association between mTBI and disability as measured by VA SCD ratings. Future research should investigate other possible combat exposure factors that contribute to SCD to better inform both DoD and VA providers and policymakers. Our findings are also important for civilian disability processes in suggesting how mTBI history and number of mTBIs may potentially affect civilian disability ratings.

Declaration of Interest

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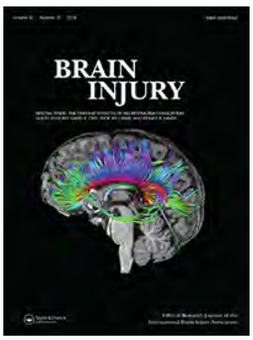
Appendix 4

Pain and chronic mild traumatic brain injury in the US military population: a Chronic Effects of Neurotrauma Consortium study



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Pain and chronic mild traumatic brain injury in the US military population: a Chronic Effects of Neurotrauma Consortium study

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ABSTRACT

Primary objectives: To describe the association between mild traumatic brain injury (mTBI) and pain intensity and pain interference outcomes while accounting for potential confounders and mediators including environmental factors and comorbidities in a cohort of US Veterans of the Iraq and Afghanistan wars.

*Research design:*Cross-sectional snapshot of baseline data from a prospective, longitudinal study.

Methods: Effects of mTBI on pain intensity and pain interference were compared between participants with or without mTBI exposure. Data were analysed using covariate-adjusted regression analyses as well as structural equation modelling (SEM) methods to assess the robustness of findings across different modelling assumptions. As results of the two approaches were consistent with respect to the overall association between mTBI exposure and pain, the results focus primarily on the SEM findings.

Results: The mTBI exposed group reported significantly greater indices of post-traumatic stress disorder (PTSD), depression, anxiety and sleep disturbance. After accounting for other factors, mTBI exposure was significantly, but indirectly associated with the pain interference and pain intensity outcomes.

Conclusions: mTBI is strongly associated with pain intensity and pain interference in this sample. However, the effect appears to be mediated by other common mTBI comorbidities: PTSD, depression, anxiety and sleep disturbance.

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Anxiety; concussion; depression; post-traumatic stress disorder; sleep disturbance; structural equation modelling

Introduction

Traumatic brain injury (TBI) is recognized as the 'signature injury' of Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn (OEF/OIF/OND). Between the year 2000 and August 2017, more than 375,000 Service Members (SMs) were diagnosed with TBI, with 82.3% of those cases being mild TBI (mTBI) (1). Veterans and SMs with a TBI report more missed work days and medical visits (2) and, on average, incur four times the healthcare cost as those without a TBI, and the cost increases with the presence of comorbidities such as pain (3). Studies of the military population have identified comorbid TBI and pain to have a prevalence rate of 43–79% (3,4) and SMs with mTBI report pain at a higher rate than those who sustained non-head injuries (5), and at twice the rate of those without a TBI (3,6). In addition, comorbid mTBI and pain is associated with significant functional impairment, with 91% of patients with mTBI reporting some level of pain interference, and 34% endorsing severe or extreme pain interference in daily life (7). Due to the high prevalence and profound impact of comorbid pain and TBI, better understanding the relationship between mTBI and pain, including identifying pre-disposing factors and mediators of mTBI-associated pain, is critical for improving prevention and treatment strategies for active-duty SMs and Veterans.

Numerous investigations have sought to elucidate the relationship between mTBI and pain in Veterans. Post-traumatic stress disorder (PTSD) is the most commonly cited co-occurring psychiatric disorder in Veterans with TBI and pain, with a prevalence of 54–73% (3,4). Stojanovic et al. found that mTBI alone was not associated with increased pain intensity, however, having comorbid mTBI and PTSD or PTSD alone resulted in significantly worse pain intensity when compared to controls (8). Powell et al. also failed to find a significant association between TBI and pain intensity, but PTSD, lower sleep quality and alcohol abuse were positively associated with ratings of pain intensity (9). Other psychiatric conditions such as depression are also demonstrated mediators for somatic post-concussive symptoms (10), including headache (2). Other investigations have shown a direct effect of mTBI on pain. Stratton et al. found that mTBI, depression and PTSD each independently predicted increased pain severity among blast-exposed patients with mTBI (11) and that mTBI was a significant predictor of head/headache pain but not axial pain

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or pain interference. Also, loss of consciousness appeared to increase incidence of pain in this sample, and other studies have suggested that injury characteristics may affect pain outcomes. Seal et al. also found that mTBI was independently associated with pain in Veterans with complex comorbidities, but those with comorbid TBI, depression and PTSD were at highest risk for chronic pain and pain disability; this risk increased with TBI severity (12). Other reports of increased physical symptoms, including pain, have been associated with longer lengths of loss of consciousness (2), post-traumatic amnesia (PTA) (13) and multiple head injuries (14).

To date, no study has firmly established the relationship between mTBI and pain, as most studies have used models which only include a handful of covariates and mediators. This study examined the associations between mTBI exposure and pain interference, pain intensity, and a wide variety of demographic factors and common comorbid conditions such as PTSD, depression and anxiety. In addition, we sought to identify the relationship between characteristics of acute mTBI exposure, including repetitive mTBI and PTA, and mTBI-related pain. The purpose of this analysis is to better understand the relationship between mTBI, pain intensity and pain interference, and other common mTBI comorbidities among Veterans and SMs.

Methods

Participants

The study population is OEF/OIF/OND era SMs and Veterans who experienced combat situation(s) and have history of exposure to mTBI that ranges from no events resulting in mTBI to many. Participants were recruited and enrolled as a part of the larger, ongoing Chronic Effects of Neurotrauma Consortium (CENC) study. Exclusion criteria included history of moderate-to-severe TBI or history of major neurologic or psychiatric disorder. All study activities were approved by and conducted in accordance with all relevant Institutional Review Boards and other relevant regulatory committees required by the VA and Department of Defense.

An interim sample of 492 participants was recruited between January 2015 and August 2016 at VA Medical Centers (VAMC) located in Richmond, VA, Tampa, FL, San Antonio, TX and Houston, TX. The 454 with pain data reported were split into two groups: participants with at least one prior mTBI (n = 379) and participants without any mTBI (n = 75). For this study, participants were excluded from analysis if they expressed symptom magnification or unknown symptom magnification per the Neurobehavioural Symptom Inventory/Mild Brain Injury Atypical Symptoms (NSI/mBIAS; Figure 1).

Measures

Primary outcome measures

Pain intensity and pain interference were measured by the EuroQol Group 5 dimension 5 level version quality-of-life (EQ-5D-5L) (15) and the TBI Quality of Life (TBI-QoL) pain interference (16) module, respectively. EQ-5D-5L for pain is a 5-point ordinal scale on which respondents rate their current pain as none, slight, moderate, severe or extreme. The TBI Qol Pain Interference Short-Form is a 10-item questionnaire that asks participants to rate the level of pain interference on a variety of functions including family life, daily tasks, mental health and quality of life. Answers are recorded on a 5-point ordinal scale (1–5), and total scores

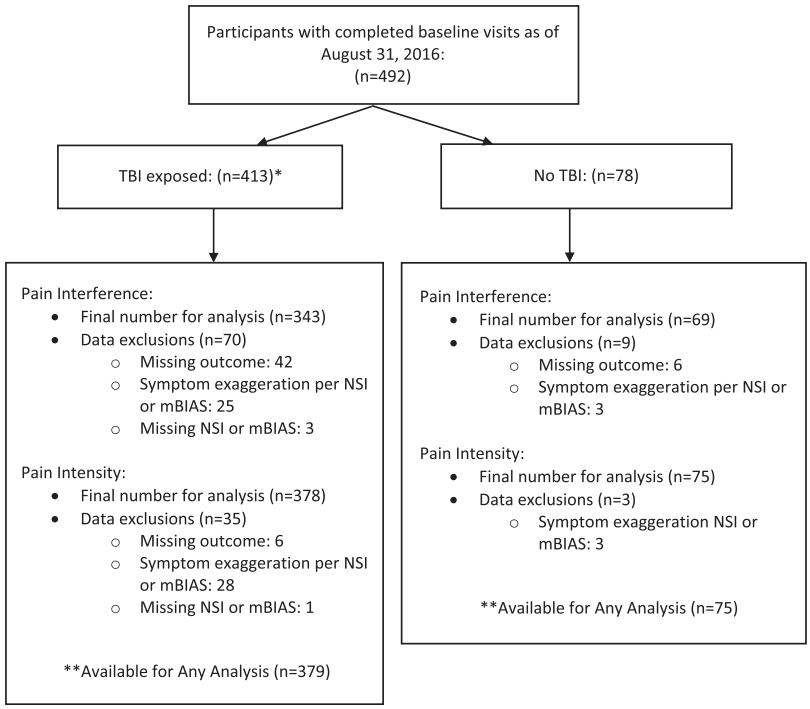

Figure 1. Consort diagram.

range from 10 to 50 points, with higher numbers indicating increased interference.

Mtbi exposure

mTBI exposure was determined as previously described in Walker et al. (17). Briefly, a modified version of the Ohio State University TBI Identification screening instrument (18) was employed to identify lifetime potential concussive events (PCEs). Each PCE identified was then investigated via a detailed structured interview, the Virginia Commonwealth University retrospective Concussion Diagnostic Interview (19), which contains an embedded algorithmic preliminary diagnosis based on the DoD/VA common definition of mTBI (20). An index date was assigned to each participant based on the date of the worst combat related mTBI, date of first mTBI after combat deployment, date of worst combat PCE without mTBI diagnosis (for controls) or the midpoint date of combat deployment (for controls without a combat PCE). Participants were categorized as either experiencing any lifetime mTBI or not experiencing a mTBI.

Covariates and mediators

The covariates and mediators examined in this analysis were assessed via the following: Patient Health Questionnaire Depression Scale (PHQ-9) for depression (21), the Pittsburg Sleep Quality Index (PHQI) for sleep disorders (22), the Mini-International Neuropsychiatric Interview (MINI) for PTSD diagnosis confirmation (23), TBI-QoL Anxiety Short-Form (TBI-QoL) for anxiety (16), the General Self-Efficacy (GSE) Scale (24) and the Deployment Risk and Resilience Inventory Section D (DRRI-2-D) to assess combat exposure (25). For symptom validity, we used the Neurobehavioral Symptom Inventory (NSI) with the Mild Brain Injury Atypical Symptoms Scale (mBIAS) (26). For a detailed description of each of these measures please see this recent publication by Walker and colleagues (17).

Data analysis

Characteristics of the sample, stratified by mTBI exposure, were summarized for continuous variables by a mean and standard deviation vs. median and interquartile range depending on the distribution of the variable, and for categorical variables by frequency and percentage. Unadjusted comparisons were made using the Wilcoxon Rank Sum test for continuous variables, all of which were non-normally distributed, a Chi-square test for categorical variables and a Negative Binomial test for over-dispersed count variables.

Standard covariate-adjusted regression models were used to analyse the relationship between mTBI exposure and the pain outcome measures, accounting for confounders, covariates and potential moderators, with linear models for pain interference and proportional odds models for pain intensity. Factors considered as covariates included time since index injury, age, extra-cranial injury, arthritis and GSE Scale (24); potential moderators included gender; and confounders included site, combat exposure (DRRI-2-D (25)), total months of combat deployment and the number of controlled and uncontrolled blast exposures.

To allow for incorporation of potential mediators of effect in the model as well as to assess the robustness of the findings to methodology assumptions, pathway analyses implemented via structural equation models (SEMs) were also completed (27). These models retained the same covariates, confounders and potential moderators as the covariate-adjusted regression models but also incorporated potential mediators. Mediators included PTSD, depression, anxiety, medication and sleep quality. We examined model fit throughout the process, with lower values of the standardized root mean square and the root mean square error approximation, higher values of the adjusted goodness-of-fit index and Bentler's comparative fit index, and smaller values of Akaike's information criterion all being indicative of a better model.

For all models, factors not exhibiting an effect were removed with the exception that age, site, and time since index injury were retained in the model regardless of significance. All analyses were performed using the SAS Version 9.3 (Cary, NC).

Results

Baseline demographics

The characteristics of the final analysis sample are displayed in Table 1 and include demographics and all variables considered in the model. Compared to the non-mTBI group, the mTBI group had a greater proportion of PTSD (31.2% vs. 11.0%), depression (43.1% vs. 24.7%), arthritis (43.3% vs. 28.0%), extra-cranial injuries (26.9% vs. 6.7%), analgesic, medication use (50.0% vs. 32.4%) and non-analgesic medication use (33.0% vs. 14.9%). They also had a greater number of uncontrolled blast exposures (median of 2.0 vs. 1.0), higher levels of combat intensity exposure (median of 38.0 vs. 28.0), higher anxiety (median of 22.0 vs. 17.0), poorer sleep quality (median of 11.0 vs. 8.0) and a lower level of self-efficacy (median of 31.0 vs. 32.5). There were no significant differences between the mTBI-exposed and no-mTBI groups in age, ethnicity, service branch, years since index date, combat duration, or number of controlled blast exposures.

Unadjusted primary outcomes

Unadjusted raw scores for the outcomes, pain interference and pain intensity are shown in Tables 2 and 3, respectively. The mTBI group reported more pain interference compared to the non-mTBI group (mean of 24.2 vs. 17.4, respectively) and were more likely to report greater pain intensity (59% reported moderate pain intensity or worse vs. 31%, respectively). Graphical displays of the correlation between pain interference and pain intensity are shown in Figure 2. The correlation between pain interference and pain intensity is moderately strong (Spearman's correlation coefficient = 0.62), with pain interference increasing as pain intensity increases. Sub-analyses of the mTBI group were also conducted to determine the effect of PTA, repetitive mTBI exposure and having sustained at least one mTBI due to blast exposure on

Table 1. Baseline demographics by TBI exposure.

Characteristic	Study Group TBI(N=379)	No TBI(N=75)	P-Value
Age at Baseline (yrs)[W]			
Median	36.0	38.0	0.1757
Min, Max	22, 64	23, 68	
Gender[C]			
Male	335 (88.4%)	59 (78.7%)	0.0231
Female	44 (11.6%)	16 (21.3%)	
Race[C]			
White	255 (67.3%)	52 (69.3%)	0.8589
Black or African American	86 (22.7%)	17 (22.7%)	
Other	38 (10.0%)	6 (8.0%)	
Ethnicity[C]			
Hispanic or Latino	89 (23.6%)	23 (30.7%)	0.1959
Not Hispanic or Latino	288 (76.4%)	52 (69.3%)	
Service Branch[C]			
Army	259 (68.7%)	49 (66.2%)	0.4621
Marines	56 (14.9%)	8 (10.8%)	
Air Force	36 (9.5%)	11 (14.9%)	
Navy	26 (6.9%)	6 (8.1%)	
Years since Index Date[W,#]			
Median	8.9	8.8	0.6569
Min, Max	1, 26	1, 29	
Total Combat-related Exposure (DRRI-2)[W,##]			
Median	38.0	28.0	<.0001
Min, Max	17, 89	16, 71	
Combat Duration (mos)[W]			
N	375	73	
Median	15.0	12.0	0.0825
Min, Max	0, 102	0, 51	
Total # of Controlled Blast Exposures[N,###]			
Median	3.0	1.0	0.8516
Min, Max	0, 99	0, 99	
Total # of Uncontrolled Blast Exposures[N]			
Median	2.0	1.0	0.0002
Min, Max	0, 11	0, 4	
PTSD (MINI)[C,##]			
N	378	73	
Yes	118 (31.2%)	8 (11.0%)	0.0004
No	260 (68.8%)	65 (89.0%)	
Depression (PHQ-9)[C,##]			
N	376	73	
Yes	162 (43.1%)	18 (24.7%)	0.0033
No	214 (56.9%)	55 (75.3%)	
Anxiety (TBI-QOL)[W,##]			
N	349	67	
Median	22.0	17.0	<.0001
Min, Max	10, 48	10, 39	
Analgesic Medications[C]			
N	376	74	
Yes	188 (50.0%)	24 (32.4%)	0.0057
No	188 (50.0%)	50 (67.6%)	
Non-Analgesic Medications[C]			
N	376	74	
Yes	124 (33.0%)	11 (14.9%)	0.0019
No	252 (67.0%)	63 (85.1%)	
Arthritis (BRFSS)[C,##]			
Yes	164 (43.3%)	21 (28.0%)	0.0139
No	215 (56.7%)	54 (72.0%)	
Extra-cranial Injury(BRFSS)[C,##]			
Yes	102 (26.9%)	5 (6.7%)	0.0002
No	277 (73.1%)	70 (93.3%)	
Sleep Quality (PSQI)[W,##]			
N	367	75	
Median	11.0	8.0	<.0001
Min, Max	1, 21	1, 18	
Self-Efficacy (GSE)[W,##]			
N	379	74	
Median	31.0	32.5	0.0134
Min, Max	19, 40	16, 40	

C=Chi-square test; W=Wilcoxon Rank Sum; N=Negative Binomial Regression

Index date is based on the worst mTBI during combat or the midpoint of deployment for those with no TBI exposure.

DRRI-2=Deployment Risk and Resilience Inventory; MINI=Mini-International Neuropsychiatric Interview; PHQ-9: Patient Health Questionnaire Depression Scale; TBI-QOL=Traumatic Brain Injury Quality of Life; BRFSS=Behavioral Risk Factor Surveillance System; PSQI=Pittsburgh Sleep Quality Index; GSE=General Self-Efficacy Scale

Total Number of Controlled Blast Exposures only considers controlled blasts during combat deployment.

Unless otherwise noted, N= 379 for the TBI group and N= 75 for the No TBI group

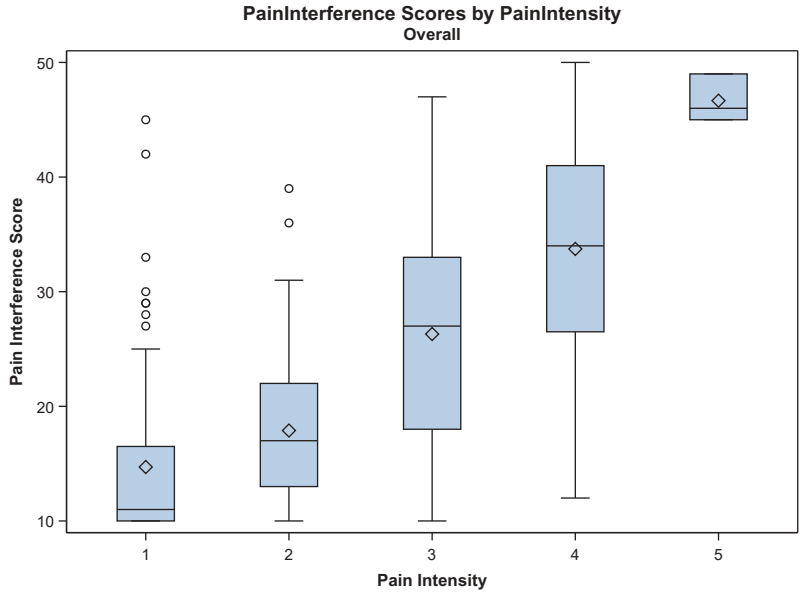

Figure 2. Pain interference scores by pain intensity, overall.

pain intensity and pain interference (Tables 2 and 3). mTBI with associated PTA, exposure to blast or exposure to multiple mTBIs does not appear to confer a greater level of pain intensity or pain interference above the mTBI exposed subjects without those characteristics or the mTBI exposed group as a whole. Consequently, we chose to focus our modelling analyses on the general mTBI exposed group.

Multivariable models

Standard covariate-adjusted regression models and SEMs both showed a significant and consistent effect of mTBI exposure on pain interference and pain intensity. Using the preliminary SEM results, factors that were significant for either outcome were used in the final models to analyse the relationship between mTBI exposure and each pain outcome. In the final model, confounders (site, combat exposure, combat duration, number of controlled blasts and number of uncontrolled blasts), mediators (PTSD, depression, anxiety and sleep difficulty) and covariates (age, gender, time since index injury, arthritis, extra-cranial injury and self-efficacy) were retained. Gender was explored as a potential moderator although no such effect was observed. For each pain outcome, we examined the direct effect of mTBI, the indirect effect of mTBI via its effect on the mediators and the total effect of mTBI (i.e. the sum of the direct and indirect effect) (28,29).

The final model parameter estimates and p-values for total, direct and indirect effects are shown in Table 4. There was a significant total effect ($p < 0.0001$) of mTBI exposure for both pain interference (parameter estimate of 5.29) and pain intensity (parameter estimate of 0.35). While neither model showed a significant direct mTBI effect on outcome (pain interference parameter estimate = 1.58; pain intensity parameter estimate = 0.19), the indirect effects on each outcome were statistically significant (pain interference parameter estimate = 3.71; pain intensity parameter estimate = 0.16). Parameter estimates for each individual factor included in the final models are presented in Figures 3 and 4. These figures also show the directional pathway of assumed effects.

Pain interference outcome

For the pain interference outcome, significant confounders to mTBI effects included combat exposure and number of controlled blasts, with increased combat exposure and fewer controlled blasts both associated with an increased incidence of

Table 2. Pain Interference, Unadjusted Summary Statistics.

Group	N	Mean	Median	Minimum	Maximum	Std Dev	N Miss
TBI Exposed	343	24.24	23.00	10.00	50.00	10.55	25
No TBI	69	17.43	15.00	10.00	43.00	8.17	2
TBI w/ PTA							
with PTA	251	24.36	23.00	10.00	50.00	10.56	21
without PTA	92	23.91	24.00	10.00	49.00	10.59	4
Repetitive TBI (categorical)							
3+ TBIs	131	26.44	27.00	10.00	49.00	10.61	9
1-2 TBIs	212	22.88	21.50	10.00	50.00	10.31	16
Blast Exposure							
1+ TBI from Blast	177	25.92	26.00	10.00	49.00	10.22	11
TBI not from Blast	166	22.46	19.00	10.00	50.00	10.64	14

Pain interference scores range from 10 to 50 points.

Table 3. EQ-5D-5L Levels of Pain or Discomfort, Unadjusted Summary Statistics.

Group	N	No pain or discomfort	Slight pain or discomfort	Moderate pain or discomfort	Severe pain or discomfort	Extreme pain or discomfort
TBI exposed	378	56 (15%)	98 (26%)	166 (44%)	54 (14%)	4 (1%)
No TBI	75	23 (31%)	29 (39%)	17 (23%)	5 (7%)	1 (1%)
TBI w/ PTA						
with PTA	279	37 (13%)	80 (29%)	122 (44%)	36 (14%)	4 (1%)
without PTA	99	19 (19%)	18 (18%)	44 (44%)	18 (18%)	0 (0%)
Repetitive TBI (categorical)						
3+ TBIs	143	18 (13%)	33 (23%)	68 (47%)	21 (15%)	3 (2%)
1-2 TBIs	235	38 (16%)	65 (28%)	98 (42%)	33 (14%)	1 (0%)
Blast Exposure						
1+ TBI from Blast	196	23 (12%)	50 (26%)	83 (42%)	37 (19%)	3 (2%)
TBI not from Blast	182	33 (18%)	48 (26%)	83 (45%)	17 (9%)	1 (1%)

Table 4. SEM.

mTBI Effect1[1]	Pain Interference	Pain Intensity
Total Effect		
Parameter Estimate	5.29	0.35
P-value	<0.0001	0.0022
Direct Effect		
Parameter Estimate	1.58	0.19
P-value	0.1422	0.0961
Indirect Effect		
Parameter Estimate	3.71	0.16
P-value	<0.0001	0.0022

[1] mTBI classified as mTBI or No mTBI

mTBI (combat exposure parameter estimate = 0.01; controlled blasts parameter estimate < −0.01). None of the confounders were significantly associated with pain interference. All mediators (PTSD, depression, anxiety and sleep difficulty) were significant along both paths. MTBI exposed participants were significantly more likely to have each mediating condition for those analysed categorically or greater severity in condition for those analysed using a continuous scale (PTSD parameter estimate = 0.21; depression parameter estimate = 0.18; anxiety parameter estimate = 4.96; sleep difficulty parameter estimate = 2.64), and the presence of each mediating condition also resulted in increased pain interference (PTSD parameter estimate = 1.63; depression parameter estimate = 1.62; anxiety parameter estimate = 0.41; sleep difficulty parameter estimate = 0.39). Covariates significantly associated with pain interference included age (parameter estimate = 0.13), arthritis (parameter estimate = 2.68), extra-cranial injury (parameter estimate = 3.62) and self-efficacy (parameter estimate = −0.24). Participants who are older, have arthritis and/or extra-cranial injury, or who have a lower self-efficacy score have increased pain interference.

Pain intensity outcome

For the pain intensity outcome, significant confounders to mTBI effects included combat exposure and number of controlled blasts, with increased combat exposure and fewer controlled blasts both resulting in an increased incidence of mTBI (combat exposure parameter estimate = 0.01; controlled blasts parameter estimate < −0.01). All mediators (PTSD, depression, anxiety and sleep difficulty) were significant on the path of mTBI to mediator, with mTBI exposed participants being significantly more likely to have each mediating condition (PTSD parameter estimate = 0.22; depression parameter estimate = 0.18; anxiety parameter estimate = 4.88; sleep difficulty parameter estimate = 2.63). Along the path of mediator to pain intensity, only sleep difficulty was significant, with increased sleep difficulties resulting in increased pain intensity (parameter estimate = 0.05). Covariates significantly associated with pain intensity included arthritis (parameter estimate = 0.52) and extra-cranial injury (parameter estimate = 0.37), with participants who have arthritis and/or extra-cranial injury having increased pain intensity.

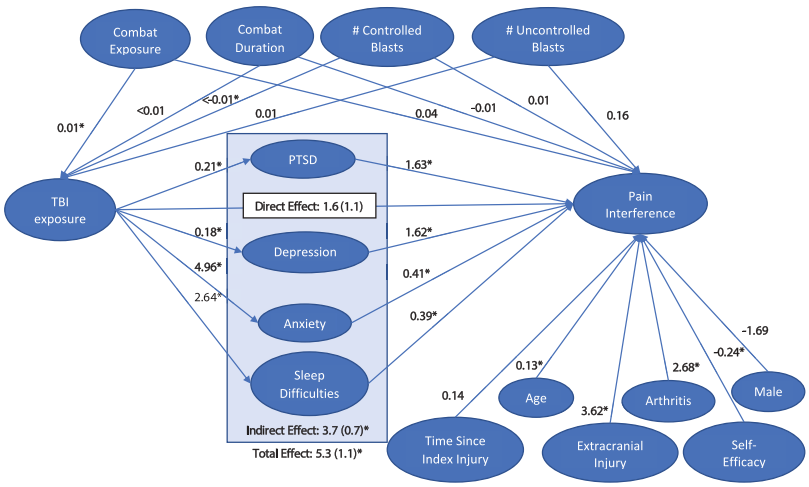

Figure 3. Parameter estimates for pathway analysis of mTBI exposure on pain interference.

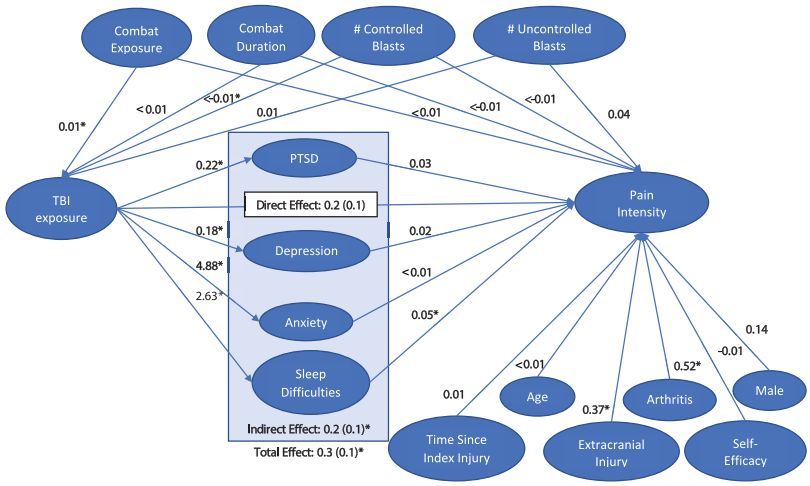

Figure 4. Parameter estimates for pathway analysis of mTBI exposure on pain intensity.

Discussion

Despite the high prevalence of comorbid pain in the population with mTBI, the relationship between these two factors remains poorly characterized. This study examined the effects of mTBI history on pain intensity and interference in OEF/OIF/OND Veterans and SMs. To our knowledge, this study is the first to use SEM to investigate the interaction between mTBI and pain outcomes and to include such an extensive number of covariates and mediators. Our SEMs demonstrate that mTBI has a significant, but indirect, effect on both pain intensity and pain interference. PTSD, depression, anxiety and sleep difficulty, the incidences of which were also significantly higher in the mTBI exposed group, each mediated the relationship between mTBI and pain interference. Sleep was the only mediator that was directly significant along the path to pain intensity, with greater sleep disturbance contributing to more severe pain. In contrast to other studies in the military population, our preliminary analyses did not suggest that, above the mTBI exposed group, repetitive mTBIs, the presence of PTA or blast exposure results in greater pain interference or pain intensity, although future analysis with the complete longitudinal dataset may generate differential results. Our findings implicate mTBI as having a significant association with pain interference and pain intensity, largely due to the indirect effects of the mediators.

The finding that PTSD, sleep disturbance, anxiety and depression mediate the effect of mTBI on pain interference is not surprising given their established associations with chronic pain, which is increasingly viewed as its own distinct neurological disorder (30). There are striking parallels between post-concussion syndrome and chronic pain phenotypes which include greater incidences of comorbid mood disorders, fatigue, sleep disturbance and cognitive deficits (31,32), suggesting a common physiological mechanism. Interestingly, the mood states did not have a similar mediating effect on pain intensity. This suggests mood states are affecting the functional consequences of pain more than the absolute levels of pain.

Alterations in neuronal function, particularly within the Default Mode Network (DMN) and other pain-related neurocircuitry, are another potential mechanism contributing to symptoms of pain after mTBI. The DMN comprises brain structures such as the medial prefrontal and posterior cingulate cortices, hippocampal formation and the precuneus which are shown to have higher levels of activation in resting states in healthy individuals and are disordered in many neurological conditions (33). Alterations in functional connectivity of the DMN following mTBI are well documented (34–36) and could exacerbate or contribute to the development of post-mTBI pain, as aberrant connectivity in the DMN is also strongly associated with chronic pain states (37,38).

Alternatively, or perhaps concordantly, mTBI may result in alterations in neuroendocrine or limbic system function that may contribute to the development of pain. Individuals with chronic pain have been shown to have elevated cortisol levels, smaller hippocampal volume and enhanced phasic pain responses in the parahippocampal gyrus compared to control subjects, suggesting a stress model of chronic pain linked to specific corticolimbic and neuroendocrine features that confer vulnerability to persistent pain states (39). Further research is needed to determine if mTBI may produce subtle alteration of corticolimbic and related neuroendocrine function forming a common maladaptive pathophysiological substrate altering response to stress or 'allostatic load' (40) so as to predispose individuals with mTBI to the development of chronic pain in conjunction with the associated mediators identified in this study.

Limitations of this study are that it is a cross-sectional analysis, which made the inclusion of medication use into our models difficult, and utilizes retrospective diagnosis of mTBI and subjective self-report of pain intensity and interference. The SEMs initially looked at medication as a mediator but it was eliminated it in the final models because the assumed relationship is that mTBI exposure impacts the mediator and then the mediator impacts the outcome of interest, pain in this case. Pain medication usage is more nuanced in that use of pain medication may impact the level of pain someone feels and thus impact the outcome of pain and the use of medication itself is also impacted by the outcome of pain. The CENC study is ongoing, and as longitudinal data are collected on this study cohort, we will be able to appropriately model the cause and effect relationship of pain

interference and intensity and use of pain medication over time. In addition, further collection of additional baseline and follow-up data will allow us to refine our SEMs. To mitigate the limitation of retrospective diagnosis, we used a validated, reliable interview to assess mTBI; this technique systematically queried participants about impaired or loss of consciousness and PTA associated with each PCE reported by the participant (19).

A strength of this study is that the data collection was performed by examiners who were uniformly trained across sites to administer the pain scales and other outcome measures that were largely Common Data Elements (41). Other strengths include the large sample size, the exclusion of participants with non-organic symptom profiles and the use of SEM, which better incorporates potential mediators to differentiate between direct and indirect effects of mTBI on each pain outcome.

Conclusion

Our findings underscore the clinical relevance of assessing comorbid pain interference and pain intensity in Veterans and SMs who may have chronic effects of mTBI. Identifying these comorbidities at early stages of post-deployment could facilitate referral for treatment and mitigate disability.

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Declaration of interest

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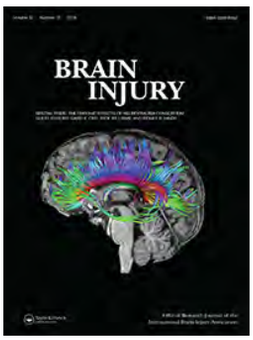
Appendix 5

Do postconcussive symptoms from traumatic brain injury in combat veterans predict risk for receiving opioid therapy for chronic pain?



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Do postconcussive symptoms from traumatic brain injury in combat veterans predict risk for receiving opioid therapy for chronic pain?

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ABSTRACT

Objectives: Opioid therapy is contraindicated in patients with traumatic brain injury (TBI) with neuropsychological impairment, yet guidelines do not consistently predict practice. We evaluated independent risk for initiation of opioid therapy among combat veterans with chronic pain diagnoses and persistent postconcussive symptoms.

Methods: We assembled a retrospective cohort of 53 124 Iraq and Afghanistan veterans in Veterans Affairs (VA) healthcare between October 2007 and March 2015 who received chronic pain diagnoses, completed a Comprehensive TBI Evaluation (CTBIE) and had not received opioid therapy in the prior year. Primary exposure variables were self-reported severe or very severe Emotional, Vestibular, Cognitive and Somatic/Sensory symptoms measured using the Neurobehavioral Symptom Inventory. Outcome measures were initiation of short-term and long-term opioid therapy within the year following CTBIE.

Results: Self-reported severe and very severe postconcussive symptoms predicted initiation of long-term and short-term opioid use for chronic pain in both unadjusted and adjusted analyses. In adjusted analyses, all four postconcussive symptom domains significantly predicted initiation of long-term opioid therapy, with Emotional symptoms being the strongest predictor [ARR = 1.68 (1.52, 1.86)].

Conclusions: Increased opioid prescribing in veterans with self-reported severe persistent postconcussive symptoms indicates a need to educate prescribers and make non-opioid pain management options available for veterans with TBI and neuropsychological sequelae.

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Introduction

Veterans suffer disproportionately higher rates of chronic pain compared to the general population (1); as many as 50% of Iraq and Afghanistan veterans report one or more chronic pain complaints despite their relatively young age (1–3). Traumatic brain injury (TBI) is also common in Iraq and Afghanistan veterans owing to the high incidence of blasts and other combat-related trauma (4,5). Indeed, multiple studies have demonstrated an independent association between TBI and chronic pain, which is most pronounced when TBI is comorbid with mental health problems (2,6).

The Department of Veterans Affairs (VA)/Department of Defense (DoD) clinical practice guidelines for both the management of opioid therapy and TBI caution against using opioids as first-line therapy in individuals with TBI (7,8). This is due to the well-documented cognitive effects of opioids, as well as evidence that opioids exacerbate mental health conditions and substance use disorders, which increase risk for serious adverse clinical outcomes, including opioid overdose (3,9–11). VA administrative data indicate, however, that Iraq and Afghanistan veterans with chronic pain and moderate-to-severe TBI are significantly more likely to initiate long-term opioid therapy for the treatment of chronic pain; the risk increasing threefold in veterans with comorbid TBI, PTSD and depression (12).

Since 2007, the VA has conducted TBI screening for Iraq and Afghanistan veterans on first presentation to VA and after each subsequent deployment (13). Those veterans who screen positive on a first-level screen for TBI are referred for a more in-depth TBI evaluation with a neurologist or other trained clinician. As part of this Comprehensive TBI Evaluation (CTBIE), using the Neurobehavioral Symptom Inventory (NSI) (14), veterans are evaluated for persistent postconcussive symptoms, which have been classified within Emotional, Cognitive, Vestibular and Somatic/Sensory domains (15). Leveraging clinical data from postconcussive symptom evaluation in a large sample of Iraq and Afghanistan veterans, we were able to examine specific TBI-related postconcussive symptom domains in association with initiation of opioid therapy for chronic pain. Given our previous findings of

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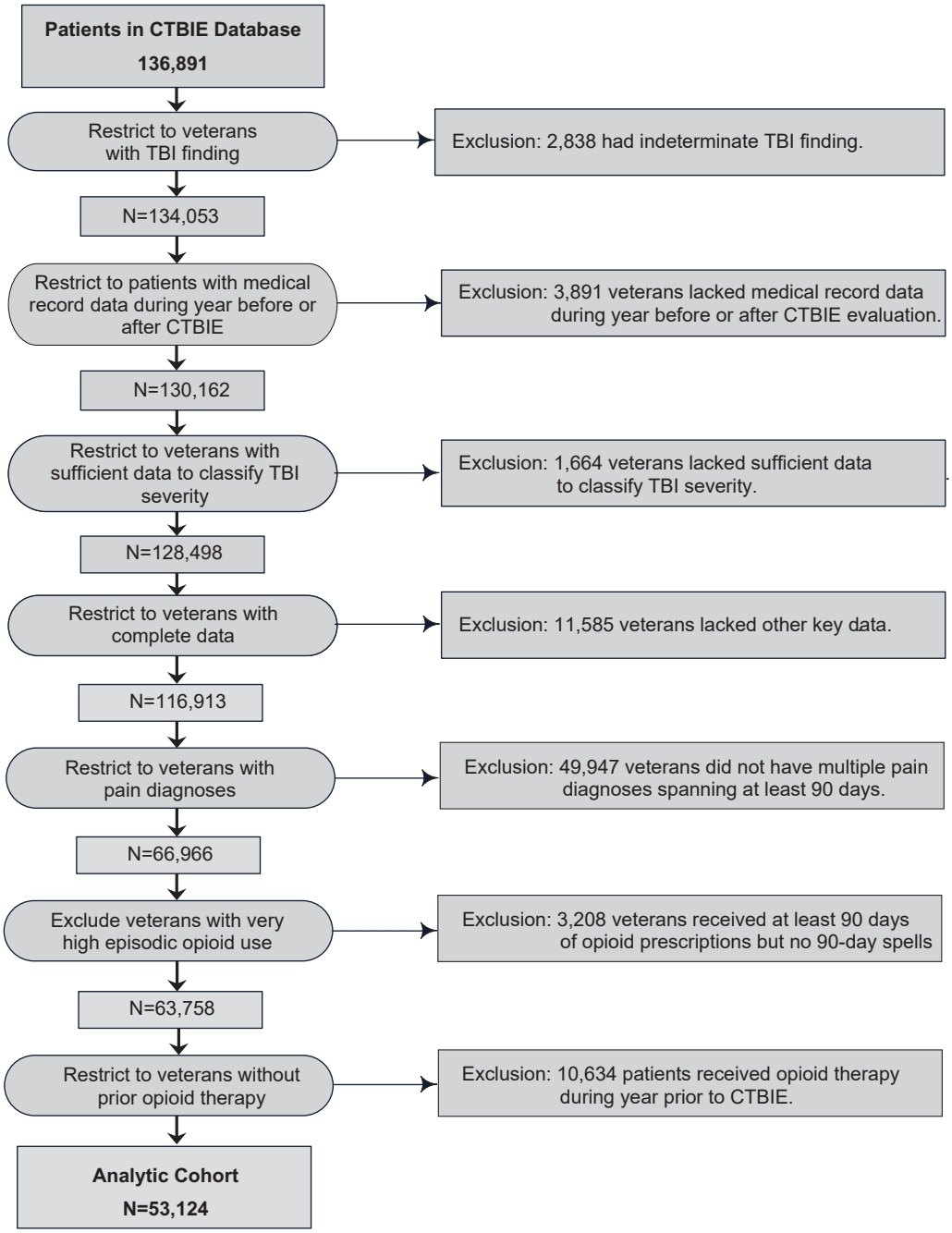

Figure 1. Derivation of the analytic cohort to show predictors of new opioid therapy in Iraq and Afghanistan veterans with chronic pain undergoing the Comprehensive Traumatic Brain Injury Evaluation (CTBIE) and Neurobehavioral Symptom Inventory (NSI).

increased opioid prescribing in veterans with more severe TBI and mental health comorbidity (12), we hypothesized that veterans with more severe neuropsychological and cognitive postconcussive symptoms would be more likely to receive short- and long-term opioid therapy for chronic pain. This is clinically important because initiation of opioid therapy poses substantial risk for exacerbating these persistent postconcussive symptoms, increasing risk for adverse clinical outcomes in an already vulnerable veteran population.

Methods

Data and participants

This retrospective cohort of Iraq and Afghanistan veterans enrolled in VA healthcare was identified using the CTBIE database, an accruing national database of Iraq and Afghanistan veterans who underwent the CTBIE since October 2007. All returning veterans are mandated to undergo screening for deployment-related injuries and possible TBI. Those who screen positive for TBI on first-level

screening are referred for the second-level CTBIE, which includes an extensive clinical history and physical exam performed by a neurologist or other trained licensed clinician, yielding a gold standard clinical diagnosis of TBI, TBI severity, postconcussive symptoms and postconcussive symptom severity (if applicable). Of 136 891 Iraq and Afghanistan veterans in VA healthcare who completed the CTBIE between October 2007 and March 2015, we included those whose TBI status was confirmed by a clinician, had received one or more International Classification of Diseases, Ninth Revision Clinical Modification (ICD-9 CM) diagnostic codes for chronic pain diagnosis, including back, neck, arthritis or joint pain, or headache or migraine pain, in the same location on at least two separate clinical encounters for ≥90 days (10), and had not received opioids in the year prior to CTBIE. The follow-up period was defined as 1 year following the index CTBIE. Our final analytic sample included 53 124 Iraq and Afghanistan veterans. (Figure 1)

We linked CTBIE data to two other VA national databases: (1) the Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn (OEF/OIF/OND) Roster, an administrative database containing basic sociodemographic and military service information of veterans of Afghanistan, Iraq and 'post-surge' veterans; and (2) Corporate Data Warehouse (CDW), which contains clinical information derived from the VA electronic medical record, including the ICD-9 CM diagnoses linked to VA clinical encounters, as well as prescribed opioid and non-opioid pain medications (including dates and quantity of opioids prescribed). The study was approved by the Institutional Review Boards of the University of California, San Francisco and the Research and Development Committee of the San Francisco VA Health Care System.

Measures

Dependent variables

Consistent with our previous work on the role of TBI, PTSD and depression as predictors of initiating opioid therapy(12), prescribing patterns for chronic pain in the 1 year following the CTBIE were categorized as none, short-term opioid therapy or long-term opioid therapy. Short-term opioid therapy was defined as receiving any quantity of opioids less than 90 days during the year following CTBIE, while long-term opioid therapy was defined as being prescribed ≥90 consecutive days of opioid medications during any 110-day period in the year following CTBIE. Patients with episodic patterns of opioid use who had received 90 or more days of opioids, but lacked 90 continuous days of prescribed opioids during the year following CTBIE, were excluded because this was a problematic group to characterize and we had difficulties tracking and validating their opioid use. There were also statistical considerations in that adding a fourth outcome category to the multinomial logistic regression models (see Statistical Analyses below) would have introduced complexity when fitting the models and reduced the precision of risk ratio estimates for the other outcomes which were our primary interest. We included all short- and long-acting oral opioids commonly prescribed for pain on the VA outpatient formulary. We excluded parenteral opioids and opioid replacement therapy for opioid use disorder (i.e. methadone and buprenorphine).

Independent variables

The CTBIE contains the NSI, which is a brief self-report survey covering 22 possible persistent postconcussive neuropsychological and cognitive symptoms after a TBI (13,14). Patients were asked about their symptom severity over the previous 30 days. Each item is represented as a 5-point Likert scale from 0 to 4, with 0 being 'None' and 4 being 'Very Severe'. Notably, a response of 2 indicated 'Moderate' symptoms, which the CTBIE defined as being 'often present, occasionally disrupts my activities; I can usually continue what I am doing with some effort; I am somewhat concerned', while a score of 3 indicated 'Severe' symptoms which were defined as 'frequently present and disrupts activities; I can only do things that are fairly simple or take little effort; I feel like I need help'. 'Very Severe' symptoms were defined as 'almost always present and I have been unable to perform at work, school or home due to this' (15). Following the work of Meterko (16) and Vanderploeg (17), and endorsed by the Defense and Veterans Brain Injury Center (DVBIC) (15), 20 of the 22 symptoms were aggregated into 4 distinct domains: Emotional (fatigue, sleep problems, anxiety, feeling depressed or sad, irritability, and low frustration tolerance); Cognitive (poor concentration, forgetfulness, impaired decision-making and slowed thinking); Vestibular (dizziness, loss of balance, and impaired coordination); and Somatic/Sensory (headaches, nausea, vision problems, light sensitivity, noise sensitivity, numbness or tingling, and changes in taste and/or smell). Two items, loss of appetite and hearing difficulties, which did not correlate with any domain, were omitted from this analysis (17). We calculated domain scores using the mean of the individual items in each domain instead of using the sum, to keep a consistent range for all domains while retaining the original statistical properties. The NSI symptom domains were then dichotomized at 3, which allowed us to compare veterans who averaged a score of severe or very severe (those averaging a score of ≥3) versus those who averaged symptoms less than 3. We initially considered using a lower cut-point of 2, which is widely used (15), which would have defined our outcome as moderate symptoms or worse. We opted to increase the threshold to severe symptoms in light of recent work highlighting the possibility of symptom over-reporting in veterans (18).

The four NSI domains were all highly correlated with one another. The Emotional and Vestibular domains were the pair that was the least correlated, at $r = 0.56$, while the Emotional and Cognitive domains were the pair that was the most strongly correlated, at $r = 0.74$. Due to this high collinearity, we ran separate models for each of the four NSI symptom domains. We did not adjust for diagnoses of TBI, PTSD or

depression, except in sensitivity analyses, because of the very high collinearity with TBI-related neuropsychological symptoms, especially 'feeling sad and depressed' and 'anxiety'. For the sensitivity analyses, veterans with moderate and severe TBI were combined into a single group.

Potentially confounding covariates included: (1) sociodemographic characteristics (sex, age and marital status), as well as race and ethnicity (White, African American, Hispanic/Latino and other); (2) military service characteristics: branch, rank and education, and deployments (single versus multiple); (3) alcohol abuse and dependence (305.00–305.03 and 303) and drug abuse and dependence (305.20–305.93 and 304); (4) self-reported pain disability; and (5) use of non-opioid treatment modalities prior to initiation of opioid treatment (or censoring at end of follow-up). We adjusted for each of these variables because of their documented or theorized association with postconcussive symptoms and opioid prescribing decisions (10,12,19,20). Non-opioid pain treatment modalities were defined as having attended at least one session of physical therapy or recreational therapy and/or having received prescriptions in any of the following classes of non-opioid medications commonly used for chronic pain: non-steroidal anti-inflammatory medications, acetaminophen, anti-epileptic drugs (gabapentin and pregabalin), serotonin norepinephrine re-uptake inhibitors, and selected topical analgesics. The non-opioid pain treatment variable was calculated as the sum of the number of non-opioid therapies prescribed (with physical and/or recreational therapy equivalent to one class). The variable was then categorized as no modalities, one modality or ≥2 modalities. This was entered as a nominal variable in order not to impose any linear assumptions about dose-response.

Statistical analyses

Continuous NSI domain scores were compared across the three levels of opioid use using a non-parametric test for trend, developed by Cusick as an extension of the Wilcoxan Rank-Sum (21). Multinomial (polytomous) logit models were used to model the adjusted relative risks of initiation of short-term or long-term prescription opioid use for chronic pain in the year following CTBIE. These models allowed for the simultaneous estimation of competing outcomes from a single regression model, while making use of the full sample to fit the model (22). We ran four separate sets of models with each set estimating adjusted relative risks for short-term and long-term opioid therapy in association with a single NSI domain (Emotional, Vestibular, Cognitive or Somatic/Sensory). We adjusted initially for sociodemographic characteristics, military service history, and alcohol and drug use disorders. Next, we added an adjustment for self-reported pain disability at baseline. Finally, we added an adjustment for prior use of non-opioid treatment modalities to arrive at our primary set of models. In order to better understand the role of non-opioid treatment modalities, an additional analysis was undertaken to explore the possibility of a temporal trend for

Table 1. Association of sociodemographic and military service characteristics with new prescription opioid use in 53 124 Iraq and Afghanistan veterans in the year following the Comprehensive TBI Evaluation (CTBIE) and Neurobehavioral Symptom Inventory (NSI).

	Total (*N* = 53 124)		No opioid use (*n* = 41 562)		Short-term opioid therapy (*n* = 9794)				Long-term opioid therapy (*n* = 1768)			
	N	(%)	*N*	(%)	*N*	(%)	RR (95% CI)	Pr > |Z|	*N*	(%)	RR (95% CI)	Pr > |Z|
Sex												
Female	3674	6.9%	2852	6.9%	735	7.5%			87	4.9%		
Male	49 450	93.1%	38 710	93.1%	9059	92.5%	0.93 (0.87, 0.99)	0.024	1681	95.1%	1.41 (1.14, 1.74)	0.002
Age at Comprehensive TBI Evaluation												
18–24	8342	15.7%	6421	15.4%	1653	16.9%			268	15.2%		
25–34	27 067	51.0%	21 150	50.9%	4969	50.7%	0.93 (0.88, 0.98)	0.004	948	53.6%	1.07 (0.94, 1.22)	0.312
35–44	11 634	21.9%	9152	22.0%	2077	21.2%	0.90 (0.85, 0.96)	0.001	405	22.9%	1.06 (0.91, 1.23)	0.465
45–54	5295	10.0%	4209	10.1%	958	9.8%	0.91 (0.84, 0.97)	0.007	128	7.2%	0.74 (0.60, 0.91)	0.004
55+	786	1.5%	630	1.5%	137	1.4%	0.87 (0.74, 1.02)	0.091	19	1.1%	0.75 (0.47, 1.18)	0.208
Race and ethnicity												
African American	6940	13.1%	5614	13.5%	1214	12.4%			112	6.3%		
White	30 767	57.9%	23 702	57.0%	5838	59.6%	1.11 (1.05, 1.18)	<0.001	1227	69.4%	2.52 (2.08, 3.05)	<0.001
Hispanic	6777	12.8%	5338	12.8%	1277	13.0%	1.09 (1.01, 1.17)	0.023	162	9.2%	1.51 (1.19, 1.91)	0.001
Other/unknown	8640	16.3%	6908	16.6%	1465	15.0%	0.98 (0.92, 1.05)	0.646	267	15.1%	1.90 (1.53, 2.37)	<0.001
Marital status												
Married	24 307	45.8%	18 853	45.4%	4544	46.4%			910	51.5%		
Never married	26 463	49.8%	20 907	50.3%	4782	48.8%	0.96 (0.92, 0.99)	0.023	774	43.8%	0.78 (0.71, 0.85)	<0.001
Divorced, Widowed, or Other	2354	4.4%	1802	4.3%	468	4.8%	1.06 (0.98, 1.16)	0.168	84	4.8%	0.97 (0.78, 1.20)	0.764
Rank and education												
Enlisted, <College Degree	49 517	93.2%	38 579	92.8%	9235	94.3%			1703	96.3%		
Enlisted, ≥College Degree	1631	3.1%	1329	3.2%	276	2.8%	0.89 (0.80, 0.99)	0.037	26	1.5%	0.45 (0.31, 0.67)	<0.001
Officer, ≥College Degree	1976	3.7%	1654	4.0%	283	2.9%	0.76 (0.68, 0.84)	<0.001	39	2.2%	0.54 (0.40, 0.75)	<0.001
Active Duty or Reserve/National Guard												
National Guard or Reserve	17 015	32.0%	13 414	32.3%	3069	31.3%			532	30.1%		
Active Duty	36 109	68.0%	28 148	67.7%	6725	68.7%	1.04 (1.00, 1.08)	0.073	1236	69.9%	1.10 (1.00, 1.22)	0.055
Branch of service												
Army	38 832	73.1%	30 141	72.5%	7287	74.4%			1404	79.4%		
Air Force	2116	4.0%	1683	4.0%	361	3.7%	0.91 (0.82, 1.00)	0.047	72	4.1%	0.92 (0.73, 1.16)	0.49
Marines	9052	17.0%	7240	17.4%	1596	16.3%	0.93 (0.88, 0.97)	0.003	216	12.2%	0.65 (0.57, 0.75)	<0.001
Navy	3124	5.9%	2498	6.0%	550	5.6%	0.93 (0.86, 1.00)	0.057	76	4.3%	0.66 (0.53, 0.83)	<0.001
Number of deployments												
Single deployment	25 641	48.3%	19 739	47.5%	4973	50.8%			929	52.5%		
Multiple deployments	27 483	51.7%	21 823	52.5%	4821	49.2%	0.90 (0.87, 0.93)	<0.001	839	47.5%	0.82 (0.75, 0.90)	<0.001

changes in use of non-opioid treatment modalities. This was tested using an ordered logit model with the number of prior non-opioid treatment modalities as the outcome and the number of calendar years since 2007 as the sole regressor. Data were prepared using SAS 9.4 (23) and analysed using Stata 14.2 (24).

Results

Of 53 124 veterans who were referred for and completed second-level screening for suspicion of TBI, 9794 (18.4%) initiated short-term opioid therapy and 3.3% initiated long-term opioid therapy. The mean age of the cohort was 32.5 years (S.D. ± 8.5), 93% of veterans were male, 93% had been enlisted with less than a college degree at the time of last deployment, 46% were married, 68% had been deployed from Active-Duty service, 58% were Caucasian, 13% were African American, 12.8% were Hispanic and 16.3% were other or unknown (Table 1).

In unadjusted analyses (Table 1), the risk of either long-term or short-term therapy increased among veterans who were younger and who had served a single deployment. White veterans were most likely to initiate short-term, and especially long-term, opioid therapy, being two and a half times more likely than African American veterans. Veterans who had served as officers or completed college were less likely to receive short-term therapy and much less likely to receive long-term opioid therapy.

In unadjusted analyses, mild TBI was weakly associated with short-term opioid use [RR = 1.17 (1.09, 1.24)] and strongly associated with long-term opioid use [RR = 1.70 (1.47, 1.97)]. Short-term opioid risk was associated with PTSD [RR = 1.31 (1.26, 1.36)], depression [RR = 1.20 (1.16, 1.25)], alcohol use disorders [RR = 1.15 (1.10, 1.20)] and drug use disorders [RR = 1.29 (1.21, 1.36)]. Long-term use was more strongly associated with these covariates: PTSD [RR = 2.32 (2.05, 2.63)], depression [RR = 1.69 (1.54, 1.85)], alcohol use disorders [RR = 1.16 (1.02, 1.30)] and drug use disorders [RR = 1.47 (1.27, 1.70)].

Three quarters of patients received at least one non-opioid treatment prior to initiating opioid therapy and nearly half received at least two modalities. There was a small but statistically significant temporal trend throughout the study period towards increasing numbers of non-opioid treatment modalities ($p < 0.001$). The proportion of patients receiving at least one non-opioid treatment increased from 73.0% in 2008 to 74.8% in 2009, but then increased more gradually to 77.3% in 2014 ($p < 0.001$), the last complete year of data. Use of non-opioid pain treatments prior to initiation of any opioid use – especially two or more modalities – was more predictive of subsequent short-term opioid use [RR = 1.96 (1.86, 2.07)] than long-term use [RR = 1.56 (1.38, 1.76)].

For the full cohort, the continuous NSI domain scores (on a scale from 0 to 4) ranged from a mean score of 1.24 (95% CI: 0.00–2.67) for the Vestibular domain to a more severe score of 2.38 (95% CI: 0.67–3.83) for the Emotional domain. For all four neurocognitive domains, the continuous scores showed a statistically significant trend towards increasing symptoms when comparing opioid groups in order from no opioid therapy to short-term to long-term therapy.

In unadjusted analyses, persistent postconcussive symptoms were consistently more strongly associated with long-

Table 2. Association of mental health diagnoses and neuropsychological symptoms with new prescription opioid use in 53 124 Iraq and Afghanistan veterans in the year following the Comprehensive TBI EVALUATION (CTBIE) and Neurobehavioral Symptom Inventory (NSI).

	Total (N = 53 124)		No opioid use (n = 41 562)		Short-term opioid therapy (n = 9794)				Long-term opioid therapy (n = 1 768)			
	N	(%)	*N*	(%)	*N*	(%)	RR (95% CI)	Pr > |Z|	*N*	(%)	RR (95% CI)	Pr > |Z|
TBI severity (DoD criteria)												
Negative TBI determination	17 277	32.5%	13 704	33.0%	3062	31.3%			511	28.9%		
Mild TBI	30 746	57.9%	24 039	57.8%	5699	58.2%	1.05 (1.01, 1.09)	0.017	1008	57.0%	1.12 (1.01, 1.24)	0.034
Moderate to severe TBI	5101	9.6%	3819	9.2%	1033	10.5%	1.17 (1.09, 1.24)	<0.001	249	14.1%	1.70 (1.47, 1.97)	<0.001
PTSD	36 848	69.4%	28 095	67.6%	7280	74.3%	1.31 (1.26, 1.36)	<0.001	1473	83.3%	2.32 (2.05, 2.63)	<0.001
Depression	22 583	42.5%	17 050	41.0%	4567	46.6%	1.20 (1.16, 1.25)	<0.001	966	54.6%	1.69 (1.54, 1.85)	<0.001
Alcohol use disorders	8457	15.9%	6405	15.4%	1743	17.8%	1.15 (1.10, 1.20)	<0.001	309	17.5%	1.16 (1.02, 1.30)	0.019
Drug use disorders	4319	8.1%	3137	7.5%	989	10.1%	1.29 (1.21, 1.36)	<0.001	193	10.9%	1.47 (1.27, 1.70)	<0.001
Prior non-opioid treatment modalities												
0	12 959	24.4%	11 056	26.6%	1536	15.7%			367	20.8%		
1	16 028	30.2%	12 849	30.9%	2709	27.7%	1.43 (1.35, 1.51)	<0.001	470	26.6%	1.10 (0.96, 1.26)	0.171
2 or more	24 137	45.4%	17 657	42.5%	5549	56.7%	1.96 (1.86, 2.07)	<0.001	931	52.7%	1.56 (1.38, 1.76)	<0.001
Pain disability during past 30 days												
None to mild	11 614	21.9%	9679	23.3%	1756	17.9%			179	10.1%		
Moderate to extreme	41 510	78.1%	31 883	76.7%	8038	82.1%	1.31 (1.25, 1.37)	<0.001	1589	89.9%	2.61 (2.24, 3.05)	<0.001
NSI Vestibular												
None to moderate	50 818	95.7%	39 877	95.9%	9291	94.9%			1650	93.3%		
Severe or very severe	2306	4.3%	1685	4.1%	503	5.1%	1.22 (1.12, 1.32)	<0.001	118	6.7%	1.65 (1.37, 1.97)	<0.001
NSI Somatic/Sensory												
None to moderate	50 796	95.6%	39 876	95.9%	9270	94.6%			1650	93.3%		
Severe or very severe	2328	4.4%	1686	4.1%	524	5.4%	1.26 (1.16, 1.36)	<0.001	118	6.7%	1.65 (1.37, 1.97)	<0.001
NSI Cognitive												
None to moderate	39 511	74.4%	31 356	75.4%	7007	71.5%			1148	64.9%		
Severe or very severe	13 613	25.6%	10 206	24.6%	2787	28.5%	1.17 (1.13, 1.22)	<0.001	620	35.1%	1.62 (1.47, 1.78)	<0.001
NSI Emotional												
None to moderate	35 941	67.7%	28 710	69.1%	6285	64.2%			946	53.5%		
Severe or very severe	17 183	32.3%	12 852	30.9%	3509	35.8%	1.19 (1.15, 1.24)	<0.001	822	46.5%	1.88 (1.72, 2.06)	<0.001

term opioid therapy than with short-term therapy (Table 2). Having severe or very severe postconcussive symptoms in any domain increased risk for short-term opioid therapy by an average of 20%. For long-term opioid therapy, Emotional symptoms were the most strongly predictive [RR = 1.88 (1.72, 2.06] (a nearly 90% increased risk for long-term opioid therapy), while the other domains had similar risks [i.e. RR = 1.62 (1.47, 1.78) for Cognitive symptoms].

Adjusted analyses followed the same pattern in which associations between self-reported severe and very severe neuropsychological and cognitive difficulties were more strongly associated with long-term opioid therapy than with short-term therapy. When models were adjusted for sociodemographic and military service characteristics, drug and alcohol use disorders, baseline pain disability and prior use of non-opioid treatment modalities, risk for short-term use was elevated slightly across NSI domains. The adjusted relative risks of short-term opioid use for each of the domains were not significantly different from each other. The pattern of the point estimates showed that the Cognitive [ARR = 1.11 (1.05, 1.16)] and Emotional [ARR = 1.11 (1.06, 1.16)] domains carried the lowest risk for short-term opioid use and the Vestibular [ARR = 1.17 (1.06, 1.30)] and Somatic/Sensory [ARR = 1.22 (1.10, 1.35)] domains presented a marginally higher risk for receiving short-term opioid therapy.

Similarly, all four domains were predictive of initiating long-term opioid therapy. Estimates for all four domains had overlapping confidence intervals, though the trend was that Emotional symptoms [ARR = 1.68 (1.52, 1.86)] were the most strongly associated while Cognitive symptoms were the least [ARR = 1.44 (1.30, 1.59)]. Vestibular and Somatic/Sensory symptoms had similar risks [i.e. ARR = 1.56 (1.28, 1.90) for Somatic/Sensory symptoms].

Table 3 does not include coefficients for covariates due to space considerations; however, the result from adjusting for non-opioid treatment modalities and race/ethnicity was notable. Having received two or more non-opioid treatment modalities prior to initiation of any opioid therapy was much less strongly associated with initiating long-term opioid therapy than with short-term therapy, with an average adjusted relative risk of 1.40 for long-term opioid therapy and 2.15 for short-term therapy. Another striking finding from the adjusted analyses was the very different risks by ethnic and racial groups. In the fully adjusted models, compared with African American veterans, Caucasian veterans were, on average, approximately 2.8 times more likely to receive long-term opioid medications (95% CI: 2.3, 3.4) and Hispanic veterans were approximately 1.5 times more likely (95% CI: 1.2, 1.9). We examined whether there were racial and ethnic differences in self-reported pain disability. However, on the 0–4 pain disability scale, Caucasian veterans reported marginally lower pain disability, with a mean of 2.10, than African American or Hispanic veterans, with means of 2.26 or 2.20, respectively ($p < 0.001$ for all pairwise comparisons, One-Way ANOVA, Bonferroni correction).

In sensitivity analyses, we explored the impact of our decision not to adjust for TBI, PTSD or depression. Adding TBI adjustments to our fully adjusted models resulted in attenuation of the relative risks of neuropsychological symptoms. Proportionally, the greatest attenuation was observed with Somatic/Sensory symptoms and long-term opioid therapy, in which adding the TBI adjustments reduced the adjusted relative risk for Somatic/Sensory symptoms by 12%, from 1.56 (1.28, 1.90) to 1.50 (1.40, 1.60). Adding further adjustments for PTSD and depression resulted in much greater attenuation proportionally for long-term opioid therapy, ranging from a 34% decrease for the Vestibular domain to a 74% decrease for the Cognitive domain.

Discussion

In this study of over 50 000 combat veterans of Iraq and Afghanistan in VA healthcare, our findings were consistent with our hypothesis in that veterans who reported the most severe persistent postconcussive symptoms were at greatest risk for initiating long-term opioid therapy for chronic pain.

Table 3. Neurocognitive predictors of new prescription opioid use in 53 124 Iraq and Afghanistan veterans in the year following the Comprehensive TBI Evaluation (CTBIE) and Neurobehavioral Symptom Inventory (NSI).

	Unadjusted[a]		Adjusted for sociodemographics, military service, and alcohol and drug use disorders[b]		Further adjustment for baseline pain disability[c]		Further adjustment for non-opioid treatment modalities[d]	
	ARR/95% CI	$p > \|z\|$	ARR/95% CI	$p > \|z\|$	ARR/95% CI	$p > \|z\|$	ARR/95% CI	$p > \|z\|$
NSI Vestibular								
Short-term opioid therapy	1.28 (1.16,1.42)	<0.001	1.27 (1.14,1.41)	<0.001	1.21 (1.09,1.34)	<0.001	1.17 (1.06,1.30)	0.002
Long-term opioid therapy	1.69 (1.40,2.05)	<0.001	1.79 (1.47,2.18)	<0.001	1.59 (1.31,1.93)	<0.001	1.56 (1.29,1.90)	<0.001
NSI Somatic/Sensory								
Short-term opioid therapy	1.34 (1.21,1.48)	<0.001	1.32 (1.19,1.46)	<0.001	1.26 (1.13,1.39)	<0.001	1.22 (1.10,1.35)	<0.001
Long-term opioid therapy	1.69 (1.39,2.05)	<0.001	1.80 (1.48,2.19)	<0.001	1.59 (1.30,1.93)	<0.001	1.56 (1.28,1.90)	<0.001
NSI Cognitive								
Short-term opioid therapy	1.22 (1.16,1.28)	<0.001	1.19 (1.13,1.25)	<0.001	1.14 (1.08,1.20)	<0.001	1.11 (1.05,1.16)	<0.001
Long-term opioid therapy	1.66 (1.50,1.83)	<0.001	1.63 (1.48,1.81)	<0.001	1.46 (1.32,1.62)	<0.001	1.44 (1.30,1.59)	<0.001
NSI Emotional								
Short-term opioid therapy	1.25 (1.19,1.31)	<0.001	1.21 (1.16,1.27)	<0.001	1.16 (1.10,1.21)	<0.001	1.11 (1.06,1.16)	<0.001
Long-term opioid therapy	1.94 (1.76,2.14)	<0.001	1.94 (1.76,2.14)	<0.001	1.72 (1.56,1.90)	<0.001	1.68 (1.52,1.86)	<0.001

[a]Multiple (polytomous) logit models estimated both short-term and long-term opioid use.
[b]Adjusted for age, sex, race/ethnicity, marital status, rank and education, military component, branch of service, number of deployments, alcohol disorders and drug disorders.
[c]Further adjusted for self-rated pain disability.
[d]Further adjusted for prior use of non-opioid treatment modalities (0, 1, or 2 or more).

This is of concern on an individual, health systems and public health level because the prescription of long-term opioids can exacerbate postconcussive symptoms, which, in turn, can worsen physical, cognitive and mental health problems, putting veterans at even greater risk for serious adverse clinical outcomes. While the association between the initiation of short-term opioid therapy and self-reported postconcussive symptoms was less pronounced, the risks were statistically and clinically significant; individuals who start and stop opioids have fluctuating tolerance which can put them at heightened risk for accidents, injuries and overdose. In sum, these higher risk veterans with persistent postconcussive symptoms were prescribed short- and long-term opioid therapy for chronic pain, despite published clinical practice guidelines admonishing against the use of opioids in veterans reporting cognitive and neuropsychological symptoms related to TBI (7,8).

The strongest predictor of long-term opioid therapy for chronic pain was reporting severe postconcussive Emotional symptoms (fatigue, sleep problems, anxiety, feeling depressed or sad, irritability and low frustration tolerance), which was associated with an increased risk of nearly 70%, while Vestibular, Cognitive and Somatic/Sensory postconcussive symptoms were each associated with an increased risk of approximately 50%. These effects were independent of self-reported pain at the time the NSI was administered, other important covariates, as well as previous efforts to control pain through non-opioid treatment modalities. Prior research demonstrates that among Iraq and Afghanistan war veterans diagnosed with chronic pain, those with comorbid PTSD (which shares many of the postconcussive Emotional symptoms), were significantly more likely to be prescribed opioids, exhibit prescription opioid misuse and be at heightened risk for serious adverse clinical outcomes related to opioids (10). Veterans with high emotional distress related to PTSD, TBI and other mental health conditions most often present to primary care providers (PCPs) for pain management. PCPs are not typically trained to manage complex chronic pain nor deployment-related mental health problems, including TBI and postconcussive symptoms, and may default to prescribing opioids to mitigate their patients' distress and de-escalate struggles around pain management. Unfortunately, prescribing opioids in the context of chronic pain, mental health conditions and postconcussive symptoms can result in worsening chronic pain conditions, psychosocial functioning, and ultimately lead to ruptures in patient and provider communication and relationships (3,25,26).

Neuropsychological or cognitive difficulties in this population were likely amplified by the high prevalence of comorbid diagnoses. While this entire cohort was evaluated based on suspicion of TBI, the high prevalence of PTSD and depression undoubtedly plays a significant role. Considering the overlap between the postconcussive symptoms and TBI, PTSD and depression, we deliberated whether to adjust for these and opted to relegate those adjustments to sensitivity analyses. When adding adjustments for TBI to models that already accounted for sociodemographics, military service, alcohol and drug use disorders, self-reported pain disability and use of non-opioid treatment modalities prior to initiation of opioid use, the TBI adjustment resulted in very little attenuation for the relative risks of the neuropsychological symptoms, however. Adding further adjustments for depression and PTSD resulted in much greater attenuation. This is consistent with previous findings on the major role of PTSD and depression in neuropsychological and cognitive impairments, and the lesser role of TBI (27,28).

The adjustments for prior use of non-opioid treatment modalities had very interesting effects on the models. The use of non-opioid treatment modalities was very strongly correlated with opioid initiation, yet inclusion in these models resulted in negligible attenuation of the adjusted relative risks for the neuropsychological measures. Of note, the use of non-opioid treatment modalities prior to opioid initiation was much more strongly associated with short-term therapy than with long-term therapy. Although this study was not set up to investigate the role of non-opioid treatment modalities in mitigating the risk of long-term opioid therapy, this observation suggests that initial treatment using non-opioid treatment modalities might protect against progression from short-term to long-term opioid therapy. Of note, however, among the long-term opioid group, one-fifth had not received any non-opioid pain management modalities prior to long-term opioid therapy, which is not concordant with VA guidelines that recommend a trial of non-opioid pain medication prior to the initiation of opioid therapy. Furthermore, the temporal trend towards increased prior use of non-opioid treatment modalities was very gradual. From 2009 to 2014, the proportion of veterans across the full cohort who received no alternative treatments only decreased from 25.2% to 22.7%.

Racial and ethnic differences in long-term opioid use were very striking, even after adjusting for self-reported pain disability, medical services utilization and previous use of non-opioid treatment modalities. Other recent studies have also found that Caucasian veterans were more likely to receive prescription opioids in VA. In a study of Iraq and Afghanistan veterans who had received an ICD-9 coded diagnosis for TBI during VA fiscal years 2010–2012, Caucasian veterans were nearly 70% more likely to initiate long-term opioid treatment than non-Caucasian veterans (19). Other VA studies have observed similar racial and ethnic disparities in opioid prescribing, but to a much lesser degree (20,29). Our study design was not set up to address this particular question, and VA has known limitations regarding the quality of race and ethnicity data(30), which could explain the varying effect sizes. In addition, the medical record data analysed in this study cannot elucidate underlying reasons for these prescribing differences, such as whether veterans from minority groups might have had different preferences about opioid medications or whether clinicians might have been less attuned to their pain – social psychological explanations for the latter possibility have been explored using other research methodologies (31–35). While lower opioid prescribing may in itself be advantageous for ethnic and racial minorities, the concern, as Burgess and colleagues have pointed out, is that

differences in opioid prescribing could indicate the persistence of broader ethnic and racial disparities in pain management (29,36–39).

This study has limitations that should be considered in interpreting the results. Importantly, data generated from the NSI were based on subjective patient self-report data. A range of studies has compared the role of subjective and objective impairments (18,28,40,41). Frequently, veterans report subjective neurocognitive complaints that do not meet thresholds of impairment on objective measures. Recent work has investigated over-reporting of symptoms and psychometric techniques have been developed to address the absence of an internal validity scale on the NSI (18,41,42), although this work focuses on the NSI as a whole and does not address the specific Emotional, Vestibular, Cognitive or Somatic/Sensory domains. To address this potential problem, we increased the threshold for the self-reported dichotomous outcome from symptoms that were moderate or worse to symptoms that were severe or very severe. In addition, the adjustment for baseline pain disability was also based on patient self-report which might be expected to follow a similar pattern of over-reporting. If true, our adjustment in multivariable analyses might mitigate bias from over-reporting. Furthermore, the NSI was only assessed at one point in time after multiple years had elapsed since deployment-related injuries. A recent study that focused on the Cognitive domain of the NSI found that persistent postconcussive symptoms were fairly stable over time, however, after several years had passed since the incident (40). Nevertheless, had the NSI been administered to this cohort at multiple time points, we could have pursued longitudinal analyses to understand with greater precision the clinical impact of opioid medications on neuropsychological or cognitive functioning over time relative to baseline. We plan to continue this line of research by exploring proxy follow-up measures for these neuropsychological or cognitive symptoms – in particular, adverse outcomes such as accidents, injuries and overdoses. Another limitation is our lack of understanding as to why some providers appeared to deviate from published guidelines for the management of TBI in prescribing their patients opioids as VA administrative data cannot capture the nuances of clinical judgement for individual patients. Finally, VA databases do not include services received outside the VA system that are not reimbursed by VA. VA clinicians are now encouraged to document health services and medications that veterans receive outside VA, including over-the-counter medications and pain management activities such as yoga and Tai Chi, but these are not yet captured systematically.

Conclusions

Despite the well-known risks of prescribing opioid medications to patients who report neuropsychological and cognitive difficulties, as well as national guidelines that admonish against this practice, this study found a strong and consistent association of increased risk for opioid prescribing in this patient population that was independent of self-reported pain disabilities, other important covariates and prior efforts to treat patients with alternative pain modalities. Providers who care for veterans or other patients who report persistent TBI-related postconcussive symptoms should be supported in their use of non-opioid pain management strategies as these appeared to protect against progression from short-term to long-term opioid use.

Declaration of interest

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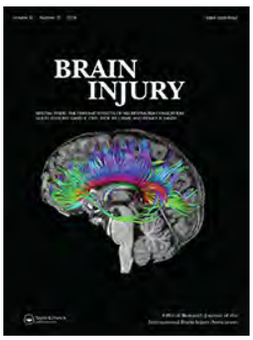
Appendix 6

Pilot investigation of a novel white matter imaging technique in Veterans with and without history of mild traumatic brain injury



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Pilot investigation of a novel white matter imaging technique in Veterans with and without history of mild traumatic brain injury

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ABSTRACT

Objective: The objective of this study is to assess utility of *in vivo* myelin imaging in combat Veterans with and without history of mild traumatic brain injury (mTBI). We hypothesized that those with history of mTBI would have lower myelin water fraction (MWF), a marker of myelin integrity and content, than those without, and lower MWF would be associated with worse speeded attention/processing speed.

Research design: Combat Veterans ($N = 70$) with ($n = 42$) and without history of mTBI ($n = 28$) underwent neuroimaging including a novel myelin-sensitive magnetic resonance imaging technique (multicomponent-driven equilibrium single-pulse observation of T1/T2; mcDESPOT) and comprehensive neuropsychological assessment.

Results: There were no group differences in MWF using a region-of-interest approach. An exploratory analysis applying limited spatial constraints, however, revealed significantly more 'potholes' (clusters of low MWF) in Veterans with history of mTBI compared to those without. Lower MWF across several ROIs was associated with worse performance on a speeded attention task across groups.

Conclusion: Veterans in the post-acute period following mTBI showed limited and spatially heterogeneous MWF changes and myelin integrity was significantly related to processing speed. This preliminary evidence for usefulness of mcDESPOT in combat Veterans with history of mTBI warrants future research to determine mcDESPOT's relative utility compared to techniques such as diffusion tensor imaging.

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Introduction

Traumatic brain injury (TBI) has long been characterized as a disorder of white matter (1–4), with white matter abnormalities likely underlying objective cognitive changes following TBI (5). White matter is particularly vulnerable to disruption from rapid acceleration and deceleration forces and secondary neurometabolic cascades after TBI (6,7), and this disruption can occur even after mild forms of neurotrauma (8,9). However, the relationship between white matter changes and mild TBI (mTBI) is complicated and less well characterized. Traumatic axonal injury (TAI) is common after mTBI (10) and can continue into the post-acute period after injury in humans (11). Conventional neuroimaging modalities (e.g. computerized tomography and structural magnetic resonance imaging [MRI]) are not appreciably sensitive to detect small clusters of damaged axons that result from TAI (12). As a consequence, there have been few structural imaging findings associated with mTBI, and by definition, significant imaging findings are absent following mTBI (13). However, as standard neuroimaging is less sensitive to microstructural axonal injuries and myelin pathology, this dearth of findings may not be surprising. New imaging techniques that provide improved sensitivity to axonal and more specifically myelin injury may provide important new insight into the pathology and pathogenesis of mTBI.

Myelin comprises about 35% of the dry weight of an adult human brain (14), accounting for a major proportion of white matter. Animal studies have demonstrated widespread myelin loss following TBI (15,16) with progressive white matter atrophy up to 1 year post-injury (17). Myelin damage, especially in the corpus callosum, may ensue from the neurometabolic cascade that occurs after diffuse shear tissue strains both acutely and chronically after TBI (18,19) and likely causes reciprocal damage to the axon (20,21). Despite this, the role of myelin pathology is understudied in TBI but likely plays a significant role in the pathophysiology following mTBI (22,23).

Alterations in white matter integrity (WMI) are significantly associated with post-concussive symptoms (more severe symptoms in those with greater white matter damage) (24–28) and can predict neurobehavioural outcome (29–31). Performance on tests of complex attention/working memory or set-shifting, which require speeded processing, is one of the most common cognitive difficulties observed post-acutely after a single (32–35) or multiple

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mTBIs (36–38). Myelin changes likely compromise the integrity of the axon, which may be the mechanism affecting neuronal signalling and subsequent cognitive function after mTBI (39,40), particularly the slowed processing speed commonly experienced following TBI (41,42). Rodent models have demonstrated changes in cognitive tasks and myelin integrity of the corpus callosum and cingulum months post-injury, and to an even greater degree after repetitive blast-related mTBI (22,43–45). Although difficulties in speeded attention and working memory are hallmarks of both TBI and commonly co-occurring psychiatric disorders, such as post-traumatic stress disorder (PTSD) and depression, myelin changes have not been strongly implicated in white matter changes seen in mental health conditions alone (46). Therefore, the relationship between myelin integrity and speeded attention and working memory would only be expected in those with history of TBI, not psychiatric disorders.

Advanced neuroimaging techniques such as diffusion tensor imaging (DTI) have shown promise in detecting subtle changes in WMI (47–49). Using DTI after mTBI, investigators have detected evidence of long-lasting changes in white matter tracts critical for processing speed, which is required for attention and working memory function (5,50). However, inconsistent relationships to injury, cognitive, and emotional symptoms and difficulty interpreting DTI measures are notable limitations of this imaging modality (51–52). Therefore, examining *in vivo* imaging of myelin may hold promise as a more specific and quantitative metric of changes following mTBI.

A recently developed neuroimaging method, termed multi-component-driven equilibrium single-pulse observation of T1 and T2 (mcDESPOT) (53,54), examines myelin water fraction (MWF) as an *in vivo* metric of myelin integrity and content. It has been more widely used in demyelinating conditions such as multiple sclerosis (55) and in neurodevelopmental studies (56) but has yet to be broadly applied to mTBI. The only two other known studies to examine MWF in individuals following concussion produced conflicting results. A small sample (n = 10) of concussed athletes was found to have reduced MWF values at 2 weeks post-injury (relative to pre-injury scans) in the corpus callosum, posterior thalamic radiation, corona radiata, superior longitudinal fasciculus, and internal capsule (52). However, MWF values were restored to pre-injury values at 2-month follow-up. The other recently published study showed generally higher MWF in the mTBI (n = 12) versus control group (n = 10) at 3 months post-mTBI (57). However, both investigations were limited to sports concussion and did not explore neurocognitive variables.

Therefore, we sought to expand the nascent work in this area and more fully explore the relationship between mTBI and myelin integrity *in vivo* by examining MWF via mcDESPOT imaging in a sample of well-characterized combat Veterans both with and without history of mTBI in the post-acute period following injury. The study will also evaluate relationships between MWF and neurocognitive performance. We hypothesize that Veterans with history of mTBI will have lower MWF values than those without and that objective performance on measures of processing speed/speeded attention will be significantly related to MWF.

Methods

Procedure

Participants were recruited from the Veterans Affairs San Diego Healthcare System (VASDHS) and from various Veterans centres at local community colleges and universities. All participants were administered the Mini-International Neuropsychiatric Interview 7.0 (MINI (58)) to assess for PTSD and other mental health disorders, the Virginia Commonwealth University (VCU) retrospective concussion diagnosis interview (rCDI (59)) to assess for TBI history, various symptom self-report measures, and a comprehensive neuropsychological assessment of cognitive functioning across a variety of domains including attention, processing speed, verbal and visual memory, and executive function. Trained research associates administered all interviews, neuropsychological tests, and self-report measures. Additionally, participants underwent a MRI scan lasting approximately 1.5 h. All procedures were approved by the Institutional Review Board of the VASDHS and all participants provided informed consent prior to participating in the study.

Participants

Participants included 70 Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn Veterans, ages 18–50, with a history of combat exposure as determined by a score of 2 or more on the Deployment Risk and Resilience Inventory, Section D: Combat Experiences (DRRI-2 (60)). Participants were in one of two groups: history of mTBI (n = 42) or no history of TBI (n = 28). Exclusionary criteria for this study included a history of moderate or severe TBI (13), a diagnosis of bipolar disorder or dementia, active psychotic disorder or substance dependence, suicidal attempt or intent within the last month, and contraindications to MRI. Veterans were included with or without other common comorbid mental health disorders (i.e. PTSD, depression, anxiety) due to the high rate of comorbidities in this population.

On average, Veterans in this study were 33.86 years old (SD = 6.21) and had 15.04 years of education (SD = 1.60). The sample was 91.4% male, 57.1% Caucasian, 8.6% African-American, 7.1% Asian, 2.9% Native Hawaiian or Pacific Islander, 8.6% American Indian or Alaska Native, and 22.9% Other/not reported, with 35.7% identifying as Hispanic or Latino. Those with history of mTBI reported a median number of 2.00 (IR = 2.0) lifetime mTBIs and 1.00 (IR = 1.0) blast injury with a median loss of consciousness (LOC) of 2.0 min (IR = 9.5) and median post-traumatic amnesia (PTA) of 2.5 min (IR = 14.0). More generally, 69% reported presence of LOC and 76.2% reported presence of PTA resulting from one or more of their lifetime mTBIs. All those in the mTBI group were in the post-acute phase following injury and were tested an average of 6.6 years (range: 8.4 months–21 years) post-mTBI. Of those in the mTBI history group, 11.9% had a diagnosis of generalized anxiety disorder (GAD), 83.3% had a

diagnosis of major depressive disorder (MDD), and 52.4% had a diagnosis of PTSD. Of those with no mTBI history, 17.9% had a diagnosis of GAD, 64.3% had a diagnosis of MDD, and 60.7% had a diagnosis of PTSD.

Measures

Diagnostic interviews

The MINI (58) is a brief structured interview used to assess for the major psychiatric disorders of the DSM-5. The VCU retrospective concussion diagnostic interview, blast (rCDI-B) and general (rCDI-G) (59) versions were used to identify and explore possible concussive events and to determine TBI history and severity.

Neuropsychological tests

All subjects were administered a comprehensive neuropsychological battery. Tests of memory included the Brief Visuospatial Memory Test—Revised (61) and the California Verbal Learning Test—Second Edition (CVLT-II (62)). The digit span, coding, and symbol search subtests of the Wechsler Adult Intelligence Scale—Fourth Edition (WAIS-IV (63)) and the Paced Auditory Serial Addition Test (PASAT (64)) were used to measure speeded attention and processing speed. The PASAT, digit span subtest of WAIS-IV, and trail making subtest of the DKEFS also were included for measures of attention. The reading subtest of the Wide Range Achievement Test—Fourth Edition (WRAT4 (65)) was used as a measure of premorbid intellectual functioning. Participants with WRAT4 scaled scores below 80 were excluded. Lastly, the Test of Memory Malingering (TOMM (66)) was used as a performance validity test. Participants who scored below the standard cut-off on TOMM Trial 2 (n = 4) were excluded from all analyses involving cognitive variables.

Self-report questionnaires

The PTSD Checklist-5 (67) was used to measure symptoms of PTSD. It is a 20-item self-report questionnaire on which participants rate the extent to which they have been bothered by each symptom in the past month, ranging from 0 (*not at all*) to 4 (*extremely*). The Patient Health Questionnaire-9 (68) is a 9-item self-report questionnaire used to measure symptoms of depression within the past 2 weeks. Section D of the Deployment Risk and Resiliency Inventory (DRRI-2 (60)) was administered to determine combat exposure, which was defined as a score of >1 on any of the 17 items assessing exposure to wartime stressors.

Imaging acquisition

The majority of neuroimaging scans were performed within 30 days of neuropsychological assessment. One participant was scanned 64 days after neuropsychological assessment due to scheduling conflicts. The scans were conducted at the University of California, San Diego School of Medicine's Center for Functional MRI. MRI data were acquired on a General Electric Discovery MR750 3.0 T scanner equipped with an *in vivo* eight-channel head coil. mcDESPOT data were collected using the multi-component relaxation time imaging method comprising a series of spoiled gradient recalled echo (SPGR) (TR = 5.3, TE = min full, flip angle = 18, field of view = 24.0) and T2/T1-weighted balanced steady-state free precession (SSFP) data acquired over a range of flip angles (71). An inversion-recovery prepared SPGR scan (TR = 5.3, TE = min full, flip angle = 5, field of view = 24.0) was acquired to allow correction for transmit magnetic field (B1) inhomogeneities; and the SSFP phase 180 (TE = min full, flip angle = 60, field of view = 24.0) and SSFP phase 0 (TE = min full, flip angle = 60, field of view = 24.0) were acquired with two phase-cycling patterns to permit correction for main magnetic field (B0) off-resonance effects. The total mcDESPOT acquisition time was under 12 min. An annual software upgrade from DV24 to DV25 supplied by General Electric took place during the study. A total of 19 participants in the sample were scanned before and a total of 51 participants were scanned after this upgrade occurred. The software upgrade was coded as a dummy variable (1 = before upgrade, 2 = after upgrade) and included as a covariate in all analyses.

Imaging processing

Following acquisition, the mcDESPOT downsampled target image for each participant underwent N3 bias field correction using the advanced normalization tool. Skull and other non-brain signals were then removed using the brain extraction tool. The mcDESPOT target and myelin volume fraction images for each participant were linearly registered to the MNI152 T1 2 mm resolution standard brain template using FMRIBI's Software Library (FSL) linear image registration tool. All target images were further non-linearly registered using FMRIB's non-linear image registration tool (FNIRT) to the MNI152 T1 2 mm template. FSL's Automated Segmentation Tool (FAST) was used to segment the registered target image into white matter, grey matter, and cerebrospinal fluid. The resulting transforms from FNIRT were applied to the white matter masks and to the myelin volume fraction maps. FSL's *fslmaths* was then used to multiply the segmented white matter masks by the region-of-interest (ROI) masks to ensure that only white matter voxels were included. The ROI masks were defined by the ICBM-DTI-81 stereotaxic white matter parcellation map, which includes white matter tract labels that were created by hand segmentation of a standard-space average of diffusion MRI tensor maps from 81 participants (69). mcDESPOT myelin volume fraction maps were multiplied by the binary parcellation maps to obtain average values for each ROI. Based on prior studies (52), ROIs examined in the present study were the corpus callosum, cingulate, and internal capsule.

To better capture the spatially heterogeneous distribution of white matter damage in mTBI, a secondary 'pothole' analysis was also implemented (70). Potholes represent white matter regions with values significantly lower than what may be expected in healthy controls and has been shown to be sensitive to mTBI in prior studies (71,72). First, a normative template was generated based on the MNI-registered MWF volumes of the

control participants using tools available within FSL. The results of FSL FAST were used to restrict the calculation of these terms to white matter voxels common to each control participant. Volumes representing the mean and standard deviation for each voxel in the white matter were calculated using *fslmaths*. Next, for each mTBI participant, their white matter map from FAST was used to restrict their MWF volume to white matter and a *z*-score map was generated by subtracting the control mean MWF and dividing by the control SD MWF. The resultant *Z*-maps were thresholded at −3 and the FSL programme *cluster* was used to label contiguous voxels below this threshold. These contiguous below threshold clusters represented the potholes. In addition, three different minimum cluster sized thresholds (≥1, ≥5, and ≥10 mm^3) were used to explore whether the sensitivity of this pothole analysis was related to spatial extent of the identified clusters. The sum of the potholes was used as the measure of reduced myelin integrity. Because of the nature of the analyses and the strength of the scanner upgrade effect, only participants scanned post-upgrade (27 with no history of TBI and 24 with history of TBI) were included in the pothole analyses.

Statistical analyses

All variables were assessed for normality and outliers (defined as greater than three standard deviations above or below the mean of the sample). In addition to MWF values, group differences were assessed with regard to demographic, self-report, and cognitive variables. False discovery rate (FDR) correction was applied to the ROI group differences analyses (73). Due to non-normal distribution, non-parametric Mann–Whitney *U* tests were used to assess group differences in average number of abnormal MWF clusters (MWF less than $z = -3$) for each cluster size (≥1, ≥5, and ≥10 mm^3).

Cognitive variables included were four measures of processing speed and speeded attention/working memory (WAIS-IV symbol search, coding, digit span total, and PASAT 3—second version) given established relationships between myelin and these variables in the literature (74–76). To determine whether the relationships were unique to processing speed and speeded attention/working memory, two measures of memory were also included (CVLT-II long delay free recall, BVMT delayed recall). To assess for significant relationships between cognitive variables and MWF, correlations were conducted between MWF in the three ROIs (corpus callosum, cingulate, and internal capsule) and the cognitive variables. Significant ROIs were then submitted to linear regressions in which the MWF variable was the dependent variable, and group, scanner upgrade, and each cognitive variable were entered as independent variables. Because raw scores were used for all analyses, any demographic variables significantly related to the cognitive variables were included in the analyses.

Results

All demographic, cognitive, and ROI-based MWF variables were normally distributed and did not have outliers. Groups

Table 1. Descriptives and group differences on demographic, injury, psychiatric, performance validity, and cognitive measures.

	Total sample		No mTBI history		mTBI history			
Demographics	Mean (SD) or %	*n*	Mean (SD) or %	*n*	Mean (SD) or %	*n*	*X* or *F*	*p*
Age	33.86 (6.21)	70	35.00 (6.60)	28	33.10 (5.90)	42	1.59	0.211
% Male	91.4	70	89.3	28	92.9	42	0.273	0.601
Years of education	15.04 (1.60)	70	15.32 (1.42)	28	14.86 (1.71)	42	1.42	0.237
% Hispanic	36.2	70	42.9	28	31.7	42	1.06	0.590
% Caucasian	57.1	70	50.0	28	61.9	42	0.972	0.324
% MDD	75.7	70	64.3	28	83.3	42	3.32	0.069
% GAD	14.3	70	17.9	28	11.9	42	0.486	0.486
% PTSD	56.5	70	60.7	28	52.4	42	0.473	0.492
TBI injury								
% with LOC presence	–	–	–	–	69.0	42	–	–
% with PTA presence	–	–	–	–	76.2	42	–	–
No. of mTBIs	–	–	–	–	3.33 (3.06)	42	–	–
% with blast history	–	–	–	–	50.0	42	–	–
Years since last mTBI	–	–	–	–	6.58 (4.44)	42	–	–
Psychiatric								
PCL-5	28.59 (18.00)	70	24.96 (17.35)	28	31.00 (18.22)	42	1.91	0.171
PHQ-9	9.65 (6.91)	70	8.48 (7.86)	28	10.40 (6.20)	42	1.28	0.262
Performance validity								
TOMM Trial 2	49.16 (3.35)	70	49.64 (1.34)	28	48.83 (4.18)	42	0.980	0.326
% Trial 2 <45	5.7	70	3.6	28	7.1	42	0.398	0.528
Cognitive								
WRAT4 reading	103.66 (10.42)	70	106.04 (10.95)	28	102.007 (9.87)	42	2.48	0.120
WAIS-IV digit span total	28.20 (5.54)	66	28.63 (4.59)	27	27.90 (6.15)	39	0.276	0.601
WAIS-IV symbol search	34.54 (8.20)	66	36.37 (7.74)	27	33.28 (8.36)	39	2.31	0.133
WAIS-IV coding	68.82 (14.70)	66	70.04 (15.65)	27	67.97 (14.16)	39	0.311	0.579
PASAT	38.45 (7.04)	66	39.59 (6.39)	27	37.67 (7.43)	39	1.20	0.278
CVLT-II LDFR	11.69 (2.62)	66	12.04 (2.79)	27	11.45 (2.50)	39	0.796	0.376
BVMT-R DR	9.79 (1.59)	66	9.78 (1.67)	27	9.79 (1.56)	39	0.002	0.966

Note: X or *F* indicates chi-square or ANOVA values of no mTBI history group versus mTBI history group. All cognitive measures, excluding the WRAT4 Reading, are raw scores. Group differences between cognitive measures were obtained via ANOVA while excluding for participants with TOMM Trial 2 scores below standard cut-off. %: Per cent; SD: standard deviation; mTBI: mild traumatic brain injury; MDD: major depressive disorder; GAD: generalized anxiety disorder; PTSD: post-traumatic stress disorder; WRAT4: Wide Range Achievement Test Fourth Edition scaled score; LOC: loss of consciousness; PTA: post-traumatic amnesia; PCL-5: Post-traumatic Stress Disorder Symptom Checklist for DSM 5; PHQ-9: Patient Health Questionnaire; TOMM: Test of Memory Malingering Trial 2; CVLT-II: California Verbal Learning Test—Second Edition; LDFR: long delay free recall; WAIS-IV: Weschler Adult Intelligence Scale—Fourth Edition; PASAT: Paced Auditory Serial Addition Test 3—second version total correct; BVMT-R DR: Brief Visuospatial Memory Test—Revised Delayed Recall.

did not differ with regard to demographic (age, gender, years of education) or psychiatric variables (all $ps > 0.05$). Groups also did not differ with regard to cognitive variables when excluding those with poor performance validity (all $ps > 0.05$). Please refer to Table 1 for full descriptive information and analyses. No significant relationships were identified between MWF and psychiatric self-report measures. Veterans with history of mTBI had higher MWF than those without history of mTBI in several ROIs when controlling for scanner upgrade; however, no significant group differences remained when applying FDR correction (see Table 2). All results were thresholded at a FDR-corrected p-value of less than 0.05.

A Mann–Whitney test indicated that the total number of pothole clusters at a z-score threshold of −3 was greater for those with a history of mTBI (median = 2.00) than for those without a history of mTBI (median = 0.00), $U = 162.0$, $p = 0.001$. However, this difference was only significant for the smallest cluster size (1 mm^3). Groups did not significantly differ in the total number of pothole clusters at a z-score threshold of −2 or at a z-score threshold of −2.5 for any cluster size (see Table 3).

Significant positive correlations between the PASAT and MWF were identified within the cingulum [right cingulate gyrus ($r = 0.363$, $p = 0.003$), left cingulate gyrus ($r = 0.340$, $p = 0.005$)], corpus callosum [genu ($r = 0.374$, $p = 0.002$), body ($r = 0.351$, $p = 0.004$), splenium ($r = 0.343$, $p = 0.005$)], and internal capsule [right anterior limb ($r = 0.363$, $p = 0.003$), left anterior limb ($r = 0.346$, $p = 0.004$), right posterior limb ($r = 0.366$, $p = 0.003$), left posterior limb ($r = 0.342$, $p = 0.005$), right retrolenticular limb ($r = 0.337$, $p = 0.006$), left retrolenticular limb ($r = 0.331$, $p = 0.007$)] (see Figure 1). No other significant correlations between cognitive and MWF variables were identified (see Table 4). PASAT performance was significantly correlated with the WRAT4 reading scaled score ($r = 0.454$, $p < 0.001$), but was not associated with age, gender, or symptoms of PTSD or depression ($ps > 0.05$). Thus, the WRAT4 reading scaled score was included in all regressions, along with the scanner upgrade and the TBI group variable.

When submitted to linear regression, PASAT was significantly associated with MWF in the genu ($\beta = 0.343$, $p = 0.001$) and body ($\beta = 0.321$, $p = 0.002$) of the corpus callosum, the right anterior limb ($\beta = 0.329$, $p = 0.002$) and right posterior limb ($\beta = 0.318$, $p = 0.002$) of the internal capsule, and the right ($\beta = 0.311$, $p = 0.003$) and left ($\beta = 0.314$, $p = 0.002$) cingulum (see Table 5) when controlling for WRAT4, TBI group, and scanner upgrade variables.

Discussion

In this pilot study using mcDESPOT imaging to examine *in vivo* myelin integrity and pathology in combat Veterans with and without a history of mTBI, there were no significant MWF differences between combat Veterans with and without history of mTBI using a traditional ROI approach once applying FDR correction. However, in partial support of our hypothesis, a secondary analytic approach applying limited

Table 2. ROI-based group differences in myelin water fraction measures.

	No mTBI history		mTBI history			
Myelin water fraction	Marginal mean (SE)	*n*	Marginal mean (SE)	*n*	*F*	Uncorrected *p*
Genu of CC	0.1735 (0.0249)	28	0.1672 (0.0313)	42	3.99	0.050
Body of CC	0.1632 (0.0286)	28	0.1556 (0.0359)	42	4.18	0.045
Splenium of CC	0.1731(0.0265)	28	0.1636 (0.0366)	42	3.73	0.058
R cingulum	0.1471 (0.0267)	28	0.1414 (0.0382)	42	5.60	0.021
L cingulum	0.1419 (0.0265)	28	0.1381 (0.0372)	42	6.91	0.011
R anterior limb of IC	0.1603 (0.0294)	28	0.1534 (0.0372)	42	3.86	0.054
L anterior limb of IC	0.1666 (0.0297)	28	0.1596 (0.0368)	42	3.83	0.054
R posterior limb of IC	0.1723 (0.0290)	28	0.1633 (0.0385)	42	4.06	0.048
L posterior limb of IC	0.1756 (0.0289)	28	0.1674 (0.0371)	42	4.01	0.049
R retrolenticular part of IC	0.1829 (0.0286)	28	0.1731 (0.0376)	42	3.87	0.053
L retrolenticular part of IC	0.1834 (0.0283)	28	0.1738 (0.0366)	42	3.86	0.054

Note: F indicates ANCOVA values of no mTBI history group versus mTBI history group. *P*-values reported are uncorrected. No significant group differences remained thresholded at a false discovery rate-corrected *p*-value <0.05.

Group differences for myelin water fraction measures were obtained via ANCOVA and controlled for scanner upgrade. SE: Standard error; mTBI: mild traumatic brain injury; CC: corpus callosum; IC: internal capsule; R: right; L: left.

Table 3. Group differences in MWF potholes by cluster size and *z*-threshold.

		Total sample		No mTBI history		mTBI history			
z-Threshold	Cluster size (mm^3)	Median (SD)	*n*	Median (SD)	*n*	Median (SD)	*n*	*U*	*p*
−2.00	1	16.00 (34.18)	51	16.00 (39.71)	27	15.00 (26.61)	24	301.5	0.671
−2.00	5	1.00 (8.85)	51	1.00 (10.38)	27	1.00 (6.67)	24	295.5	0.583
−2.00	10	0.00 (4.77)	51	0.00 (5.99)	27	0.50 (2.77)	24	301.5	0.645
−2.50	1	4.00 (9.60)	51	2.00 (10.42)	27	4.50 (8.78)	24	259.9	0.220
−2.50	5	0.00 (1.98)	51	0.00 (2.36)	27	0.00 (1.50)	24	273.5	0.255
−2.50	10	0.00 (0.999)	51	0.00 (1.19)	27	0.00 (0.761)	24	299.5	0.465
−3.00	1	1.00 (3.08)	51	0.00 (3.01)	27	2.00 (3.01)	24	162.0	0.001*
−3.00	5	0.00 (0.717)	51	0.00 (0.456)	27	0.00 (0.924)	24	291.5	0.332
−3.00	10	0.00 (0.440)	51	0.00 (0.192)	27	0.00 (0.612)	24	322.0	0.911

Note: *$p < 0.05$; *U* indicates Mann–Whitney test values for the group with history of mTBI versus the group without history of mTBI. SD: Standard deviation; mTBI: mild traumatic brain injury.

Table 4. Correlations between myelin water fraction in regions of interest and cognitive measures.

	PASAT	Digit span	Symbol search	Coding	BVMT-R delay	CVLT-II LDFR
Genu of CC	0.374*	0.106	0.046	0.033	0.003	−0.133
Body of CC	0.351*	0.085	−0.007	0.007	−0.054	−0.102
Splenium of CC	0.343*	0.093	−0.017	−0.005	−0.053	−0.125
Left anterior limb of IC	0.346*	0.067	−0.005	0.008	−0.019	−0.117
Right anterior limb of IC	0.363*	0.080	0.004	0.024	−0.001	−0.103
Left posterior limb of IC	0.342*	0.059	−0.002	0.002	−0.066	−0.094
Right posterior limb of IC	0.366*	0.093	0.005	0.016	−0.045	−0.082
Left retrolenticular limb of IC	0.331*	0.074	−0.035	−0.035	−0.053	−0.125
Right retrolenticular limb of IC	0.337*	0.088	0.001	0.000	−0.032	−0.100
Right cingulum (cingulate gyrus)	0.363*	0.119	0.015	0.038	−0.052	−0.103
Left cingulum (cingulate gyrus)	0.340*	0.076	0.012	0.031	−0.046	−0.116

Note: *$p < 0.05$. All cognitive measures are raw scores. CC: Corpus callosum; IC: internal capsule; PASAT: Paced Auditory Serial Addition Test 3—second version total correct; CVLT-II: California Verbal Learning Test—Second Edition; LDFR: long delay free recall; BVMT-R DR: Brief Visuospatial Memory Test—Revised Delayed Recall.

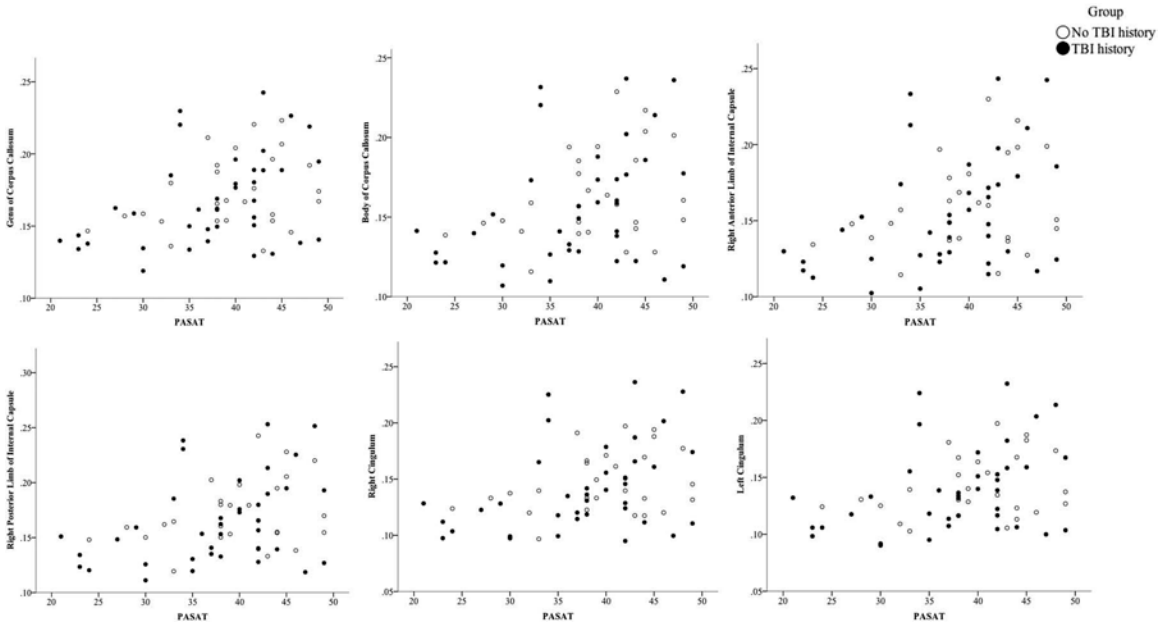

Figure 1. Scatter plots of myelin water fraction in regions-of-interest and Paced Auditory Serial Addition Test (PASAT) raw scores in Veterans with and without history of mild traumatic brain injury.

spatial constraints revealed significantly more clusters of low MWF in Veterans with history of mTBI compared to those without. Also consistent with our hypothesis, MWF values were significantly related to objective auditory processing speed scores such that better performance on a speeded attention task was significantly related to higher MWF. This relationship between myelin integrity and processing speed was present regardless of mTBI group membership.

Our failure to find MWF differences between groups using a traditional ROI approach is consistent with the study conducted by Wright and colleagues showing acute but not persistent decrements in MWF following sports concussion and findings from animal models showing myelin changes in closed-skull impacts in mice up to 6 weeks post-injury (52). Although non-significant after applying FDR correction, the ROI analyses reported here were opposite of the hypothesized direction (higher MWF in the group with mTBI history compared to those with no mTBI history). Despite examination of different ROIs, the present results are consistent with Spader and colleagues who reported both higher and lower MWF values in athletes with history of concussion compared to those without (57).

The conflicting and even null findings may be a function of ROI-based analyses that may not be optimal to identify the multifocal, subtle, and diffuse white matter changes that are typical following mTBI. MWF differences between mTBI groups were identified using a less spatially constrained pothole analysis, though only small clusters of low MWF were significantly different between mTBI and no mTBI groups. Similarly, Jorge and colleagues also reported null findings when using voxel based DTI analyses but significant differences between those with and without TBI when using pothole analyses (72). This emerging data suggest limited and spatially heterogeneous white matter and specifically myelin changes in humans in the post-acute period following mTBI. The current preliminary data further highlight that persisting white matter damage following mTBI may be sparse and difficult to detect using a traditional ROI approach. Future research is certainly warranted to more fully characterize changes in myelin after mTBI.

This is the first study to evaluate relationships between MWF and objective cognitive measures in those with a history of mTBI. The significant relationships reported herein

Table 5. Linear regression analyses: relationship between myelin water fraction and PASAT in ROIs.

	Genu of CC				Body of CC				Right anterior limb of IC				Right posterior limb of IC				Right cingulum				Left cingulum			
	β	df	R^2	*p*	*β*	df	R^2	*p*	*β*	df	R^2	*p*	*β*	df	R^2	*p*	*β*	df	R^2	*p*	*β*	df	R^2	*p*
		61	0.52			61	0.54			61	0.49			61	0.56			61	0.53			61	0.55	
WRAT4 reading	−0.26			0.011*	−0.28			0.006*	−0.25			0.019*	−0.25			0.012*	−0.22			0.031*	−0.28			0.006*
Group	0.21			0.039*	0.21			0.036*	0.21			0.044*	0.2			0.037*	0.24			0.016*	0.27			0.007*
Scanner upgrade	0.68			<0.001*	0.71			<0.001*	0.66			<0.001*	0.72			<0.001*	0.7			<0.001*	0.72			<0.001*
PASAT	0.34			0.001*	0.32			0.002*	0.33			0.002*	0.32			0.002*	0.31			0.003*	0.31			

Note: *$p < 0.05$. Group = no mTBI history versus mTBI history. CC: Corpus callosum; IC: internal capsule; mTBI: mild traumatic brain injury; WRAT4: Wide Range Achievement Test Fourth Edition Reading scaled score; PASAT: Paced Auditory Serial Attention Test 3—second version total correct.

between an objective measure of speeded attention and MWF in the corpus callosum, internal capsule, and cingulum are consistent with studies in cognitively healthy adults who found myelin content predicts processing speed (75,77). MWF has been shown to correspond to timed cognitive measures in clinical populations such as multiple sclerosis (78), and other measures of white matter and myelin integrity have demonstrated associations with speeded attention and executive functioning tasks (73, 79). Although the relationship between processing speed and myelin was not unique to those with a history of mTBI in our sample, it still holds relevance as a contributor to cognitive slowing and further exploration of additional etiologic contributions to this relationship is warranted.

There are several limitations to the present study. The sample was largely male and thus should be replicated with a female sample, as sex differences have been noted broadly within the TBI literature (80) and human and animal model studies show some sex differences in myelin during development (81) and following injury (82). The study was cross-sectional and therefore inferences regarding causality cannot be drawn. Information regarding TBI history was collected via self-report, which can lead to inaccurate injury details due to recall bias and alteration or LOC at the time of injury. However, this is a common limitation in TBI, particularly among Veteran samples. Finally, the sample was small and therefore results should be interpreted with much caution. Nonetheless, the relationship between MWF and auditory processing speed was robust and dissociated from other cognitive (i.e. memory) functions and warrants further exploration.

Overall, our findings in this preliminary study of Veterans in the post-acute period following mTBI showed limited and spatially heterogeneous MWF changes distally from the mTBI event and contribute to the growing body of evidence by demonstrating that myelin content is related to an objective cognitive measure of speeded attention in combat Veterans. This relationship between *in vivo* myelin and a behavioural symptom suggests that examining myelin integrity after mTBI using mcDESPOT MWF has the potential to serve as an objective biological marker of myelin damage associated with persistent symptoms after mTBI. At present, however, more research is needed to examine longitudinal and/or causal relationships between TBI and myelin. Additionally, a 'pothole' analysis showed more regions of deficient myelin in the group with history of mTBI compared to those without, further supporting the idea that white matter injury after mTBI is subtle and spatially heterogeneous and may require novel methods to detect. Further research of myelin content after mTBI would provide a foundation for more accurate injury severity grading, prognosis, and therapeutic opportunities.

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Declaration of interest

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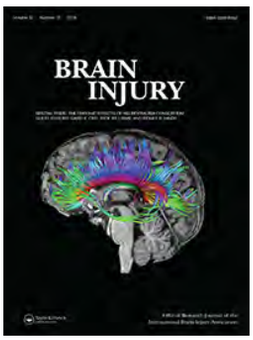
Appendix 7

Higher exosomal phosphorylated tau and total tau among veterans with combat-related repetitive chronic mild traumatic brain injury



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Higher exosomal phosphorylated tau and total tau among veterans with combat-related repetitive chronic mild traumatic brain injury

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ABSTRACT

Objective: The objective of the study is to measure plasma and exosomal levels of tau, phosphorylated tau (p-tau), and amyloid beta (Aβ) in Veterans with historical mild traumatic brain injury (mTBI) and chronic neuropsychological symptoms.

Methods: Tau, p-tau, Aβ40, and Aβ42 were measured by ultrasensitive immunoassay in plasma and exosomes from 195 Veterans enrolled in the Chronic Effects of Neurotrauma Consortium Multicenter Observational Study. Protein biomarkers were compared among groups with and without mTBI with loss of consciousness (LOC) or post-traumatic amnesia (PTA), and also in those with and without repetitive (≥3) mTBI (rTBI) compared to those with 0 (TBI-neg) and 1–2 mTBI.

Results: There were no differences in measures of plasma and exosomal protein levels among mTBI with LOC or PTA, mTBI with alteration of consciousness only or TBI-neg. Exosomal tau and exosomal p-tau were elevated in rTBI compared to those with 2 or fewer mTBIs and TBI-neg ($p < 0.05$). Elevations of exosomal tau and p-tau significantly correlated with post-traumatic and post-concussive symptoms, with exosomal tau also relating specifically to cognitive, affective, and somatic post-concussive symptoms ($p < 0.05$).

Conclusion: rTBI is associated with elevations of exosomal p-tau and exosomal tau, suggesting that blood-based exosomes may provide a peripheral source of informative, centrally derived biomarkers in remote mTBI and that rTBI may contribute to chronic neuropsychological symptoms.

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Introduction

Chronic neuropsychological symptoms following traumatic brain injury (TBI) in military personnel are common and can include global disability, neurobehavioural impairment, and psychological comorbidities (1–5). There is strong evidence that secondary injury processes including neuronal, inflammatory, and vascular injuries contribute to long-term TBI symptoms and deficits (6,7). It is hypothesized that TBI and subsequent pathogenic processes induce neurons, glial, and endothelial cells to release molecules into the extracellular space that transit into both blood and cerebrospinal fluid (8–11). Release of these molecules may occur through breakdown of cell membranes (e.g. neurodegeneration) or via secretion as part of intercellular communication (e.g. cytokines or angiogenic factors); both may contribute to the development and maintenance of chronic symptoms and deficits following TBI (12–16).

Blood-based brain-derived proteins have received much attention for their potential as diagnostic and/or prognostic TBI biomarkers (17,18). Extracellular vesicles (EVs) and other nanoparticles are increasingly being studied for their potential for improving diagnosis, prognosis, and treatment of various diseases, including acquired neurological disorders. Exosomes form when an endocytic, multi-vesicular body (MVB) fuses with the plasma membrane, and the MVB's contents are exocytosed (19). After release into the extracellular milieu, exosomes fuse with other cells, and their cargo (e.g. RNA, enzymes, peptides) is transferred to the recipient cell where it can participate in signalling processes, thereby orchestrating cellular responses. Exosomes are released from all types of brain cells, such as neurons, oligodendrocytes, astrocytes, and microglia (20).

Because they readily cross the blood brain barrier and can be isolated from peripheral circulation, exosomes also hold promise in TBI research (21–23). Within the membrane of exosomes are various proteins present from the cell of origin, allowing identification and separation of central nervous system (CNS)-derived exosomes from the peripheral circulation (21,24,25). The cargo of exosomes reflects the microenvironment of the site of exosome production and may be informative as a noninvasive measure of CNS metabolism and function (26–28).

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Blood-based tau and amyloid beta (Aβ) are candidate biomarkers because of the pivotal role they play in TBI-associated neurodegenerative disorders. There is evidence linking remote TBI to dementia (29,30), suggesting that TBI may place individuals at risk for chronic neurocognitive disorders, such as Alzheimers disease, chronic traumatic encephalopathy, and frontotemporal dementia (13). Pathologically, each is associated with neuronal loss and accumulations of abnormal protein deposits, especially tau, p-tau, and Aβ (31). Tau is a neuronal structural protein that regulates microtubules and stabilizes neuronal axons (32). Abnormally phosphorylated tau forms paired helical filaments and aggregates into the neurofibrillary tangles observed in these neurodegenerative disorders (32). Aβ is a cleavage product of amyloid precursor protein with both neuroprotective and neurotoxic effects as it also aggregates in neurodegenerative disorders when normal clearance does not keep pace with production (33). In the only clinical study of exosomes in TBI, higher exosomal tau was observed in former professional American football players and was linked to cognitive deficits (34). Exosomes have been studied in preclinical models of acute TBI and other neurocritical care disorders (e.g. stroke; spinal cord injury) (20,23,28,35–41), but there remains a critical gap in the knowledge surrounding the role of exosomes and blood-based proteins as biomarkers in remote mild TBI (mTBI) and their relationship to chronic TBI-like symptoms and outcomes.

In this study, we examine plasma and exosomal levels of tau, p-tau, Aβ40, and Aβ42 in 3 cohorts: (1) 98 Veterans with remote mTBI associated with loss of consciousness (LOC) or post-traumatic amnesia (PTA), (2) 52 Veterans with remote mTBI with alteration of consciousness (AOC) without LOC or PTA, and (3) 45 Veterans without a history of TBI (TBI-neg). We also compared Veterans with repetitive (≥3) mTBI (rTBI) to those without repetitive (≤2) mTBI. We measured levels of these candidate TBI-related biomarkers and compared the results to TBI characteristics (number and aetiology) and clinical outcomes. We hypothesize that biomarker profiles in plasma and exosomes would relate to mTBI exposure as well as chronic neuropsychological symptoms.

Methods

Study design

This study utilized an observational design with interim cross-sectional analysis of participants enrolled in Chronic Effects of Neurotrauma Consortium (CENC) Multicenter Observational Study, a longitudinal study of mTBI among post-9/11 era Veterans and Service Members (SM) with combat exposure. Details of the overarching study have been previously described (42).

Participants

CENC Study 1 participants were recruited from four Veteran Affairs Medical Centers (Richmond, VA; Tampa, FL; Houston, TX; San Antonio, TX) focusing on post-9/11 era SMs and Veterans who were combat-deployed and suffered possible concussive events (PCE) and are diagnosed with a spectrum of mTBI exposures (ranging from no events to multiple combat-related mTBI). Exclusion criteria included the following: (1) history of moderate or severe TBI as defined by either (a) initial Glasgow Coma Scale < 13, (b) coma duration > 0.5 h, (c) PTA duration > 24 h, or (d) traumatic intracranial lesion on head computerized tomography, or (2) history of (a) major neurologic disorder (e.g. stroke, spinal cord injury), (b) major psychiatric disorder (e.g. schizophrenia) with major defined as resulting in a significant decrement in functional status or loss of independent living capacity. Notably, post-traumatic stress disorder (PTSD) and mood disorder were not considered exclusionary. For these analyses, the primary independent variable was mTBI history as determined and measured below.

Determination of TBI

Potential concussive event identification and TBI diagnoses

This study's structured interview process entailed screening for all PCEs during military deployments and across the entire lifetime, including childhood, using a modification of the Ohio State University TBI Identification instrument (43). Each PCE identified is then interrogated to determine whether or not it was a true clinical mTBI via a detailed structured interview, the Virginia Commonwealth University retrospective Concussion Diagnostic Interview (VCU rCDI) (44). Each VCU rCDI renders a preliminary TBI diagnosis of either mTBI with LOC/PTA, mTBI without LOC/PTA, or not mTBI (TBI-neg) through an embedded algorithm using the structured interview data and based on the Department of Defense and Department of Veterans Affairs/VA common definition of mTBI (45). Every preliminary TBI diagnosis is reviewed and vetted against the unstructured free text portion of the interview, and against any available medical documents recorded in proximity to the event (i.e. first responder, emergency department, or in-theatre documentation). Using this process, the site principal investigator confirms or overrides every preliminary mTBI diagnosis to yield the final diagnosis. The event is also assessed for TBI severity to ensure eligibility (any severity greater than mild excluded from this study). If any doubt remains on TBI diagnosis, the event is adjudicated by a central diagnosis committee consisting of national experts in TBI.

Time since index event

Based on responses from the PCE and TBI structured interviews, an index key event and date were established for every participant. Given the military focus of this study, if any diagnosed mTBI was sustained during combat deployment, the most severe one is considered the index event. If no TBIs occurred during combat deployment, then the most severe post-deployment mTBI becomes the index event. Alternatively, if both deployment and post-deployment TBI history was entirely negative, then a predefined 'no TBI' (or TBI-neg) index date is assigned using the self-identified most severe PCE during combat deployment.

Procedures for determining mTBI groups

The lifetime mTBI diagnostic process described above led to two main mTBI groups, positive versus negative history. Positive mTBI histories were further classified as follows: (1) mTBI with at least one mTBI with LOC/PTA; (2) mTBI with AOC only and without LOC/PTA. We also undertook a comparison of those with and without repetitive TBIs by undertaking the following comparisons: (1) repetitive (≥3) mTBI (rTBI), (2) only 1–2 mTBIs, and (3) TBI-neg. We also compared those participants with and without blast exposure, irrespective of TBI designation.

Neuropsychological symptom measures

Post-concussive symptom severity was assessed using the Neurobehavioural Symptom Inventory (NSI). The NSI is a 22-item assessment with a three-factor structure (somatic/sensory, affective, and cognitive) with higher total score indicating greater symptom burden (46). Symptom validity was assessed using the NSI Validity-10 scale. The NSI Validity-10 scale is an embedded measure of distorted or embellished symptom profile. The NSI has a high internal consistency (total alpha = 0.95; subscale alpha = 0.88–0.92) and reliability (r = 0.88–0.93) (47).

The Patient Health Questionnaire Depression Scale (PHQ-9) was used to measure symptoms of depression, with higher scores indicating greater symptom severity. The PHQ-9 is a nine-item self-administered tool that is half the length of many other depression measures, has comparable sensitivity and specificity, and consists of the actual nine criteria upon which the diagnosis of DSM-IV (and DSM-V) depressive disorders is based (48).

Symptoms of PTSD were assessed by the PTSD Checklist Military Version (PCL-M), resulting in a score of 0–80, with higher scores indicating greater symptom burden. PCL is widely used in military and Veterans populations and has high reliability and validity (49,50).

Samples from 195 CENC Study 1 subjects were selected from the CENC database for this biomarker discovery analysis: 98 with mTBI with LOC or PTA, 52 with mTBI with AOC only without LOC or PTA, and 50 without a history of TBI based on participants who had plasma available in the CENC Biorepository, had given permission for their analysis and complete clinical data available for correlation.

Laboratory methods

Exosome isolation from human plasma

Exosomes were isolated from 0.5 ml of frozen human plasma containing ethylene diamine tetraacetic acid (EDTA) by using ExoQuick (System Biosciences). Briefly, after sample thawing, thrombin was added to each sample and incubated at room temperature (RT) for 5–10 min, with mixing. Samples were then centrifuged at 10,000 rpm for 5 min and the supernatant was transferred into a clean tube for exosome isolation. Exoquick solution (System Biosciences, Inc., Mountainview, CA) was added to thrombin-treated plasma samples. Resulting solutions were incubated for 30 min at 4°C then centrifuged at 1500×g for 30 min. After centrifugation, the supernatant was aspirated and the exosome pellet was resuspended in 500 µL PBS, followed by incubation of 30 min.

To lyse exosomes, each tube received equal amounts of M-PER mammalian protein extraction reagent (Thermo Scientific, Inc., Rockford, IL), containing three times the suggested concentrations of protease and phosphatase inhibitors. These suspensions were then stored at −80°C or assayed for biomarker concentrations using the SIMOA™. Extracted exosome and human plasma were subjected to TSG101 (human tumour susceptibility gene 101 protein) enzyme-linked immunosorbent assay test as manufacture instructed (Cosmo Bio USA, CA, USA).

Protein quantification

All analyses were conducted utilizing site-specific Simoa HD-1 analyser instruments together with a single lot of Simoa pTau 181 Discovery Kit (Quanterix, Lexington, MA; cat 102656) and Simoa Neuro 3 Plex Advantage Kit (Quanterix, Lexington, MA; cat 101995). The instrument transferred two replicates from each well into sample cuvettes. Specifically, the coefficient of determination R^2 is above 99%. The coefficient of variation (CV) of back-calculated concentrations is ≤ 15%. Data presented includes exosomal p-tau and tau, and plasma tau, Aβ40 and Aβ42, as they met quality control standards, with average CVs of 0.126, 0.132, 0.087, 0.062, and 0.061 respectively. Measurements of exosomal Aβ40 and Aβ42 were either undetectable or the CV was over 20% in more than half the samples, and thus data were not of sufficient quality to be included in the analyses.

Statistical analyses methods

Descriptive statistics for all demographic and clinical variables were calculated using SPSS Statistics (IBM SPSS Inc., Chicago, IL; Table 1). Comparisons were made between the three groups using chi-square for categorical variables, analysis of variance (ANOVA) for continuous variables. For biomarker analyses, ANOVA models were used to compare first: mTBI with LOC/PTA, mTBIs with AOC only, and TBI-neg. We also correlated those with and without rTBI by undertaking the following comparisons: (1) rTBI, (2) only 1–2 mTBIs, and (3) TBI-neg. We also compared those with and without blast exposure. As above, if homogeneity of variance could not be assumed, the more robust Welch's test was used. p-Values <0.05 were considered significant after adjustment for multiple comparisons using Bonferroni correction for multiple comparisons. Lastly, we used Pearson correlations to examine relationships between biomarkers and symptoms of PTSD, depression, and neurobehavioural symptoms.

Results

Demographic and clinical characteristics

The demographic and clinical characteristics of the 195 participants used in this analysis are described in Table 1. The mean age of this predominately male (85%) sample was 40 years (±10.73). Comparisons between cases of mTBI with LOC/PTA (n = 98), mTBI with AOC only (n = 52), and TBI-neg (n = 45) were carried out. Among participants reporting TBI (n = 150), 37% (n = 56) reported ≥3 mTBI (rTBI). Participants with any TBI, reported greater symptoms of PTSD and depression compared

Table 1. Baseline demographics and clinical characteristics.

Characteristic	Study group: mTBI with PTA or LOC (n = 98)	mTBI without PTA or LOC (n = 52)	No TBI (n = 45)	Significance	p-Value
Age, mean (SD) (year)	41.05 (10.65)	37.90 (10.36)	40.20 (11.18)	$F_{2,\ 192} = 1.5$	0.231
Male, no. (%)	85 (86.7)	43 (82.7)	39 (86.7)	$\chi^2 = 0.501$	0.778
Education, no. (%)					
High school graduate or GED	11 (11.2)	7 (13.5)	5 (11.1)	$\chi^2 = 0.759$	0.944
Some college or technical training	44 (44.9)	25 (48.1)	19 (42.2)		
College graduate or higher	43 (43.9)	20 (38.5)	21 (46.7)		
Number of TBI, mean (SD)	2.8 (1.8)	1.9 (1.7)	0.1 (0.6)	$F_{2,\ 192} = 47.47$	**0.000**
Number of blast TBI, mean (SD)	0.9 (1.0)	0.5 (0.8)	0.0 (0.1)	$F_{2,\ 192} = 19.26$	**0.000**
Number of general TBI, mean (SD)	1.9 (1.5)	1.4 (1.3)	0.1 (0.4)	$F_{2,\ 192} = 33.16$	**0.000**
Years since first TBI, mean (SD)	19.1 (11.8)	18.6 (11.8)	21.2	$F_{2,\ 147} = 0.05$	0.952
Years since last TBI, mean (SD)	9.0 (7.4)	12.3 (10.4)	5.3	$F_{2,\ 147} = 2.70$	0.071
PHQ-9 total, mean (SD)	9.9 (6.6)	8.8 (5.8)	5.6 (5.8)	$F_{2,\ 190} = 7.46$	**0.001***
PCL-M total, mean (SD)	32.4 (21.2)	28.0 (16.7)	18.7 (17.9)	$F_{2,\ 189} = 7.60$	**0.001****
NSI, mean (SD)					
NSI total	31.3 (17.4)	28.8 (13.7)	17.0 (15.4)	$F_{2,\ 190} = 12.40$	**0.000***
Somatic	8.3 (5.3)	7.3 (4.4)	3.8 (4.6)	$F_{2,\ 190} = 13.24$	**0.000***
Affective	11.3 (6.3)	10.7 (4.9)	7.2 (5.9)	$F_{2,\ 191} = 7.98$	**0.000***
Cognitive	6.2 (4.0)	6.4 (3.7)	3.6 (3.5)	$F_{2,\ 191} = 8.24$	**0.000***
Vestibular	3.0 (2.6)	2.5 (2.2)	1.2 (1.9)	$F_{2,\ 191} = 8.92$	**0.000***

Traumatic brain injury, TBI; post-traumatic amnesia, PTA; loss of consciousness, LOC; General Equivalency Diploma, GED; Patient Health Questionnaire, PHQ-9; PTSD Checklist-Military Version, PCL-M; Neurobehavioral Symptom Inventory, NSI.

Note: * significance between controls and TBI cases (with PTA\LOC) AND controls and TBI cases (without PTA\ LOC); **significance between controls and TBI cases (with PTA\LOC) only.

to controls who are TBI-negative (ps < 0.01). Total NSI symptoms, as well as the subgroupings were significantly higher in those with TBI compared to TBI-neg (ps < 0.05). Those with rTBI also had greater symptom of PTSD, depression and neurological symptoms, compared to those with 1–2 mTBIs as well as TBI-neg (Table 2).

Biomarker comparisons

In the initial group analyses of cases of mTBI with LOC/PTA, mTBI with AOC only, and controls without TBI, there were no significant differences in concentrations of any of the biomarkers tested (exosomal p-tau, exosomal tau, or plasma tau, Aβ40 or Aβ42, ps > 0.10) (Figure 1(a–c)). In the second group analyses, comparing cases rTBI (≥3 mTBIs) to participants with 1–2 mTBIs and TBI-negative controls, there was a significant elevation in exosomal p-tau ($F_{3,\ 164} = 3.85$, $p = 0.026$), exosomal tau ($F_{2,\ 177} = 4.59$, $p = 0.012$), and a trend of plasma tau ($F_{2,\ 174} = 2.715$, $p = 0.081$) in cases without rTBI compared to participants with 1–2 mTBIs and TBI-negative controls (Figure 2(a–c)). We also examined ratios of Aβ40/Aβ42, and peripheral tau/exosomal tau, and exosomal tau/plasma tau, and there were no significant differences in the three or two group comparisons (ps > 0.30) (data not shown). There were also no differences in those with and without blast exposures (ps > 0.3). In these two group analyses, there were no significant differences

Table 2. Baseline demographics and clinical characteristics.

Characteristic	Controls: No TBI (n = 45)	Cases: Less than three TBI (n = 94)	Cases: Three or more TBI (n = 56)	Significance	p-Value
Age, mean (SD) (year)	39.91 (11.41)	40.34 (11.34)	39.55 (9.77)	$F_{2,\ 192} = 0.096$	0.908
Male, no. (%)	38 (84.4)	82 (87.2)	47 (83.9)	$\chi^2 = 0.380$	0.827
Education, no. (%)					
High school graduate or GED	5 (11.1)	10 (10.6)	8 (14.3)	$\chi^2 = 0.860$	0.930
Some college or technical training	19 (42.2)	43 (45.7)	26 (46.4)		
College graduate or higher	21 (46.7)	41 (43.6)	22 (39.3)		
Number of TBI, mean (SD)	0.00	1.44 (0.499)	4.30 (1.71)	$F_{2,\ 192} = 265.53$	**0.000**
Number of blast TBI, mean (SD)	0.00	0.45 (0.56)	1.25 (1.15)	$F_{2,\ 192} = 39.57$	**0.000**
Number of general TBI, mean (SD)	0.00	0.99 (0.68)	3.05 (1.43)	$F_{2,\ 192} = 158.18$	**0.000**
Years since first TBI, mean (SD)		16.81 (11.53)	23.48 (10.67)	$F_{1,\ 148} = 14.44$	0.952
Years since last TBI, mean (SD)		11.78 (9.97)	7.27 (4.44)	$F_{1,\ 148} = 10.23$	0.002
PHQ-9 total, mean (SD)	5.42 (5.78)	9.37 (6.48)	9.98 (6.09)	$F_{2,\ 190} = 7.94$	**0.001***
PCL-M total, mean (SD)	18.13 (17.96)	29.68 (19.68)	33.30 (19.59)	$F_{2,\ 189} = 8.29$	**0.000***
NSI, mean (SD)					
NSI total	16.64 (15.29)	28.00 (16.50)	34.80 (14.71)	$F_{2,\ 190} = 16.66$	**0.000**
Somatic	3.64 (4.48)	7.00 (4.90)	9.69 (4.81)	$F_{2,\ 190} = 19.80$	**0.000**
Affective	7.04 (5.82)	10.65 (6.20)	11.93 (5.13)	$F_{2,\ 191} = 9.30$	**0.000***
Cognitive	3.53 (3.53)	5.84 (3.98)	7.04 (3.60)	$F_{2,\ 191} = 10.90$	**0.000***
Vestibular	1.18 (1.89)	2.35 (2.44)	3.62 (2.25)	$F_{2,\ 191} = 14.46$	**0.000**

Traumatic brain injury, TBI; post-traumatic amnesia, PTA; loss of consciousness, LOC; Patient Health Questionnaire, Version, PHQ-9; PTSD Checklist-Military Version, PCL-M; Neurobehavioral Symptom Inventory, NSI.

Note: *significance between controls and TBI cases (≥3) AND controls and TBI cases (<3).

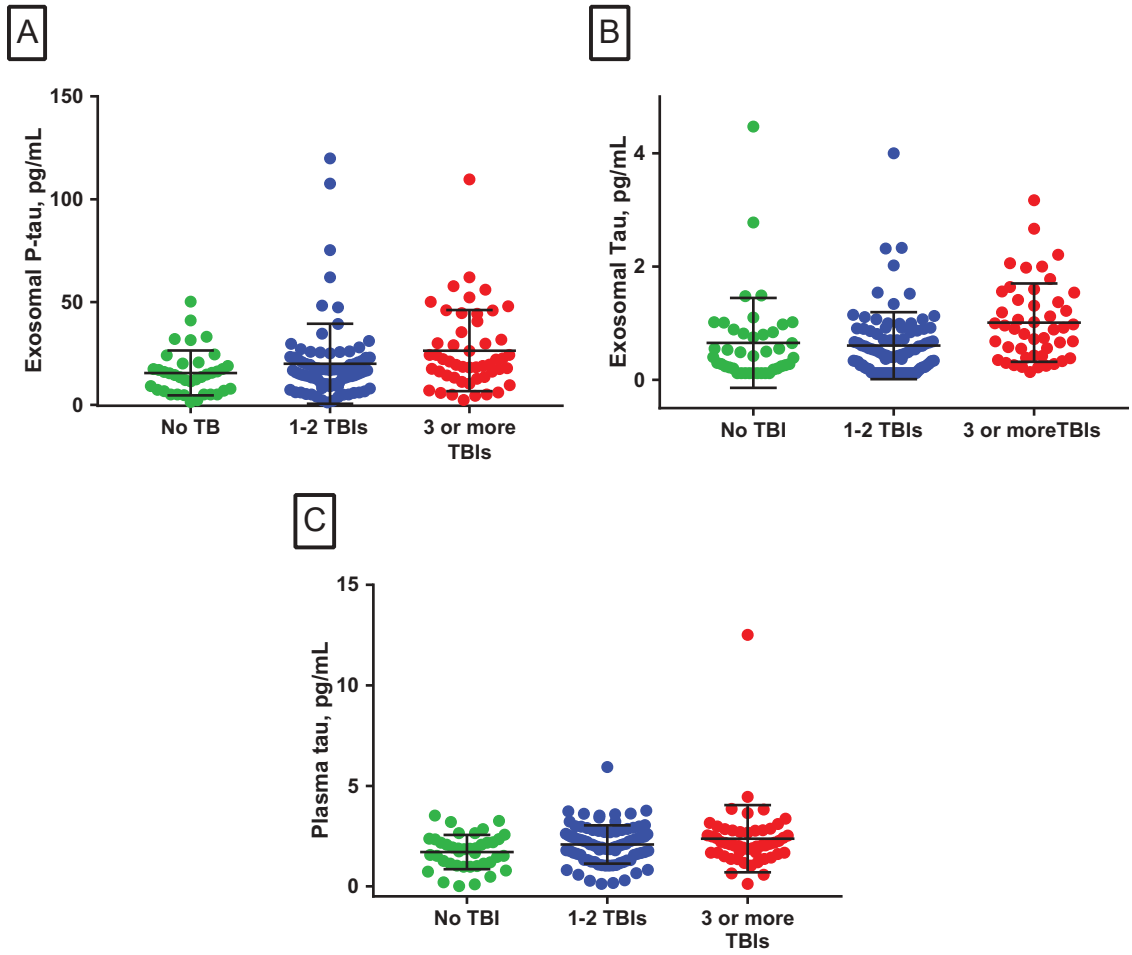

Figure 1. Exosomal p-tau, exosomal tau, and plasma tau, Aβ40 and Aβ42 concentrations in individuals with no TBI, TBI no PTA or LOC, and TBI with PTA or LOC. No significant differences in any biomarker concentration were observed (*p*s > 0.10).

in demographic features between the groups. Those with rTBIs had higher symptoms of PTSD, depression, and post-concussive symptoms (*p*s < 0.01) (Table 2).

To examine relationships among biomarkers that significantly differed in rTBI cases compared to controls, we undertook correlations to determine if symptoms were linked to exosomal p-tau, exosomal tau, or plasma tau within the rTBI group. Exosomal p-tau correlated weakly, but significantly, with: PCL-M total score: $r = 0.326$, $p = 0.026$, NSI affective (NSI-Aff) symptoms: $r = 0.33$, $p = 0.02$ (Figure 3(a)). Exosomal tau significantly correlated with: PCL-M total score: $r = 0.37$, $p = 0.011$; NSI total score: $r = 0.036$, $p = 0.012$; NSI somatic (NSI-Som) symptoms: $r = 0.35$, $p = 0.02$; NSI-Aff symptoms: $r = 0.33$, $p = 0.015$; and NSI cognitive (NSI-Cog) symptoms: $r = 0.33$, $p = 0.032$ (Figure 3(b)). Plasma tau significantly correlated with PHQ-9 total score: $r = 0.29$, $p = 0.042$; PCL-M total: $r = 0.40$, $p < 0.01$; and NSI total: $r = 0.39$, $p < 0.01$ (Figure 3(c)), but not with any NSI symptom domains (somatic, cognitive, affective). Correlations were corrected for multiple comparisons with the Bonferroni correction.

Discussion

Here, we report for the first time that concentrations of tau proteins within exosomes differ in a sample of Veterans with rTBI, and specifically that exosomal p-tau is higher in those reporting 3 or more mTBI. This finding has implications, as elevated p-tau levels have been linked to a greater risk for older patients with mild cognitive impairment to develop AD (2). This finding is important, as our sample includes relatively young personnel who may be at increased risk for developing chronic neurological disorders in late life (51). Here we also report that plasma levels of total tau are higher, and exosomal tau levels tend to be higher, providing further evidence that rTBI may initiate biological changes that are associated with the development of neurodegenerative disorders.

When brain injury occurs, tau dissociates from tubulin fibrils, exposing multiple phosphorylation sites (52). Once exposed, tau can become hyper-phosphorylated and aggregate with normal tau proteins or other p-tau moieties to facilitate the accumulation of insoluble neurofibrillary tangles (53). It is the maturation and spreading of these tangles that are characteristic of individuals with tauopathies, including chronic traumatic encephalopathy (15). TBI is also linked to neuropsychological and cognitive deficits in military personnel (54). Further study is needed to determine if these increases in exosomal p-tau are associated with neurodegenerative disorders.

Recently, elevated plasma p-tau levels have been linked to acute mTBI and chronic TBI patients with persistent impairments following more severe TBI, up to 2 years after injury (11). That study was the first to show that plasma p-tau is

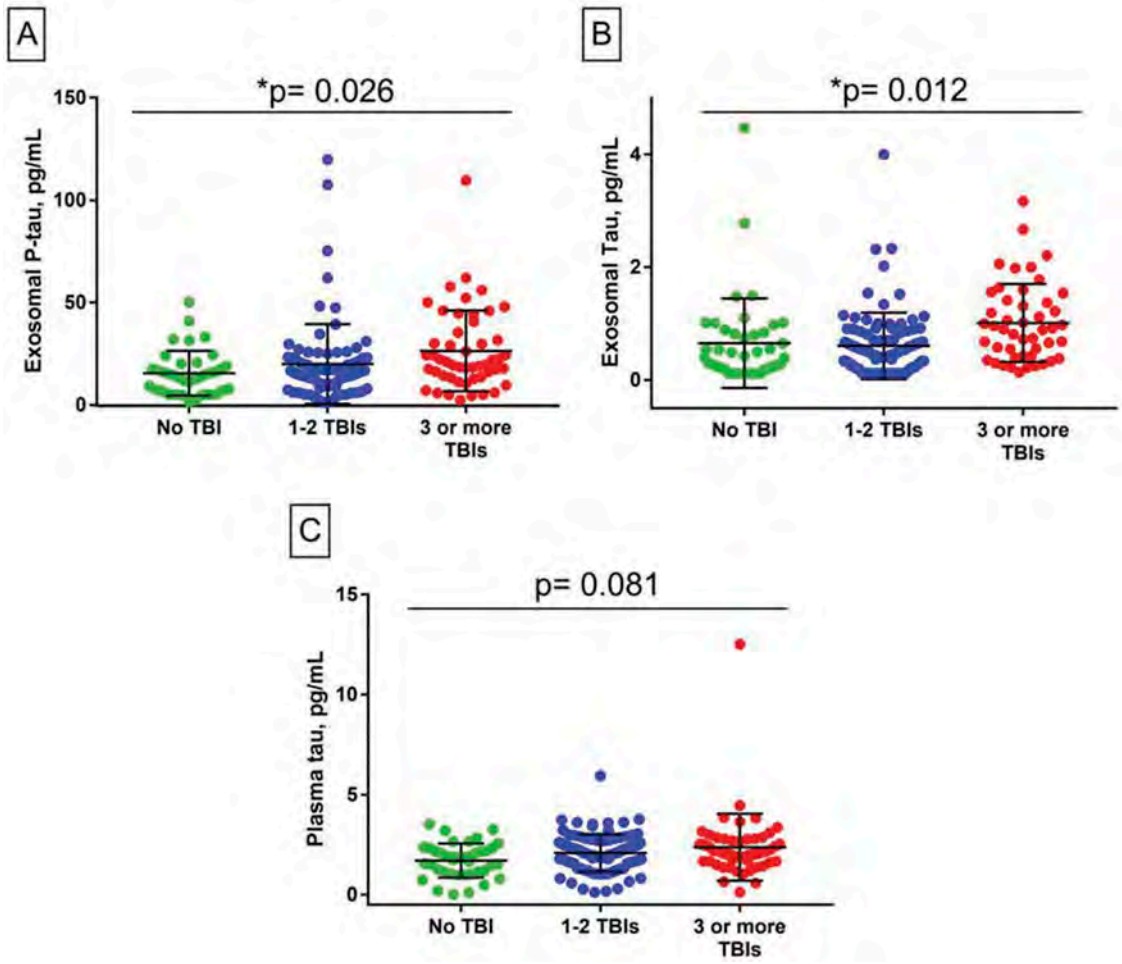

Figure 2. Exosomal p-tau, exosomal tau, and plasma tau concentrations in cases with rTBI (≥3 TBIs resulting in LOC), cases without rTBI (1–2 TBIs), and TBI-negative controls. There was a significant elevation in (A) exosomal p-tau ($F_{3,\ 164} = 3.85$, $p = 0.026$), (B) exosomal tau ($F_{2,\ 177} = 4.59$, $p = 0.012$), and a trend of (C) plasma tau ($F_{2,\ 174} = 2.715$, $p = 0.081$) in cases without rTBI compared to participants with 1–2 TBIs and TBI-negative controls.

elevated chronically after TBI. Our current findings extend the previous findings, by demonstrating that p-tau is increased in blood-based exosomes many years following mTBI, with these elevations being most notable in those who sustain rTBIs. We also observed that exosomal tau, plasma tau as well as exosomal p-tau correlate with greater neuropsychological symptoms, and that exosomal tau and plasma tau relate to greater behavioural symptoms. These findings suggest that tau may play a role in the development, and possibly maintenance, of chronic post-TBI symptoms, and support neuropathologic studies in severe TBI showing that p-tau neuronal aggregation are higher in the cortex after fatal TBI compared to TBI patients who die from other non-CNS conditions (55). In the same study of severe TBI survivors, elevated cerebral spinal fluid *cis* p-tau levels predicted poor outcomes at 1 year after TBI, suggesting that p-tau may have both peripheral and central activities related to TBI recovery (56). Our finding of higher exosomal p-tau in Veterans with rTBI associated with chronic neurobehavioural symptoms suggests that exosomal p-tau may be a predictive biomarker for poor outcomes after rTBI.

Our finding of higher exosomal tau and a trend to higher plasma tau in Veterans with remote rTBI supports a previous finding of high concentrations of total tau in the peripheral blood in a similar cohort of military personnel with multiple TBIs (10). This finding extends a previous report that elevated exosomal tau is observed in symptomatic National Football League players compared to controls, but no measures of circulating total tau were reported in that analysis (41). Together, our finding that elevated exosomal tau in rTBI, along with a trend towards elevated plasma tau, and higher exosomal p-tau suggests that there are dynamic relationships among exosomal content and peripheral circulation in chronic mTBI that require additional study. In addition, these findings suggest that exosomal measures of these proteins may serve as better biomarkers than circulating plasma or serum levels. These relationships are important to understand, as rTBI in preclinical models is linked to increased grey matter tau deposition and neurological symptoms, suggesting that elevated peripheral tau levels in our study population may have central effects (57). Understanding the role of exosomes in chronic TBI is essential, as exosomes are responsible for the delivery of pathogenic proteins, such as hyperphosphorylated tau, and may accelerate the progression of neurodegenerative disorders. Finally, because they are associated with the transport of different cellular entities across the BBB,

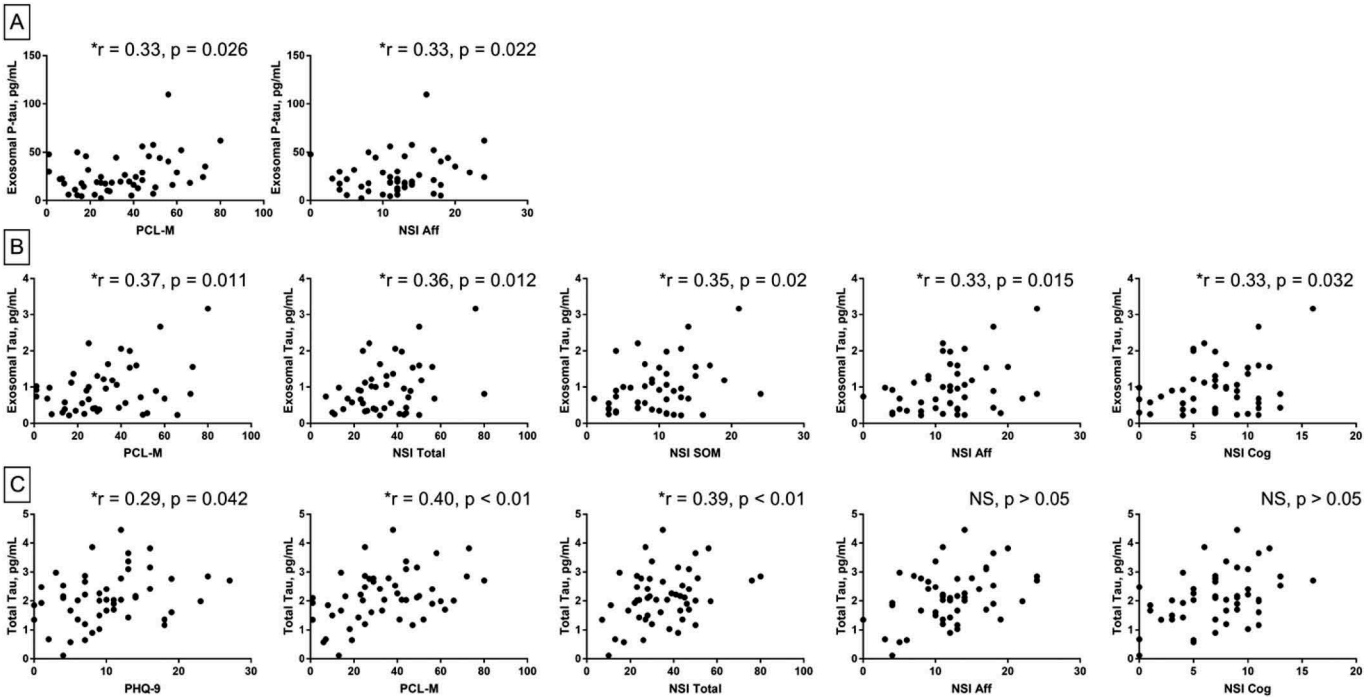

Figure 3. Correlations between symptoms and levels of exosomal p-tau, exosomal tau, or tau in plasma within the rTBI group. (A) Exosomal p-tau significantly correlated with PCL-M total score: $r = 0.326$, $p = 0.026$; NSI somatic (NSI-Som) symptoms: $r = 0.33$, $p = 0.02$. (B) Exosomal tau significantly correlated with PCL-M total score: $r = 0.37$, $p = 0.011$; NSI total score: $r = 0.036$, $p = 0.012$; NSI-Som symptoms: $r = 0.35$, $p = 0.02$; NSI affective (NSI-Aff) symptoms: $r = 0.33$, $p = 0.015$; and NSI cognitive (NSI-Cog): $r = 0.33$, $p = 0.032$. (C) Tau in plasma significantly correlated with PHQ-9 total score: $r = 0.29$, $p = 0.042$; PCL-M total: $r = 0.40$, $p < 0.01$; and NSI total: $r = 0.39$, $p < 0.01$, but not with any NSI symptom subsets.

exosomes may even prove useful for delivering therapeutic molecules for CNS disorders (58).

Findings from this study are limited by a relatively small sample that included participants with a wide range of times from index TBI, as well as varying intervals between TBI incidents. As a result, differences between groups are relatively small and there is overlap among the groups. In addition, there was high variability in TBI timing and mechanism, which included deployment-associated blast TBI as well as TBIs sustained prior to and after active duty service. Our determination of concentrations of p-tau, tau, and Aβ were also limited, as not all proteins were detectable in exosomes, and p-tau was not detectable in plasma. Further, exosomal protein levels were determined in peripherally circulating exosomes rather than CNS-derived exosomes and peripheral sources of tau may have affected the study results. Finally, we did not distinguish between participants who had rTBI with and without blast exposure in this analysis but hope to in future analyses with a larger overall subject number.

Conclusion

This study provides novel insights into the impact of rTBI and suggests that sustaining a high number of mTBI, over a variety of time periods, is associated with elevations of p-tau in exosomes and plasma total tau and increased chronic neurobehavioural symptoms. These elevations may prove predictive biomarkers of poor outcomes after rTBI. Additional studies that include a larger samples size, multiple time-points, additional measures of cognitive and functional outcome and combine neuroimaging are needed to understand the consequences of these biomarker observations and their relevance to chronic clinical symptoms and deficits.

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Declaration of interest

The authors report no conflicts of interest. The views, opinions, and/or findings contained in this article are those of the authors and should not be construed as an official Veterans Affairs or Department of Defense position, policy or decision, unless so designated by other official documentation.

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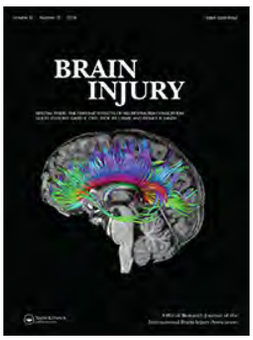
Appendix 8

Longitudinal changes in neuroimaging and neuropsychiatric status of post-deployment veterans: a CENC pilot study



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Longitudinal changes in neuroimaging and neuropsychiatric status of post-deployment veterans: a CENC pilot study

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ABSTRACT

Primary objective: The purpose of this study was to evaluate preliminary data on longitudinal changes in psychiatric, neurobehavioural, and neuroimaging findings in Iraq and Afghanistan combat veterans following blast exposure.
Research design: Longitudinal observational analysis.
Methods and procedures: Participants were invited to participate in two research projects approximately 7 years apart. For each project, veterans completed the Structured Clinical Interview for *DSM-IV* Disorders and/or the Clinician-Administered PTSD Scale, Neurobehavioral Symptom Inventory, and magnetic resonance imaging (MRI).
Main outcomes and results: Chi-squared tests indicated no significant changes in current psychiatric diagnoses, traumatic brain injury (TBI) history, or blast exposure history between assessment visits. Wilcoxon signed-rank tests indicated significant increases in median neurobehavioural symptoms, total number of white matter hyperintensities (WMH), and total WMH volume between assessment visits. Spearman rank correlations indicated no significant associations between change in psychiatric diagnoses, TBI history, blast exposure history, or neurobehavioural symptoms and change in WMH.
Conclusion: MRI WMH changes were not associated with changes in psychiatric diagnoses or symptom burden, but were associated with severity of blast exposure. Future, larger studies might further evaluate presence and aetiology of long-term neuropsychiatric symptoms and MRI findings in blast-exposed populations.

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Blast exposure; traumatic brain injury; posttraumatic stress disorder; depression; military

Traumatic brain injury (TBI) was reported in 375 230 Iraq and Afghanistan-era service members from 2000 through November of 2017 (1), the vast majority of which (82.3%) were consistent with mild TBI (i.e. concussion). Due to the high usage of improvised explosive devices (IEDs), rockets, and mortars in the recent conflicts, a large number of deployment TBIs are blast related (2). A large VA study of over 55 000 Veterans found that 36% of deployment TBIs were related to blast and 44% were blast plus blunt force causes (3). More recent research has also evaluated the effects of subconcussive blast exposure (4–6), in other words, exposure in which criteria for concussion are not met. The long-term effects of primary blast exposure on veterans returning from the wars in Iraq and Afghanistan are currently unknown. Although the prognosis of mild TBI is a fast and full recovery for most individuals, including veterans (7–9), initial studies (reviewed below) vary on how blast exposure (with or without TBI) may reflect a different underlying pathology and a potentially different set of outcomes. Given the high number of veterans who have been exposed to significant blasts in recent conflicts (10), it is imperative to identify any persisting underlying neuropathology and subsequent neuropsychiatric disruption secondary to blast wave exposure to inform large-scale diagnostic and treatment efforts with returning veterans.

Service members may be exposed to a multitude of different blast forces during their military service both throughout training and deployment (11). These events may or may not be accompanied by symptoms congruent with TBI. Primary blast exposure in the absence of other blunt force mechanisms is relatively unique to veterans not only due to the mechanism (s) of action, but to a number of other variables surrounding the injury event when experienced in combat (12). A post-mortem study comparing military service members with blast exposures to civilians with blunt TBI reported that astroglial scarring at interfaces between tissue types (e.g. grey matter/white matter, fluid/brain parenchyma) was unique to blast exposure (13). Characterizing blast exposure is difficult due to variability in exposure including mechanism (e.g. rocket, mortar, IED), distance from the blast, magnitude of the blast, and environmental barriers, among other factors (6).

The long-term neuropsychiatric outcomes following primary blast exposure in veterans are unknown. Assessment is complicated by presence of common comorbidities, including TBI and posttraumatic stress disorder (PTSD). For example, a recent systematic review found no difference in clinical or functional outcomes across TBI studies that were blast or blunt force related (14). However, results were inconsistent for PTSD, hearing issues, headaches, and some cognitive variables. A study of

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neurocognitive impairments found no differences in cognition across blast versus blunt force-related TBI after accounting for psychiatric symptoms (15). More recently, a longitudinal study compared cognitive and neuropsychiatric outcomes of veterans with blast-related TBI compared to combat controls with and without exposure to non-concussive blast (16,17). Early in the chronic stage (6–12-month follow up) symptom burden was elevated in blast-exposed controls compared to controls without blast exposure, indicating possible subconcussive effects (17). Although there was no significant difference between groups for any of the cognitive variables after controlling for family-wise error, there was notable worsening in global disability ratings and neuropsychiatric symptoms in the blast-related TBI group, leading the authors to suggest that veterans 'with concussive blast TBI experience evolution rather than resolution of symptoms from the 1- to 5-year outcomes' (16). Of note, in the predictive model for global disability status at 5 years, variables from year 1 included neurobehavioural symptoms and premorbid ability. This echoes the findings of Lange and colleagues (15) in which psychiatric variables accounted for the differences seen in blunt compared to blast-related TBI. Another study evaluating comorbidities and differing trajectories across 3 years following TBI found comorbid conditions, including psychiatric conditions, pain, and other medical conditions the rule rather than the exception (18). A common theme across studies are the numerous neuropsychiatric comorbidities that complicate the ability to distinguish the chronic effects of TBI and blast exposure.

Neuroimaging findings following blast exposure have also been mixed. An increase in the number and/or volume of white matter hyperintensities (WMH) seen on fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) in military members or veterans with blast-related TBI compared to controls has been found by some but not by others (19–21). Some of the difference may be due to how each study adjusted for age as a gradual increase in the number of such areas is considered a normal aspect of brain aging (19). Several studies have reported elevated levels of spatially heterogenous abnormal findings on diffusion tensor imaging (DTI) in groups with blast-related mild TBI (22). Individuals with blast-related TBI have shown to have a higher incidence of spatially heterogeneous white matter abnormalities detected with DTI, with no effect of blunt force TBI (23). However, an expanded sample including participants with PTSD did not replicate this effect (24). Blast-related TBI involving loss of consciousness (LOC) has been associated with increased numbers of regions of interest with white matter abnormalities (25). This is consistent with other work showing an increased likelihood of spatially heterogeneous white matter abnormalities associated with blast-related TBI involving LOC compared to injuries not involving LOC or blast exposure without resulting TBI (20). MacDonald and colleagues (26) demonstrated abnormalities in three of four individuals with a history of TBI due only to blast exposure, without history of blunt force TBI (i.e. primary blast TBI). Taber and colleagues (27) found that primary blast exposure both with and without symptoms at the time consistent with TBI was associated with increased spatially heterogenous abnormal DTI findings compared to non-exposed veterans.

Though the literature on blast exposure suggests the possibility of direct effects on brain function and structure, there is a dearth of information about the long-term consequences of primary blast exposure in the absence of other blunt force mechanisms. MacDonald and colleagues (28) found that white matter injuries remained, and potentially evolved, over a 5-year period in service members with blast-related mild TBI; however, most injuries involved additional non-blast mechanisms. Thus, the aim of this longitudinal study was to evaluate long-term neuroimaging changes and neuropsychiatric symptoms following primary blast exposure in a small sample of post-deployment veterans. The present analysis utilized clinical interviews, symptom self-report, and neuroimaging data collected from veterans who participated in two studies investigating outcomes associated with blast exposure conducted approximately 7 years apart. Based on existing literature on mild TBI and typical symptom course, we expected that (1) psychiatric symptoms would improve over time, such that there would be little incidence of new-onset PTSD and major depressive disorder (MDD) and that most participants with diagnoses at Time 1 (T1) would no longer meet current criteria for that diagnosis at Time 2 (T2); (2) neuropsychiatric symptom burden would decrease between T1 and T2; and (3) incidents of WMH observed on neuroimaging would remain stable between T1 and T2.

Methods

Data for the present analyses were obtained from two separate IRB-approved studies at the Salisbury Veterans Affairs Health Care System in North Carolina, USA. Participants from T1 (N = 48), conducted from 2007 to 2010, were invited 6.08–9.33 years (M = 7.39, SD = 1.00) later to participate in T2, which began in 2015. The second study was not a planned longitudinal follow-up to the first; therefore, the current sample represents a fortuitous convenience sample. Each study involved two in-person visits. The first was an assessment visit that included structured clinical interviews and symptom questionnaires; the second was a neuroimaging visit.

Nineteen participants from T1 completed the assessment visit for T2. Eleven participants completed the neuroimaging visit for both T1 and T2. Two participants did not complete T1 neuroimaging (unable to schedule) and seven participants did not complete T2 neuroimaging (six ineligible, one declined). Of note, 30 participants from T1 who may have been eligible to participate in T2 declined to be assessed (*moved* = 9, *uninterested* = 11, *other* = 2) or were unable to be contacted (n = 8).

Eligibility

Inclusion criteria for both studies were deployment after 11 September 2001 in support of the wars in Iraq and Afghanistan, English speaking, 18 years of age or older, and able to provide informed consent. Participants were excluded if they reported a lifetime history of moderate or severe TBI; history of any penetrating head injury or a non-deployment TBI with LOC for any period of time; history of major neurological disorder such as stroke, seizure, or spinal cord

injury; history of serious mental illness such as bipolar disorder or schizophrenia; and current presence of dementia, substance use disorder, or psychosis. Eligibility was determined through screening and confirmed by information from structured interviews. Exposure to conditions or events during or following deployment likely to result in a TBI due to forces other than primary blast (e.g. motor vehicle accident, contact sports, assault) was an additional exclusion criterion for T1. Exclusion criteria specific to neuroimaging activities included pregnancy, inability to tolerate an enclosed space for MRI, presence of ferrous metal other than fillings, including orthodonture or implanted objects known to generate magnetic fields (e.g. prosthetic devices, pacemakers, neurostimulators, etc.) that may interfere with neuroimaging data acquisition and/or be an MRI safety concern.

Psychological measures

All measures were administered in a standardized manner by licensed psychologists, neuropsychologists, and/or trained and supervised research staff and postdoctoral fellows. The Mid-Atlantic Mental Illness Research, Education and Clinical Center (MA-MIRECC) TBI Interview is a clinician-administered, structured interview developed at the MA-MIRECC to evaluate history of TBI (29). The cause, duration of LOC, alteration of consciousness, and post-traumatic amnesia, as well as symptoms immediately following each occurrence are evaluated. TBI severity was based on Department of Veterans Affairs (VA) and Department of Defense (DoD) consensus criteria (30). TBI history was determined using the MA-MIRECC TBI Interview for T2, and TBI history was determined by a VA polytrauma provider for T1. The Salisbury Blast Exposure Interview is a clinician-administered, structured interview evaluating blast exposure across the lifespan. Participants are asked about any history of exposure to blasts or explosions regardless of the setting (i.e. civilian, military training, combat) across the lifetime. Circumstances (e.g. in a vehicle, wearing protective gear, behind cover), effects (e.g. thrown to the ground), characteristics (i.e. wind, ground shaking, pressure change, temperature change, debris, sound), distance, and other information about each blast exposure are collected. Subjective ratings on anchored Likert scales (0–5) are obtained for all six characteristics. For the present analyses, blast exposure was operationalized as any explosion for which the participant reported feeling a slight pressure gradient (rating of 1 = *slightly, noticeable but not uncomfortable*), or more. For the purposes of this article, 'blast exposure' refers to the experience of pressure following a blast, which may or may not have been accompanied by symptoms congruent with a TBI.

The Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID) (31) is a structured interview to evaluate criteria of *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (*DSM-IV*) Axis I psychiatric disorders. All modules were administered to all veterans who participated in T1. All modules except for PTSD were administered to T2 participants. Outcome variables included current and lifetime presence/absence of all Axis I psychiatric disorders. The Clinician-Administered PTSD Scale (CAPS-5) (32) was used to evaluate *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (*DSM-5*) criteria of PTSD for T2. The CAPS-5 is a 30-item clinical interview that provides current and lifetime diagnosis of PTSD. This was administered in lieu of the SCID PTSD module.

Neuropsychiatric symptom burden was evaluated using the Neurobehavioral Symptom Inventory (NSI) (33). The NSI is a 22-item self-report questionnaire that evaluates neuropsychiatric symptoms. Each item is measured on a 5-point Likert scale, indicating the extent to which each symptom bothered the individual over the prior two weeks (0 = *none*, 4 = *very severe*). Higher scores are reflective of greater symptom severity. The mild TBI Brain Injury Atypical Scale (34) was also administered. All participants scored a 0, indicating good validity.

Neuroimaging

MRI data for T1 was acquired on a General Electric Signa HDxt 1.5 T scanner with an eight-channel receive coil. Imaging included T1-weighted, T2-weighted, and FLAIR pulse sequences. MRI data for T2 acquired on a 3 T Siemens Skyra MRI scanner using a high-resolution 32-channel human head/neck coil (Siemens Medical, Malvern, PA, USA) in accordance with the National Institute of Neurological Disorders and Stroke Common Data Elements advanced protocol recommendations including structural T1-weighted, T2-weighted, and FLAIR pulse sequences. Scan parameters for T1 are as follows: T1 SPGR TR 7876 TE 2.24 TI 300 FOV 208 voxel 0.5 × 0.5 × 1.5 mm; T2w GRE TR 517 TE 30 FOV 180 voxel 0.5 × 0.5 × 1.5mm; T2 FLAIR TR 9000 TE 143 TI 2250 FOV 260 voxel 0.5 × 0.5 × 1.5 mm. Scan parameters for T2 are as follows: T1 MPRAGE TR 2300 TE 2.98 TI 900 FOV 256 voxel 1 × 1 × 1.2 mm; T2 TSE TR 3200 TE 222 FOV 256 voxel 1 × 1 × 1.2 mm; T2 FLAIR TR 6000 TE 263 TI 2100 FOV 256 voxel 0.5 × 0.5 × 1.2 mm. Outcome variables included the number of WMH identified on FLAIR as well as the total volume of those areas calculated at both time points (procedure described below). It was expected that visibility of WMHs would be improved at T2, resulting in some increases in both numbers and total volumes (35).

Procedures

Both studies included an assessment visit preceding the neuroimaging visit to fully evaluate eligibility for enrolment into imaging. The T1 assessment visit included completion of the SCID, NSI, and structured interviews to determine TBI and blast exposure history. TBI history was determined by a VA polytrauma TBI provider. If the participant report and medical record conflicted, the medical record TBI status was used. The T2 assessment visit included completion of the SCID, CAPS-5, NSI, TBI interview, and blast interview. Additionally, participants were excluded from the neuroimaging visit of T2 if they invalidated performance validity (Medical Symptom Validity Test and b Test) or symptom validity (Structured Inventory of Malingered Symptomatology) measures during the assessment visit.

Areas of abnormally increased signal intensity (WMH) were identified on FLAIR images using the lesion prediction algorithm (LPA) (36) as implemented in the Lesion Segmentation

Toolbox (www.statistical-modelling.de/lst.html) for statistical parametric mapping. LPA was chosen for speed and reproducibility because no user input of parameters is required. Lesion maps were then manually reviewed and edited to remove artefacts. These maps were analysed using custom Python code to extract the number and volume of WMHs.

Data analysis

Data was analyzed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Non-parametric statistics were used due to small sample size. Change in psychiatric diagnoses (SCID), TBI history (MA-MIRECC TBI Interview), and blast exposure history (Salisbury Blast Exposure Interview) were evaluated using chi-squared tests for the presence/absence (coded dichotomously, 0 = *absent*, 1 = *present*) of diagnosis of interest at T1 and T2. Due to the small sample size, *p*-values for Fisher's exact test are provided in addition to chi-squared results. Diagnoses selected for analysis included current PTSD and MDD. Changes in neurobehavioural symptoms (NSI), number of WMHs, and WMH volume were evaluated using Wilcoxon signed-rank tests. To evaluate associations between changes in psychiatric diagnoses, neurobehavioural symptoms, and imaging, change scores were calculated by subtracting T1 scores from T2 scores for each variable. Change scores were then analysed with Spearman rank correlations.

Table 1. Participant characteristics at Time 1 and 2 (N = 19).

	T1		T2	
Variable	*n*	%	*n*	%
Sex				
Male			16	84.21
Female			3	15.79
Race/ethnicity				
White			11	57.89
Black			7	36.84
Hispanic			1	5.26
Blast exposed*				
No	10	52.63	5	27.28
Yes	9	47.37	13	72.22
TBI history				
None	17	89.47	7	36.84
Mild	2	10.53	10	52.63
Moderate	0	0	2	10.53
MDD current				
No	16	81.25	18	94.74
Yes	3	18.75	1	5.26
PTSD current**				
No	13	68.42	13	72.22
Yes	6	31.58	5	27.78
Branch of service				
Air Force			1	5.26
Army			6	31.58
Army National Guard			6	31.58
Army Reserves			2	10.53
Navy			2	10.53
Navy Reserves			2	10.53

Note. *Blast Interview missing for 1 T2 participant.
**Clinician Administered PTSD Scale (CAPS-5) missing for one participant in T2. Percentages only include available data. Branch of Service refers to the most recent branch of service. TBI = traumatic brain injury; MDD = major depressive disorder; PTSD = posttraumatic stress disorder.

Results

Aggregate demographic information for the sample is presented in Table 1. Table 2 reports participant-level exposure and outcome data. Participants were 19 veterans (15.79% female) between the ages of 24 and 60 at T1 (M = 39.05, SD = 9.42) and 30 and 68 at T2 (M = 46.32, SD = 9.63). The time between T1 and T2 participation was 6.08–9.33 years (M = 7.39, SD = 1.00). Participants reported between 12–19 years of education at T2 (M = 15.74, SD = 2.31). At T2, participants had 1–4 (M = 1.89, SD = .99) combat deployments, and 5 participants redeployed between T1 and T2. Service connected disability at T2 ranged from 0% to 100% (M = 44.47, SD = 35.94). At T2, three participants had no blast exposure or history of TBI (control group; Table 2 IDs 1–3). Three participants had no blast exposure but did have TBI (blunt TBI group; IDs 4–6). Of the 13 participants reporting primary blast exposure, 4 had only primary blast exposure (blast only group; IDs 7–10), and 9 also reported a history of TBI (blast and TBI group; IDs 11–19).

Chi-squared analysis indicated no significant differences in current PTSD diagnosis, χ^2 = 0.14, p = .710, Fisher's exact test p = .385, current MDD diagnosis, χ^2 = .20, p = .656, Fisher's exact test p = .842, TBI status, χ^2 = 0.17, p = .683, Fisher's exact test p = .491, or blast exposure history, χ^2 = 2.49, p = .114, Fisher's exact test p = .132, between T1 and T2. Results for Wilcoxon signed-rank tests are reported in Table 3. Analysis indicated that the median NSI scores at T2 were significantly higher than median NSI scores at T1. NSI scores were not significantly correlated between time points, $r_s(16)$ = .44, p = .088. Although most participants were in the normal range at both T1 and T2, the median total number of WMHs and total WMH volume were significantly higher at T2. As shown in Figure 1, this was primarily due to four participants (IDs 7, 8, 14, 19). All four participants had blast exposure at T1, two had TBI at T1, one of which had another TBI by T2. Visual comparisons of sectional images from T1 and T2 indicated that the higher quality of imaging at T2 was an influence, as several of the 'new' hyperintense areas were faintly present on the T1 images (see Figure 2 for an example).

Spearman rank correlations between difference scores on imaging metrics and psychiatric variables of interest are reported in Table 4. Notably, zero-order Pearson correlations between total number of WMHs, WMH volume, and psychiatric outcome variables at T1 were not significant (p = .808–.114). Correlations between current PTSD diagnosis and number of WMH (r = .61, p = .047) and total WMH volume (r = .66, p = .025) at T2 were significant. No other correlation between WMH number or volume and psychiatric outcome was significant at T2 (p = .845–.324). Overall, these outcomes indicate that changes in imaging metrics were unrelated to changes in PTSD and MDD diagnosis, TBI history, blast exposure, and NSI scores.

No participant in either the control group or the blunt TBI group had current PTSD or MDD at either time point. NSI scores increased from T1 to T2 for four participants in those groups (IDs 1, 3, 4, 5). Three had redeployed, one of whom also experienced a new TBI event between T1 and T2. One participant (25%) in the blast only group (ID 9) had PTSD at T1, which had not resolved at T2 (0% recovery). Another (ID 8) had new-onset MDD at T2. NSI increased from T1 to T2 for both participants. Five participants in the blast and TBI group (IDs 11, 12, 17, 18, 19) did not report another TBI between T1 and T2. Three (60%) of these participants (IDs 12, 18, 19) had PTSD at T1, all of which had resolved by T2 (100% recovery). Four participants in the blast and TBI group experienced another TBI between T1 and T2 (IDs 13–16). Two (50%) of these

Table 2. Individual participant data.

					T1				T2			
Subject	Blast Exposed	TBI History	Redeployed	New TBI	PTSD	MDD	NSI	WMH	PTSD	MDD	NSI	WMH
1	N	N	2	N	–	N	0	–	–	N	17	–
2	N	N	1	N	N	N	7	0	N	N	7	2
3	N	N	0	N	N	N	2	–	N	N	12	–
4	N	Y	1	N	N	L	11	2	N	L	16	3
5	N	Y	1	Mild	N	N	19	–	L	N	78	–
6	N	Y	0	N	N	N	–	2	N	N	3	4
7	Y	N	0	N	N	N	1	2	L	N	9	26
8	Y	N	0	N	N	N	7	11	L	C	22	51
9	Y	N	0	N	C	N	39	0	C	L	48	0
10	Y	N	0	N	N	N	4	0	N	N	2	2
11	Y	Y	0	N	N	N	1	–	C	N	58	–
12	Y	Y	0	N	C	C	53	–	L	L	22	–
13	Y	Y	1	Mild	N	N	10	–	C	N	42	–
14	Y	Y	0	Mild	N	N	7	49	C	L	33	208
15	Y	Y	0	Mod	C	C	27	–	C	N	31	–
16	Y	Y	0	Mild	C	C	–	–	L	N	20	–
17	Y	Y	0	N	N	N	4	2	N	N	3	3
18	Y	Y	0	N	C	N	17	0	L	N	35	1
19	Y	Y	0	N	C	N	–	1	N	N	18	13

Note. For blast-exposed and TBI history, Y = yes, N = no. No participants reported new blast exposure between T1 and T2.
TBI = traumatic brain injury, PTSD = posttraumatic stress disorder, MDD = major depressive disorder, NSI = Neurobehavioral Symptom Inventory. Redeployed = number of times redeployed between T1 and T2. New TBI = TBI acquired between T1 and T2, N = no new TBI, Mild = mild TBI, Mod = moderate TBI. T1 = baseline assessment. T2 = follow-up assessment. For PTSD and MDD, N = no history, L = lifetime history, C = current. WMH = number of white matter hyperintensities.
'–' indicates data not available.

Table 3. Wilcoxon signed-rank tests outcomes (N = 19).

	T1						T2							
	n	*M*	*SD*	Mdn	Min	Max	*n*	*M*	*SD*	Mdn	Min	Max	Z	*p*
NSI	16	13.06	15.02	7	0	53	19	25.05	20.27	20	2	78	45	.008
Number of WMH	11	6.27	14.51	2	0	49	11	28.45	61.52	3	0	208	27.5	.002
Total WMH volume	11	370.45	1178.50	12	0	3923	11	1369.27	4187.77	54	0	13987	27.5	.002

Note. T1 = study 1; T2 = study 2; *M* = mean; *SD* = standard deviation; Mdn = median; Min = minimum; Max = maximum; Z = *z*-value for Wilcoxon signed-rank test; *p* = significance; NSI = Neurobehavioral Symptom Inventory; WMH = white matter hyperintensity.

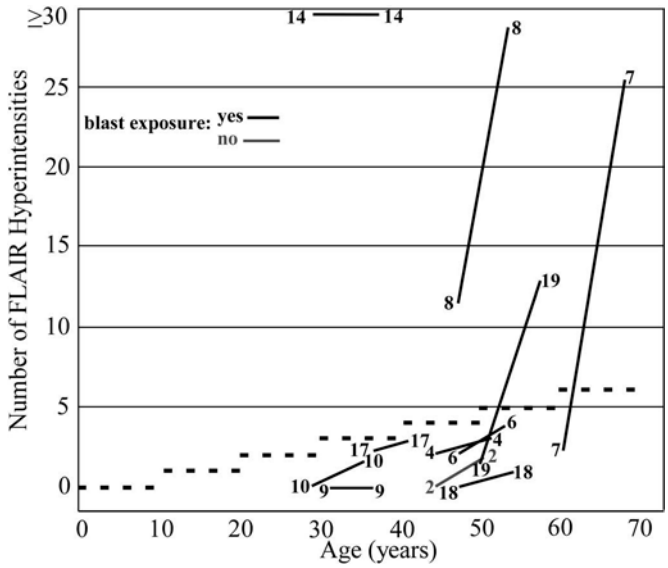

Figure 1. Number of FLAIR white matter hyperintensities (WMH) at T1 and T2. This figure illustrates the findings of number of WMH for each participant who was imaged at T1 and T2. The dashed lined indicates number of expected WMHs, based on one additional per decade of life as normal (19). Participant numbers correspond with subject number in Table 2. Of note, all but two participants are in the normal range at T1. Two additional participants have elevated number of WMHs at T2. Visual comparison of the sectional images indicated the higher quality of imaging at T2 was a major influence as most of the additional hyperintense areas were faintly present on T1 images.

participants (IDs 15, 16) had PTSD at T1, with one resolving by T2 (ID 16; 50% recovery). There were two cases (IDs 13, 14) of new-onset PTSD, both in the blast and TBI group, one with a new TBI event occurring between T1 and T2. Both cases were associated with increases in NSI scores at T2.

Exploratory analyses were conducted to determine if certain blast characteristics (frequency; severity, based on most severe overall) were correlated with WMH number and volume at both T1 and T2. Additional Pearson correlations were conducted to determine if blast characteristics and occurrence of new TBI (coded by severity) were correlated with changes in WMH number and volume between T1 and T2. At T1, the severity of blast exposure was significantly correlated with WMH number (r = .72, p = .011) and there was a trend towards WMH volume (r = .73, p = .061). Number of blasts was not correlated with either WMH number (r = –.06, p = .851) or volume (r = –.16, p = .735) at T1. Similarly, at T2 severity of blast exposure was significantly correlated with both number of WMHs (r = .76, p = .007) and WMH volume (r = .69, p = .019). Number of blasts was not correlated with either number of WMHs (r = –.06, p = .86) or WMH volume (r = –.14, p = .678) at T2. Regarding change between T1 and T2, there were significant associations between severity of blast exposure on changes in WMH number (r = .54, p = .018) and volume (r = .50, p = .031). There was no association between number of blasts on change in WMH number (r = –.07, p = .769) or volume (r = –.09, p = .720). There was also no association between new

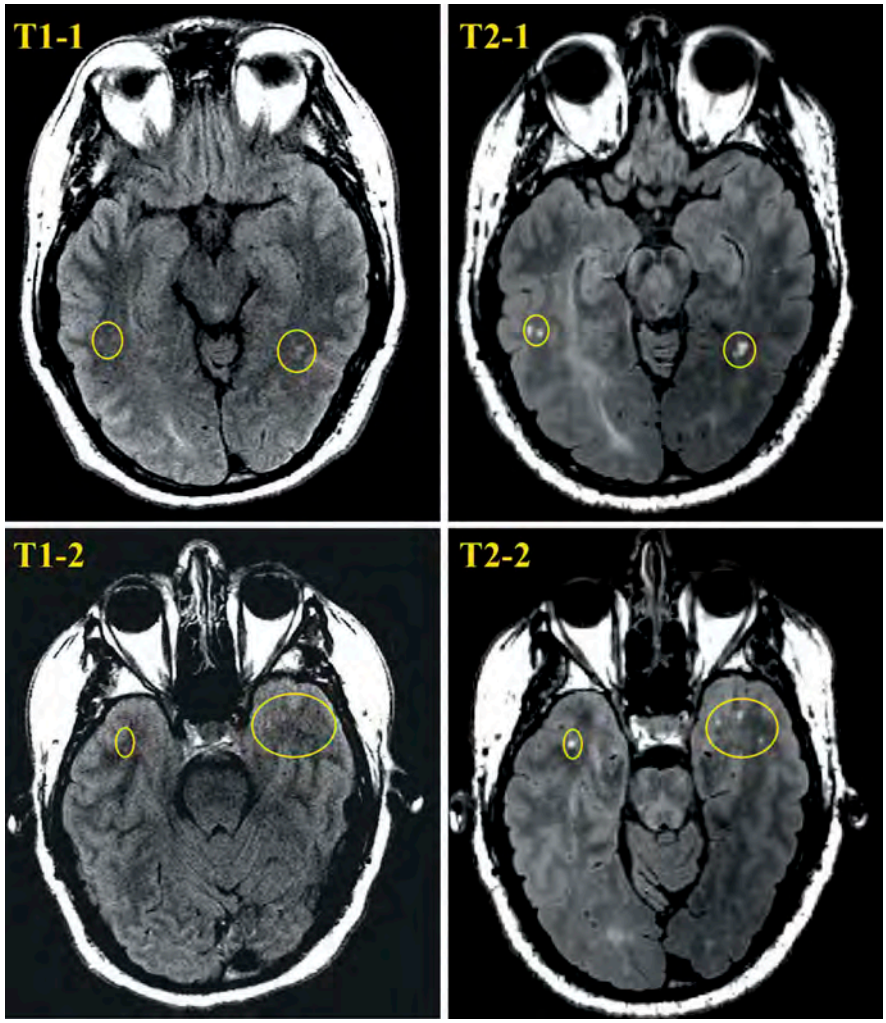

Figure 2. Visual comparisons of sectional images at T1 and T2. This figure illustrates differences in two sections (indicated by −1 or −2) at T1 and T2 of the same participant (Table 2 ID 14). Several 'new' white matter hyperintensities (WMH) detected at T2 (T2-1, T2-2) were faintly visible on images obtained at T1 (T1-1, T1-2).

Table 4. Correlation matrix of difference scores between imaging metrics and psychiatric variables.

	PTSD (n = 11)		MDD (n = 11)		TBI (n = 11)		Blast (n = 11)		NSI (n = 9)	
	ρ	p	ρ	p	ρ	p	ρ	p	ρ	p
Total number of WMHs	.325	.329	.408	.214	.026	.940	.041	.905	.289	.450
Total WMH volume	.377	.377	.400	.223	.280	.404	−.131	.702	.267	.488

Note. All variables represent difference scores (T2–T1).
PTSD = current diagnosis of posttraumatic stress disorder; MDD = current diagnosis of major depressive disorder; TBI = history of blunt traumatic brain injury; Blast = history of blast exposure; NSI = Neurobehavioral Symptom Inventory; ρ = Spearman rank correlation coefficient; WMH = white matter hyperintensity.

TBI and change in WMH number (r = .21, p = .384) or volume (r = .27, p = .257).

Discussion

The aim of this pilot study was to describe long-term neuropathological changes and neuropsychiatric symptoms following blast exposure with and without TBI during deployment. As would be expected, a history of both types of exposures (TBI, blast) was associated with worse outcomes at T1 than either exposure alone. In the absence of additional events (TBI, redeployment), a trend towards improved outcomes at T2 was observed.

Overall, our results indicated no significant changes in psychiatric diagnoses, TBI history, or blast exposure history over the course of 7 years. Though the overall trend was towards fewer psychiatric diagnoses, there were three new-onset PTSD diagnoses (one redeployed with new-onset TBI, all with blast exposure) and one new-onset MDD diagnosis (with blast exposure) in the sample. Five veterans in this sample redeployed following T1, though new blast exposure following T1 participation was not reported by any participant. Therefore, additional blast exposure was unlikely to affect our results.

Incongruent with our hypothesis, self-report of neurobehavioural symptoms increased between T1 and T2. Due to the non-specific nature of the symptoms evaluated by this measure, there are several possible reasons for this

including changing life circumstances, new-onset medical conditions, new-onset non-deployment-related injuries, or new-onset psychiatric conditions. Iverson and Lange (37) found post-concussive symptoms present in 36–76% of healthy adults, and symptoms were highly correlated to depression, suggesting the presence of neurobehavioural symptoms is not pathognomonic to TBI, and the increase seen in this sample not necessarily indicative of TBI or blast symptom evolution. Additionally, our results suggest the increase is unrelated to any changes in neuroimaging results, inconsistent with previous findings (20).

Possibly incongruent with our expectations, we detected significant increases in WMH number and volume, such that a greater number and volume of WMHs were seen at T2 compared to T1. This was primarily due to changes in four of the 11 participants who completed imaging, all with blast exposure at T1. However, five other participants also had blast exposure at T1 without significant increase in WMHs at T2. It is possible this increase is related to characteristics of blast exposure that were unable to be included as part of the current analysis. Interpretation of this finding is complicated by several issues, and we discuss the significant caveats associated with this below; however, if this finding were to generalize to the larger population of blast exposed service members and veterans, it would merit further study to clarify the mechanisms resulting in WMH progression as well as the relationship of such progression to clinical outcomes.

Because of differences in MRI scanner technology between the two studies, it is possible the observed changes in WMH are due to the improved image quality at T2. For example, a study of 15 healthy participants (M_{age} = 44 years) found a significant increase in WMH detectability on FLAIR at 3 T compared to 1.5 T (35). Two other studies using healthy participants and subjects with multiple sclerosis also found a similar increase (38,39). The general trend in our cohort of increased WMH number and volume at T2 might be attributed to increased sensitivity as opposed to WMH evolution. This is supported qualitatively through visual comparisons of sectional images from T1 and T2, with several 'new' hyperintense areas faintly visible at T1 (see Figure 2). The pattern of relationship between imaging data and characterization data could be said to support this interpretation as well. Imaging data from T2 demonstrated stronger relationship with PTSD diagnosis and blast exposure severity than either T1 imaging data or change scores. Thus, it is possible that the higher resolution of T2 imaging data allowed observations of relationships between brain structure, PTSD, and blast exposure severity that were not observable at previously obtained lower resolutions. These results are congruent with our previously published manuscript using the full T1 data set (N = 45) that demonstrated an association between PTSD, blast exposure, and altered values of DTI metrics (27). Given the small sample size in the current analysis, the higher resolution imaging at T2 may have been necessary to observe the effect. This could indicate a need for higher resolution structural imaging to observe the subtle and diffuse effects of blast exposure on the brain; however, further work is necessary to fully support this conclusion.

Further work is needed to clarify these relationships and address confounding factors. However, if our findings are the result of increased resolution due to improved imaging technology, they provide additional evidence for a relationship between blast exposure, PTSD, and WMH. If our findings represent progression of neuropathology following blast exposure and TBI, they would provide new evidence of a worrying relationship between events that occur frequently during deployment (blast exposure, mild TBI) and progression of WMH typically interpreted as pathological in clinical examinations. Unfortunately, due to changes in imaging technology, the question of progression remains unanswered and the conservative interpretation should be one of improved resolution.

There are several limitations to note for the present analysis. The small sample size limited quantitative methods. Different measures were used to evaluate TBI and blast exposure history across studies, which may have further influenced results. Five participants reported sustaining a new-onset TBI (*mild* = 4, *moderate* = 1) following participation in T1 though there were 10 new reported TBIs. In addition, one participant no longer met criteria for a TBI diagnosis at T2. These incidents indicate a potential difference in report of TBI symptoms between T1 and T2. A potential contributor to this was the difference in context between T1 and T2. At T1, the VA polytrauma evaluation results in the medical record were used to capture TBI diagnosis; at T2 an interview was conducted by research staff and the results were unavailable for clinical purposes. As mentioned above, imaging was acquired at 1.5 T for T1, whereas this data was acquired at 3.0 T at T2. This potentially biased the results towards finding increased numbers of lesions at T2 due to the higher resolution and tissue contrast, providing the ability to resolve smaller lesions that may have been present at T1 (40,41). There was a low rate of diagnoses in the overall sample at T1, limiting the ability of the analysis to observe remission of disorders. However, this did provide opportunity to observe new onset of disorders, which was not supported statistically. It should be noted that interviewers at T2 were blind to the diagnoses established at T1. In addition, 30 participants from T1 who may have been eligible to participate in T2 declined to be assessed (*moved* = 9, *uninterested* = 11, *other* = 2) or were unable to be contacted (n = 8), potentially biasing the sample. PTSD diagnosis was evaluated under *DSM-IV* criteria using the SCID at T1, but *DSM-5* criteria using the CAPS-5 at T2, and differences in interview tools and diagnostic classification might have affected results and general comparability for PTSD diagnosis.

Conclusions

In conclusion, this pilot study describes temporal increases in WMHs in a small cohort of veterans with history of blast exposure. These changes in WMHs were unrelated to neurobehavioural factors, though were associated with severity of blast exposure. Number of WMHs at T2 was additionally associated with a current diagnosis of PTSD at T2. Major limitations included differences in measurement at T1 and

T2, change in MRI sensitivity, and small sample size. Because the contribution of improved resolution is unclear, our results suggest one of two things: (1) if increases in WMH are solely due to improved imaging resolution, our results suggest that there is a relationship between blast exposure and WMH. or; (2) if increases in WMH are not due to improved imaging resolution, this would provide support for a relationship between blast exposure and progression of neuropathology. Considerable further research is needed to clarify these relationships and address confounding factors.

Declaration of interest

The authors report no conflicts of interest. The views, opinions and/or findings contained in this article are those of the authors and should not be construed as an official Veterans Affairs or Department of Defense position, policy or decision, unless so designated by other official documentation.

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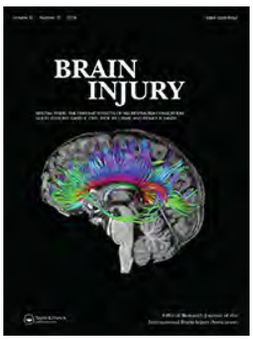
Appendix 9

Impact of age on acute post-TBI neuropathology in mice expressing humanized tau: a Chronic Effects of Neurotrauma Consortium study



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ARTICLE

Impact of age on acute post-TBI neuropathology in mice expressing humanized tau: a Chronic Effects of Neurotrauma Consortium study

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ABSTRACT

Objectives: We hypothesized that polypathology is more severe in older than younger mice during the acute phase following repetitive mild traumatic brain injury (r-mTBI).

Methods: Young and aged male and female mice transgenic for human tau (hTau) were exposed to r-mTBI or a sham procedure. Twenty-four hours post-last injury, mouse brain tissue was immunostained for alterations in astrogliosis, microgliosis, tau pathology, and axonal injury.

Results: Quantitative analysis revealed a greater percent distribution of glial fibrillary acid protein and Iba-1 reactivity in the brains of all mice exposed to r-mTBI compared to sham controls. With respect to axonal injury, the number of amyloid precursor protein-positive profiles was increased in young vs aged mice post r-mTBI. An increase in tau immunoreactivity was found in young and aged injured male hTau mice.

Conclusions: We report the first evidence in our model that r-mTBI precipitates a complex sequelae of events in aged vs young hTau mice at an acute time point, typified by an increase in phosphorylated tau and astroglisosis, and a diminished microgliosis response and axonal injury in aged mice. These findings suggest differential age-dependent effects in TBI pathobiology.

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Traumatic Brain Injury; neurodegeneration; tau; axonal injury; animal models; age; inflammation

Introduction

Traumatic brain injury (TBI) is the leading cause of mortality and morbidity in the world for individuals under the age of 45 (1). Mild TBI (mTBI) accounts for approximately 70–90% of all TBIs and is a major source of morbidity, with up to 15% of patients experiencing long-term symptoms (2–5). Since epidemiological data do not account for the substantial number of individuals who do not seek hospital treatment post-injury and the lack of a clinical consensus on diagnostic criteria for mTBI remains, the prevalence of mTBI and consequences on health are likely underestimated from the limited prospective studies conducted to date.

Studies on the epidemiology of mTBI have shown that age is a major factor influencing the clinicopathological outcomes following exposure to mTBI, with a bimodal distribution between young adults (13–20 years old) and older adults (>65 years old) recovering differently from injuries of a similar severity (6–8). However, a recent review on the chronic consequences of mild and moderate/severe TBI (9) reported that the association between mTBI and the long-term mortality (at least 5 years after mTBI) depended largely on the sample population. The role that age plays in the pathological response to mTBI remains controversial (10–12). Disparity in these findings may be related to environmental factors such as drug abuse, level of education, rehabilitation length and familial support (13).

Nevertheless, it has been accepted that age at injury also has a significant influence on dementia risk in patients > 65 years of age following exposure to mTBI (14). Characterization of autopsy-acquired tissue from long-term survivors of repetitive mTBI reveals a complex neuropathology, best described as a 'polypathology', including abnormal tau and amyloid protein aggregation, neuroinflammation, white matter degradation and axonal degeneration (15). This pathology is masked by effect of normal ageing and may augment or accelerate pre-existing age-related pathologies. Therefore, it is important to develop a greater understanding of the age-dependent pathophysiological process following mTBI, to improve diagnostic and therapeutic interventions and recognize age-related risk factors for patients.

The present study investigated the 'polypathology' associated with repetitive mTBI in 3- and 12-month-old mice at an acute time point post-injury (24 h). To our knowledge, only a few pre-clinical studies have investigated the influence of age and injury mechanism after TBI (16–19). Therefore, our study aims to address the impact of TBI on acute neuropathology in the young adult vs aged brain. We hypothesized that polypathology is more severe in older mice than younger mice during the acute phase following repetitive mild

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traumatic brain injury (r-mTBI). Our second objective is to determine whether sex differences in the animals play a role in their recovery. The focus on pathogenic tau pathology has been well documented chronically after exposures to repetitive mTBI in postmortem human brain tissue of patients (20,21); however, the origin of this tau pathology and relationship to the inciting injury are undetermined. Therefore, we have chosen to assess the mouse brain tissue at early time points (24 h) following repetitive injuries. We utilized hTau mice that have been genetically modified to express all six isoforms of non-mutant human Microtubule-Associated Protein Tau (MAPT) in a murine *Mapt* knockout background. These mice start to express membranous tau redistribution at 3 months of age and present tau hyperphosphorylation and aggregation by 12 months of age (22–24). Here, we explore the influence of age at injury (young [3 months] and aged [12 months]) on acute neuropathological sequelae in hTau mice.

Materials and methods

Animals

Young (3 months old) and aged (12–13 months old) male and female mice, expressing all six isoforms of human tau (hTau) on a C57BL/6 and null murine tau background (Jackson Laboratories, Bar Harbor, ME), were housed singly under standard laboratory conditions (23°C ± 1°C, 50 ± 5% humidity, and 12-h light/dark cycle) with free access to food and water. All procedures were carried out under Institutional Animal Care and Use Committee approval and in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Injury groups and schedule

Forty-eight young and fifty-two aged hTau mice were randomly assigned to TBI or sham conditions. Unless otherwise noted, histochemical studies were performed with: young male TBI (n = 6), young female TBI (n = 8), young male sham (n = 6), young female sham (n = 7), aged male TBI (n = 11), aged female TBI (n = 8), aged male sham (n = 11), and aged female sham (n = 10). The rest of the brains were stored for additional future analyses. Mice assigned to r-mTBI conditions received five injuries over 9 days, with an inter-injury interval of 48 h. Sham (r-sham) animals were anaesthetized with the same frequency and exposure time as their r-mTBI counterparts, but without injury. As described in our original publication on this model (25), the inter-injury interval was chosen to accommodate repeated injuries occurring within an asymptomatic window of vulnerability from the previous injury that had been described in a rat model (26). We have extensively characterized this model in wild-type mice (25,27,28) and therefore have knowledge of the outcomes observed that can be used as point of reference.

Injury protocol

Mice were subjected to closed head mTBI as previously described (25). Prior to mTBI all mice were anaesthetized with 1.5 L/min of oxygen and 3% isoflurane, the top of their heads were shaved, and they were transferred to a stereotaxic frame (Just For Mice™ Stereotaxic, Stoelting, Wood Dale, IL) placed on a heating pad to maintain body temperature at 37°C and maintained under anaesthesia through a nose cone. A 5mm blunt metal impactor tip was retracted and positioned midway relative to the sagittal suture before each impact. Injury was triggered using the myNeuroLab controller at a strike velocity of 5 m/s, strike depth of 1.0 mm, and dwell time of 200 ms over the shaved area of the head. To be considered as a concussive injury, our injury paradigm should follow the following criteria: no skull fractures, hematomas or other gross signs of injury, and the presence of amyloid precursor protein (APP) immunoreactivity profiles in the corpus calossum as a sign of traumatic axonal injury. No mortality was observed with these mice during these experiments. At the end of the procedure, each animal was removed from the stereotaxic table, allowed to recover in its home cage resting on a heating pad until the animal was ambulatory. To control for the effects of repeated anaesthesia, sham animals underwent the same procedures and were exposed to anaesthesia for the same length of time as the mTBI animals, but were not exposed to head trauma.

Histology

All mice were euthanized 24 h after the last mTBI/sham injury by anaesthetization with isoflurane, followed by transcardial perfusion with heparinized Phosphate Buffered Saline (PBS) (pH 7.4) and PBS containing 4% paraformaldehyde. After perfusion, brains were post-fixed in 4% paraformaldehyde (4°C) for 48 h, embedded in paraffin using Tissue-Tek VIP (Sakura,Torrance, CA, USA), cut at 6 µm on a 2030 Biocut microtome (Reichert/Leica, Germany), and mounted on positively charged glass slides (Fisher, Superfrost Plus). Sections were deparaffinized in xylene and rehydrated in an ethanol-to-water gradient. Slides were analysed using a bright field microscope (BX60, Leica, Germany) and digital images were visualized and acquired using a MagnaFire SP camera (Olympus, Tokyo, Japan). Sets of adjacent sections were stained for glial fibrillary acid protein (GFAP, 1:20 000; Dako, Glostrup, Denmark, ZO334), ionized calcium binding adaptor molecule 1 (Iba1. 1:5000; Abcam, Cambridge, MA, ab5076), or amyloid precursor protein (APP, 1:20 000; Millipore, Billerica, MA, MAB348). Tau immunohistochemistry was performed using the following monoclonal antibodies at a 1:500 dilution: CP13 [pS202], PHF1 [pS396/404], and RZ3 [pThr231]. CP13, PHF1, and RZ3 were generously provided by Dr Peter Davies, The Feinstein Institute for Medical Research, Bronx, NY. As a negative control, for each antibody, a single section was processed for immunostaining without the inclusion of the primary antibody. Tissue sections were subjected to antigen retrieval with either heated trisethylenediaminetetraacetic acid (EDTA) buffer (pH-8.0) or citrate buffer (pH-6.0) under pressure for 7 min. Endogenous

peroxidase activity was quenched with a 15 min H_2O_2 treatment (3% in water). Each section was rinsed and incubated with the appropriate blocking buffer (ABC Elite kit, MOM kit, Vector Laboratories, CA) for 20 min, before applying the appropriate primary antibody overnight at 4°C. Then, the diluted biotinylated secondary antibody from the ABC Elite Kit was applied. Antibodies were detected using the avidin-peroxidase complex, after incubation with the chromogen 3,3-diaminobenzidine (DAB) peroxidase solution (0.05% DAB - 0.015% H_2O_2 in 0.01M PBS, pH 7.2) for 6–7 min and counterstained with hematoxylin. Immunofluorescence was performed with an antibody for p-tau RZ3 (1:500). Prior to immunostaining, samples were deparaffinized in xylene and rehydrated through a gradient of ethanol solutions of decreasing concentrations (2 × 100%, 95%, 70%). Antigen retrieval consisted of heating slides in a citrate solution (pH 6.0) under pressure, washing with PBS, and transferring into a Sudan black solution (EMD Millipore, MA) (15 min) to inhibit autofluorescence. Before primary antibody treatment, slides were blocked for 1 h with 10% donkey serum. The primary antibody for RZ3 was applied on the slides and left overnight at 4°C. The next day, donkey anti-Mouse IgG secondary antibody Alexa Fluor 488 was applied for RZ3. Slides were mounted with ProLong Gold Antifade DAPI Mount.

Quantitative immunohistochemistry

Mice from both age groups ($n = 4$) were euthanized 24 h post-injury, and sagittal sections were immunostained and then analysed by an observer blinded to experimental conditions using ImageJ software (US National Institutes of Health, Bethesda, MD). Images were separated into individual colour channels (red hematoxylin counter stain and DAB brown chromogen) using the colour deconvolution algorithm (29). Three non-overlapping areas of 100 μm (2) from each of two sagittal sections in the corpus callosum (CC) were randomly selected within which the area of GFAP or Iba-1 immunoreactivity was calculated and expressed as a percentage of the field of view as previously reported. The numbers of APP-positive profiles were manually counted in three non-overlapping areas of 100 μm (2) within the CC. The immunohistochemical outcomes were expressed as percent area of GFAP, Iba-1, and RZ3. Variables of interest included sex, injury group (mTBI vs sham), age (young vs aged), and their interactions. Descriptive statistics, including means and standard errors, were calculated from the percent area of GFAP and Iba-1 measurements for each age, injury group, and sex. Average percent areas were calculated within an animal (across sections), prior to calculating age, injury group, and sex averages and standard errors. Descriptive statistics, including medians and 25th and 75th percentiles, were calculated from the number of APP-positive profiles for each age, injury group, and sex. The raw percent area data were assessed for normality using the Shapiro–Wilk test as well as four alternative transformations (square root, base-10 logarithm, logit, and arcsine square root). The transformation that most closely approached normality was used for all subsequent analysis. The GFAP and Iba-1 data were analysed using a mixed ANOVA model with age, sex, and injury group, and their interactions, as explanatory variables. In addition to these model terms, a random variance component for mouse was included such that multiple observations on the same mouse were weighted together and not individually. This model was used to estimate the size and significance of the difference in percent area between ages (overall and within injury group and gender), injury groups (overall and within age and gender), and between genders (overall and within age and injury group).

For the APP data, no APP-positive profiles were observed in any of the Sham animals. The APP data were analysed using a mixed Poisson regression model with age, sex, and their interaction as explanatory variables. In addition to these model terms, a random variance component for mouse was included such that multiple observations on the same mouse were weighted together and not individually. This model was used to estimate the size and significance of the difference in the number of APP-positive profiles between ages (overall and within gender) and between genders (overall and within age). All statistical analyses were performed using SAS (ver. 9.4) and all results are reported using the 0.05 level of significance.

Results

Repetitive mTBI induces a stronger astrogliosis response in the CC in aged mice

For all groups, the entire CC (splenium, body, and genu) was assessed in GFAP-stained sections. Quantitative analysis revealed TBI-dependent differences in GFAP immunopositivity in the body of the CC among females and males and in the young and aged cohorts (Figure 1(b, d, f, h); $p < 0.001$). Interactions between age and injury group, age and gender, injury group and gender, and the three-way interaction between age, injury group, and gender were not significant. The quantification of GFAP immunostaining is summarized in Table 1.

Repetitive mTBI induces a stronger microgliosis response in the CC in young mice

To gain insight into whether age influences the degree of inflammation following mTBI, we investigated Iba-1, a marker of microglia in young and aged animals. Microglial cell structures were similar across comparable groups displaying a primed morphology characteristic of an aged mouse brain in the 12 months cohort (with a more inflammatory microglia phenotype, e.g., increased major histocompatibility complex II [MHCII], IL-1β, CD68, complement receptor [CR]3) (30). Similar to the GFAP analysis, the entire CC was assessed for Iba-1 immunoreactivity. There were TBI-dependent quantitative difference in the level of Iba-1 immunopositivity detected in the body of the CC among females and males and in the young and aged cohorts (Figure 2(b, d, f, h); $p < 0.001$). The interaction between age and injury group was significant, but the interactions between age and gender, injury group and gender, and the three-way interaction between age, injury group, and gender were not significant. The quantification of Iba-1 immunostaining is summarized in Table 2.

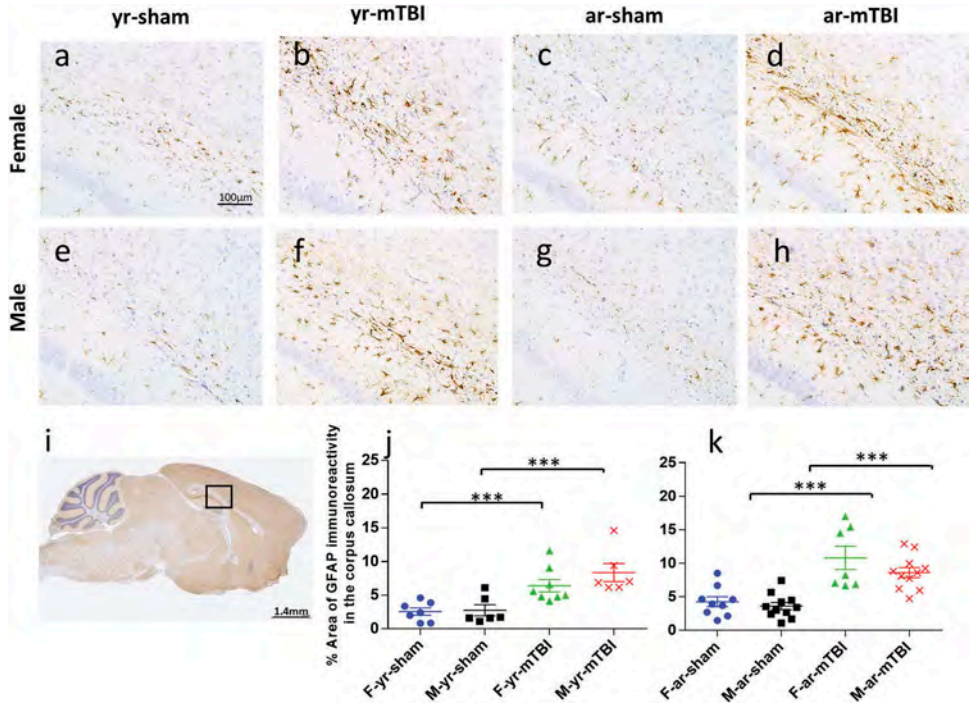

Figure 1. Repetitive mTBI increases astrogliosis in the corpus callosum at 24 hours post-injury. Black box (i) indicates the area of interest shown at higher magnification (a–h) in a sagittal section of a mouse brain. Sagittal sections of the mouse brain approximately 0.2 mm lateral to midline in the body of the CC with GFAP stained in male (a-d) and female (e-h). Graphs showing that the average percent area for the r-mTBI group was greater compared to the sham control group for females (averaged over age, $p < 0.001$), males (averaged over age, $p < 0.001$), aged (averaged over sex, $p < 0.001$), young (averaged over sex, $p < 0.001$), and overall (averaged over sex and age, $p < 0.001$) (j, k). Tissue sections were counterstained with hematoxylin; each symbol represents 1 mouse. Scale bar, 1.4mm and 100 µm, respectively. Blue symbols, F-yrsham: Female young repetitive sham; Black symbols, M-yr-sham: Male young repetitive sham; Green symbols, F-yr-mTBI: Female young repetitive mTBI; Red symbols, M-yr-mTBI: Male young repetitive mTBI.

Table 1. Summary of GFAP quantification.

Effect	Effect *p*-value	Variable comparison	Model estimated average percent area		Comparison *p*-value
Injury (mTBI vs sham)	<0.001*		mTBI	Sham	
		Within young	6.93	2.27	<0.001*
		Within aged	9.20	3.52	<0.001*
		Within females	7.99	3.02	<0.001*
		Within males	8.07	2.71	<0.001*
Age (young vs aged)	<0.001*		Young	Aged	
		Within mTBI	6.93	9.20	0.034*
		Within sham	2.27	3.52	0.051
		Within females	3.89	6.72	0.001*
		Within males	4.70	5.37	0.427

* Significant at the alpha = 0.05 level of significance.

APP immunoreactivity is reduced following r-mTBI in aged compared to young mice

APP-immunoreactive axonal profiles, a marker of axonal injury, were observed 24 h post-injury in the CC (Figure 3(i)) of both young and aged r-mTBI groups (Figure 3(b, d, f, h)) but not in controls (Figure 3(a, c, e, g)). These APP immunoreactive axonal profiles were observed as small, granular immunoreactive profiles within the CC (Figure 3(b, d, f, h)). The difference in the number of APP-immunoreactive profiles observed was greatest in the young r-mTBI vs aged r-mTBI comparison (Figure 3(j, k); $p < 0.001$), with no gender effects detected ($p > 0.05$). The quantification of APP immunostaining is summarized in Table 3.

Repetitive mTBI induces an elevation of hippocampal RZ3 p-tau 24 h post-injury

To investigate the effect of TBI on tau in our model, we performed a quantitative immunohistochemical analysis of RZ3, CP13, and PHF1 (an antibody that recognizes early and late tau pathology). The average percent area of RZ3 immunoreactivity in the hippocampal pyramidal layer (Figure 4(a, c, e, g, i, j)) was significantly increased in the mTBI group compared to the sham control group among male (averaged over age, $p < 0.001$), aged (averaged over gender, $p = 0.002$), young (averaged over gender, $p = 0.015$), and overall (averaged over gender and age, $p < 0.001$) mice. Additionally, the average percent area was reduced in young vs aged male mice (averaged over

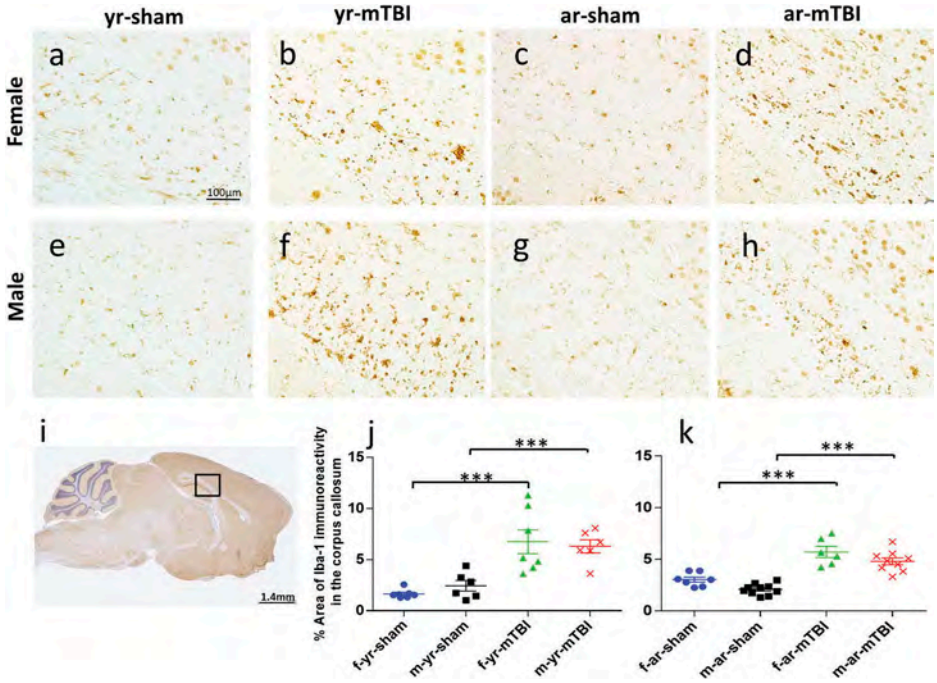

Figure 2. Corpus callosum Iba1 immunohistochemical anaylsis. Sagittal sections of the corpus callosum (± 0.4 mm lateral to midline) in female (a–d) and male (e–h) mice. Black box (i) indicates the area of interest shown at higher magnification (a–h) in a sagittal section of a mouse brain. There was no microglial activation in the sham groups (a, c, e, g). An increased area of anti-Iba1 immunoreactivity was observed in the corpus callosum at 24h post r-mTBI in young and aged animals (b, d, f, h).

Table 2. Summary of Iba-1 quantification.

Effect	Effect *p*-value	Variable comparison	Model estimated average percent area		Comparison *p*-value
Injury (mTBI vs Sham)	<0.001*		mTBI	Sham	
		Within young	6.27	1.73	<0.001*
		Within aged	5.03	2.42	<0.001*
		Within females	5.85	2.15	<0.001*
		Within males	5.42	1.97	<0.001*
Age (young vs aged)	0.913		Young	Aged	
		Within mTBI	6.27	5.03	0.023*
		Within sham	1.73	2.42	0.034*
		Within females	3.55	4.00	0.327
		Within males	3.74	3.24	0.242

* Significant at the alpha = 0.05 level of significance.

injury group, $p = 0.026$), within the mTBI group (averaged over gender, $p = 0.034$), and overall (averaged over gender and injury group, $p = 0.009$). The average percent area was also reduced in females vs males among aged mice (averaged over injury group, $p = 0.038$) and for the mTBI group (averaged over age, $p = 0.002$). There was no overall gender effect. The interactions between age and injury group, age and gender, and the three-way interaction between age, injury group, and gender were not significant, but the interaction between injury group and gender was significant ($p = 0.008$). Immunohistochemical assessment of soluble phosphorylated tau pSer-202 (CP13) was similar to RZ3 and none of the brains showed neurons positive for PHF1 (data not shown). The quantification of RZ3 immunostaining is summarized in Table 4.

Discussion

In the current study, we have examined the acute pathological outcome (24 h post-last injury) of r-mTBI in the brains of young and aged hTau mice. Our data support a TBI-dependent difference between young and aged animals, with increased astrogliosis and tau pathology in older animals, whereas an opposite pattern was observed for microgliosis and axonal degeneration. In addition, as we and others have previously reported (17,27,31), we observed age-dependent changes in astrogliosis, microgliosis, and axonal injury within the CC, an area of the white matter of the brain known to be particularly vulnerable to repetitive brain injuries in our model. This study also revealed a possible sex-dependent link between age at injury and a subsequent acute increase in phosphorylated tau species observed in pre-tangle neurons in both the hippocampus and cortex.

We previously identified an increase in PHF1 positive hyperphosphorylated tau in male TBI mice compared to females using a similar injury model at 15 days post-injury (17); herein, we now demonstrate that sex-dependent differences in p-tau pathology appear as early as 24 h post-last injury. The present study revealed an increase in RZ3 phosphorylated tau in the hippocampus without any appreciable increase in PHF1 levels,

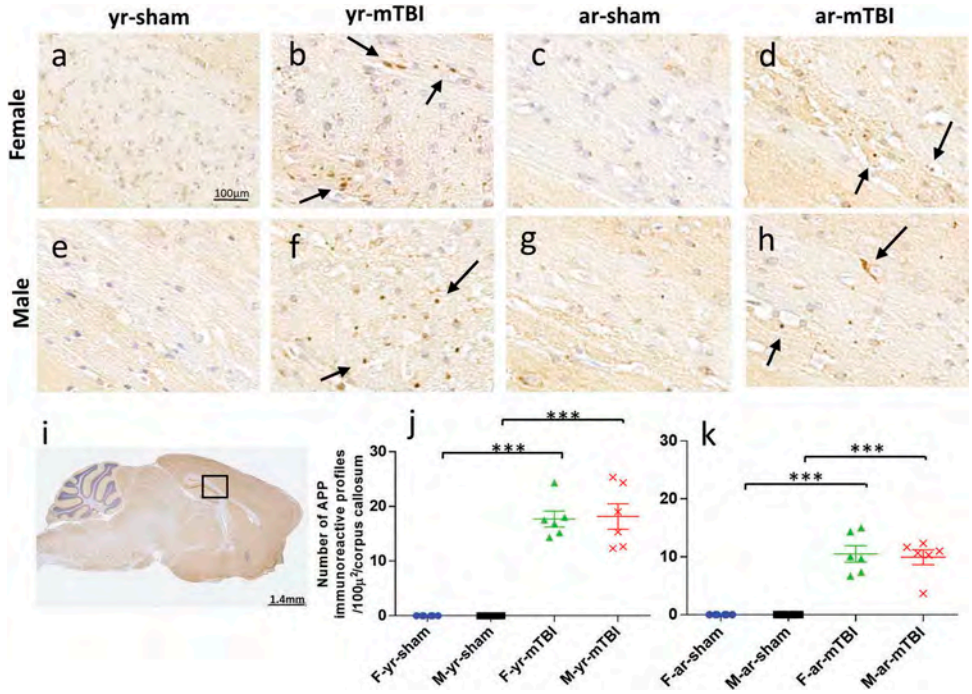

Figure 3. Amyloid Precursor protein (APP) immunohistochemistry of sagittal sections of the mouse brain at ± 0.4 mm lateral to midline in the corpus callosum in female (a–d) and male (e–h). Black box (i) indicates the area of interest shown at higher magnification (a–h). Young and aged sham tissue (a, c, e, g) was negative for APP immunostaining. Corpus callosum immunoreactive fragments appeared as discrete axonal profiles in all injured animals (b, d, f, h). The number of APP-positive profiles was greater in young compared to aged mice among females ($p = 0.010$) and males ($p < 0.001$) and overall (averaged over sex, $p < 0.001$) (j, k).

Table 3. Summary of APP quantification.

Effect	Effect *p*-value	Variable comparison	Model estimated average number of APP-positive profiles		Comparison *p*-value
Age (young vs aged)	<0.001*		Young	Aged	
		Within females	15	10	0.010*
		Within males	18	10	<0.001*
Gender (female vs male)	0.723		Female	Male	
		Within young	15	18	0.364
		With age	10	10	0.745

* Significant at the alpha = 0.05 level of significance.

supporting time-dependent changes for different p-tau epitopes specific for pre-tangle structures. While p-tau protein is a key component of the pathology seen in neurodegenerative tauopathies (32–34), it also plays an important role in neuroplasticity, including dendritic/synaptic remodelling observed in the brain in response to environmental challenges, such as TBI (35,36) and hypothermia/hibernation (37,38). Therefore, the physiological changes reported in the brains of these mice may be the emergence of an insidious pathological process; however, they may also be part of an attempt by the brain to repair the structural damage caused by repeated head trauma. Regardless of the biological repercussions, our observations at 24 h, in addition to our previous work at 15 days post-injury, indicate that the levels of RZ3 and PHF1 phosphorylated tau are both increased in male mice, while no significant changes were observed in female mice at 24 h or 15 days post-injury. We cannot, however, rule out that these observations are unique to hTau mice, because no clinical studies to date have addressed the role of sex on tau pathology after TBI. It is worth noting that because it has been previously reported that male PS19 mice (mutant tau) develop tau pathology more consistently than females, almost all preclinical studies exclusively use male animals to reduce the variability of tau pathology (39). Similar to the conditions in preclinical models, the autopsied brain samples used for many of the current clinical histopathological reports of tauopathy following TBI are almost exclusively male in origin; thus, the speculation as to how sex influences the outcome on tau pathology has yet to be determined. Further work is necessary to address the gender difference in tau pathology in both, animals and most especially, in clinical studies.

Our study has several limitations. The first limitation is that the hTau mouse line has shown that naïve animals start to express signs of early tau pathology at 3 months of age and neurofibrillary tangles at 9 months of age (23,24). Given the increasing evidence that a disruption in the normal phosphorylation state of tau plays a key role in the pathogenic events that occur in other neurodegenerative conditions (40), our results may not reflect the pathology that would have been observed in wild-type animals. The second limitation of this study lies in its design as it cannot be determined whether the pathology observed is due to the first or last mTBI. However, the results observed from our previous work in wild-type

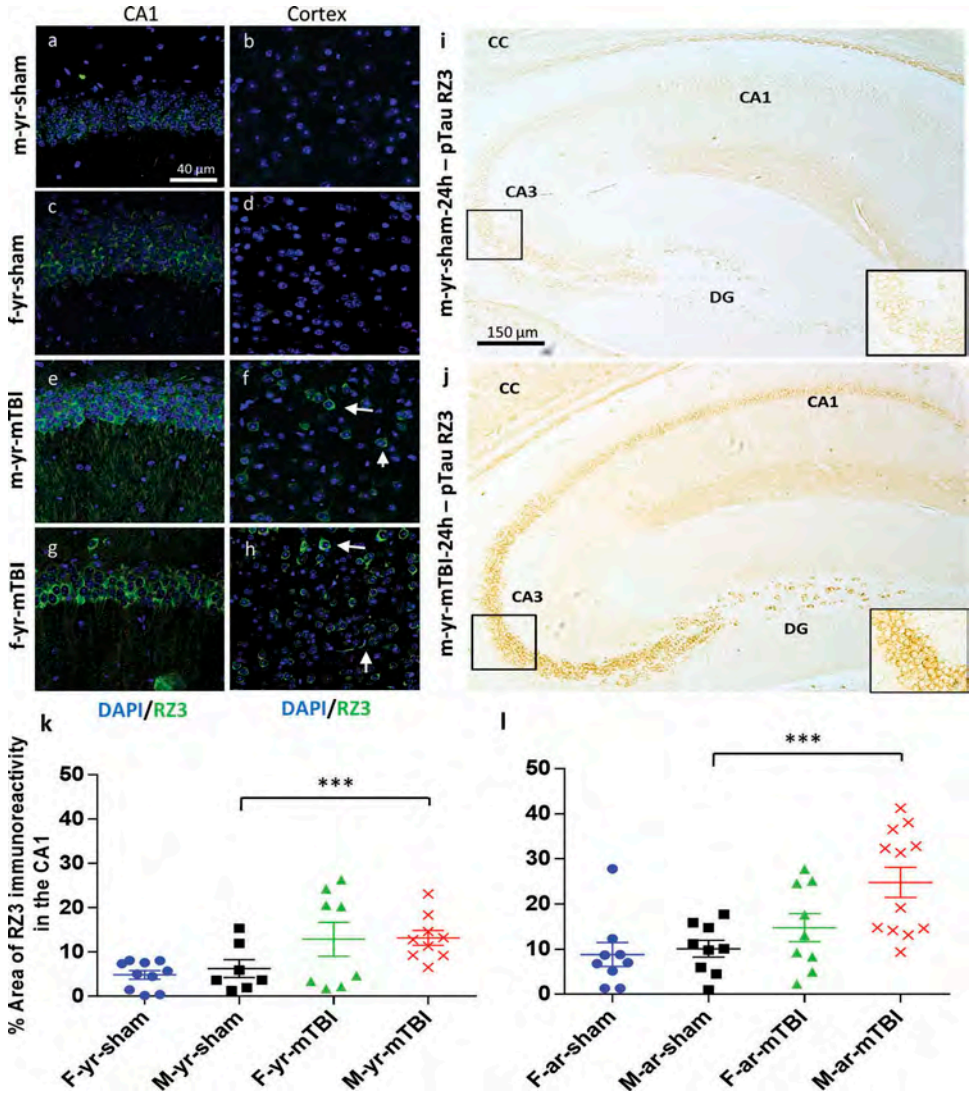

Figure 4. Immunohistochemical assessment of soluble phosphorylated tau pThr231 (RZ3) at approximately 0.5 mm lateral to midline in the CA1 region of the hippocampus (a, c, e, g) and in the neocortex (b, d, f, h) at 24h post injury in young female and male mice. Qualitatively, the r-mTBI group showed greater dendritic and membranous staining (green fluorescent signal) in both the CA1 and cortical neurons (arrows in Figure 4f, h) compared to their respective shams (a-d). An increase of RZ3 immunoreactivity was also observed in the hippocampus region of the injured animals for both genders and in the young and aged animals (Figure 4i, j). The red box indicates the region of interest, which is shown at a higher magnification. The average percent area of RZ3 immunoreactivity was increased in the mTBI group compared to the control group among male mice (averaged over age, p=0.001; Figure 4k, l). Additionally, the average percent area was significantly reduced in young vs. aged mice among male mice (averaged over injury group, p=0.0264; Figure 4k, l) and the mTBI injury group (averaged over gender, p=0.034; k, l). The average percent area was also observed to be significantly reduced in females vs. males among aged mice (averaged over injury group, p=0.038; k,l).

Table 4. Summary of RZ3 quantification.

Effect	Effect *p*-value	Variable comparison	Model estimated average percent area		Comparison *p*-value
Injury (mTBI vs sham)	0.0003*		mTBI	Sham	
		Within young	10.30	3.16	0.0153*
		Within aged	17.35	7.69	0.0022*
		Within females	8.84	5.53	0.1800
		Within males	19.38	4.83	0.0002*
		Averaged over gender and age	13.60	5.17	0.0003*
Age (young vs aged)	0.0088*		Young	Aged	
		Within mTBI	10.30	17.35	0.0339*
		Within sham	3.16	7.69	0.0836
		Within females	5.36	9.06	0.1348
		Within males	7.13	15.43	0.0264*
		Averaged over injury and gender	6.21	12.04	0.0088*

animals suggest that our five injury paradigm exacerbates the pathology that would have been observed after a single injury (25). Another limitation is that even young mice may have early tau pathology and therefore could affect normal TBI

pathology. Because we published and demonstrated a lack of injury effect of tau pathology in wild-type mice, we decided to use the hTau mice which expressed all six hTau isoforms and demonstrate age-related changes in tau pathology as observed in normal ageing. It is well established that age-related tauopathy is a normal feature of ageing (see progressive age-related tauopathy (41) and hyperphosphorylated tau in young and middle-aged subjects (42)). Therefore, using this model despite the progressive age-related increase in phospho-tau pathology between 3 months (approx. 14-21 years – humans) and 12 months (approx. 30–39 years – humans) of age, we consider to be related to the pattern of normal tau pathology observed with humans over time and in individuals exposed to injuries at these age groups. Finally, further studies with the inclusion of additional post-injury time points throughout the lifespan of the animal are required to understand how tau interacts with the polypathology resulting from the cumulative effects of repetitive mTBI. Multiple lines of evidence in pre-clinical (27,28,35) and clinical work (9) suggest that TBI is a chronic, evolving, and perhaps lifelong disorder. Such cohorts could serve as a platform and aid in the design and implementation of clinical trials of new therapies considering the different types of pathological markers present at acute and chronic time points post-injury. For example, exploring the long-term efficacy of different treatment regimens aimed at reducing potentially pathogenic tau species such as the use of an antibody against cis phospho tau conformations (43,44) or sodium selenate (45). Given the prominent changes in glial cells, a second possible treatment at chronic time points could target post-traumatic neuroinflammation by minimizing the detrimental neurotoxic effects and creating the optimal condition for regeneration.

Despite a growing body of clinical evidence suggesting that r-mTBI is an important risk factor for neurodegenerative diseases (14,15,21,46), the causal link and the role of tau as a common pathology remain unclear. Moreover, how the aged brain responds to repetitive mTBI compared to a younger brain remains unknown. Nonetheless, considering that older patients demonstrate worse outcomes despite sustaining less high energy impact (47,48), several studies have suggested that aged patients are more vulnerable to TBI (49–53). However, the particular relationship between mTBI and increased risk for dementia or morbidity is less clear (reviewed in Gardner and Yaffe, 2015 (54) and Wilson and colleagues 2017 (9)). To that end, we investigated whether an increased level of total tau and p-tau in the brains of aged hTau mice (12 months of age (22–24)) is associated with a stronger neuroinflammatory response after r-mTBI. We observed that increased astrogliosis and p-tau was more pronounced in aged mice when compared to young mice; however, this was not observed with respect to traumatic axonal injury and microgliosis, at 24 h post-injury. While our results highlight that older age at injury produces more pronounced astrogliosis and tau phosphorylation, these changes were relatively mild in nature (< two-fold change), suggesting that the polypathology resulting from the exposure of r-mTBI in mid-age animals is likely the result of normal ageing and the primed state of the resident glial cells (31). Another potential limitation is that our aged mice are only between 12 and 13 months old, and therefore are not representative of the clinical studies of 65+ year-old human's mentioned in the introduction. Although mouse and human developmental stages are generally not a linear relationship, middle age is considered to be around 12–15 months in mice. In addition to increased astrogliosis, our results support a TBI-dependent increase in RZ3 p-tau observed in male hTau mice. Yet, this increase in p-tau pathology at 24 h post-injury was not associated with a more robust glial response in males when compared to their females' counterparts, suggesting a diminished role for p-tau on acute neuroinflammation (24 h post-injury). Finally, we found that axonal injury was decreased in the aged injured group at 24 h post-injury. Whether this represents a true age-related effect on axonal injury will require future studies; it is noteworthy that APP immunostaining only captures a subpopulation of injured axons, and thus further measure of detecting the full extent of axonal injury is needed. Nonetheless, our results are consistent with our previous reports showing an attenuation of axonal swelling in older mice (17). Although the many differences in TBI models and experimental designs make direct comparison challenging, these results are consistent with the recent work of W.H. Cheng et al. that showed a robust decrease in axonal neurofilament pathology after mTBI in aged WT and transgenic mice harbouring the APP/PS1 mutations (55). Whether this pathology is unique to rodents remains to be determined. Further studies are necessitated in human autopsy cases.

Conclusion

This study shows that r-mTBI in young adult hTau mice induces age-dependent, sex-specific differences on pathological outcome at 24 h post-injury. Of particular interest here, we only found a sex-dependent difference for phosphorylated tau stained with RZ3 in young and aged male hTau mice. However, this increase in p-tau was not associated with an increase of Iba-1 and GFAP staining typically seen in this model of r-mTBI, suggesting a diminished role of phosphorylated tau in young and aged hTau mice at 24 h post-injury. Altogether, these findings suggest that future studies should incorporate both males and females to provide a greater understanding of injury prognosis and better inform clinical practice.

Declaration of interest

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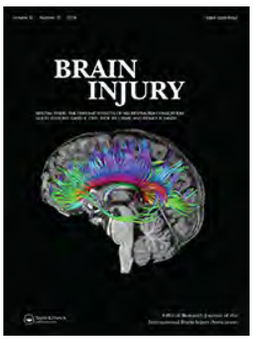
Appendix 10

Functional brain connectivity and cortical thickness in relation to chronic pain in post-911 veterans and service members with mTBI



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Functional brain connectivity and cortical thickness in relation to chronic pain in post-911 veterans and service members with mTBI

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ABSTRACT

Objectives: Investigate the relation of chronic pain interference to functional connectivity (FC) of brain regions and to cortical thickness in post-911 Veterans and Service Members (SMs) who sustained a mild traumatic brain injury (mTBI).

Methods: This is an observational study with cross-sectional analyses. A sample of 65 enrollees completing initial evaluation at a single site of the Chronic Effects of Neurotrauma Consortium (CENC) reported pain interference ratings on the TBI QOL. Functional connectivity and cortical thickness were measured.

Results: Severity of pain interference was negatively related to FC of the default mode network (DMN), i.e., participants who reported more severe pain interference had less FC between mesial prefrontal cortex and posterior regions of the DMN including posterior cingulate cortex and precuneus. Cortical thickness of specific regions was positively related to severity of pain interference.

Conclusion: The more that pain was perceived to interfere with daily life, the less the FC between regions in a network associated with self-referential thought and mind wandering. Although cortical thickness in specific brain regions was positively related to severity of pain interference, follow-up longitudinal data, control group data, and study of individual differences in this cohort will expand this initial report and replicate these findings.

KEYWORDS

Traumatic brain injury; pain; imaging; functional connectivity; cortical thickness

Introduction

Chronic pain is a frequent comorbidity and source of functional impairment in post-911 Veterans and Service Members (SMs) who have sustained mild traumatic brain injury (mTBI) (1-3). The proportion of SMs reporting pain is higher in those who have sustained an mTBI than those without a history of head injury (3). Chronic pain, which refers to pain persisting longer than 3 months, often occurs in post-911 Veterans and SMs with mTBI as part of a triad that also includes depression and post-traumatic stress disorder (PTSD) (1,4). This constellation of conditions is also associated with a general decline in physical and mental health (5). Pain intensity refers to how severely an individual hurts, whereas pain interference refers to the extent that pain hinders engagement in relevant domains of a person's life including social, cognitive, emotional, physical and recreational functions (6). Combat exposure in Veterans and SMs, particularly those from recent conflicts in Afghanistan, Iraq and follow-on conflicts, has been associated with significantly higher pain intensity and pain interference, with mTBI, PTSD and depression either independently contributing to or mediating the relationship with pain (7-10).

Our understanding of the neural basis of pain has been enhanced through using structural and functional neuroimaging techniques. Morphometric analysis of structural magnetic resonance imaging (MRI) has disclosed reduction of grey matter density in dorsolateral prefrontal cortex (DLPFC) of patients with chronic back pain as compared with controls of similar age (11). This reduction was directly related to severity of pain intensity, duration, and affective aspects of pain (11). PTSD, another condition associated with complex mTBI in Veterans and SMs, is also related to structural MRI findings. In a morphometric MRI study of post-911 Veterans, severity of current and lifelong PTSD was inversely related to cortical thickness in the postcentral and temporal gyri (12). Functional magnetic resonance imaging (fMRI) is based on the inference of changes in neuronal activity by measuring alterations in blood flow and subsequent changes in the ratio of deoxyhaemoglobin and oxyhaemoglobin (13). Specifically, the blood oxygen level dependent (BOLD) technique evaluates the difference in magnetic susceptibility between oxygenated blood (oxyhaemoglobin) required by active neurons and deoxygenated blood (deoxyhaemoglobin) and creates the fMRI signal from this difference.

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Although there are differences across studies in brain imaging findings related to the imaging modality utilized, and the etiology, nature (e.g. inflammatory versus neuropathic), and chronicity of pain-related symptoms, investigators have identified altered brain connectivity in complex networks of brain regions such as the thalamus, primary/secondary somatosensory areas, insular, anterior cingulate and prefrontal cortices (14). Studies of resting-state network functional connectivity (FC) in individuals with chronic pain have demonstrated disrupted network properties, especially failure to deactivate core regions of the default mode network (DMN) along with disrupted correlation and anti-correlation of regions of the DMN with attentional networks during performance of a cognitive task (15). The DMN is composed of the medial prefrontal cortex (mPFC), posterior cingulate, precuneus, lateral parietal and temporal lobes, and the hippocampal formation (16-18). Mechanistically, the DMN is activated by processing self-generated thoughts and feelings and deactivated by performing external tasks or otherwise attending to external stimuli. Consequently, preoccupation with chronic pain would be predicted to alter the DMN, including mPFC, which is a key region for self-generated activity. Most FC studies of civilian mTBI have focused on the first 1–3 months post-injury, often reporting altered FC of regions within the DMN and between regions of the DMN (e.g. precuneus) and regions outside the DMN, such as the ventrolateral prefrontal cortex that are specialized for complex cognitive operations involved in external tasks (19,20). Recent brain imaging research in civilians with chronic pain, including back pain, complex regional pain syndrome and knee osteoarthritis, found that all patient groups showed decreased connectivity of MPFC to the posterior constituents of the DMN, and increased connectivity to the insular cortex in proportion to the intensity of pain (21).

In the ongoing Chronic Effects of Neurotrauma Consortium (CENC) to investigate the long-term outcome of mTBI in post-911 Veterans and SMs, the participants undergo assessment of pain interference with activities of daily living as part of the observational study. To elucidate the neural underpinnings of chronic pain in this cohort, we correlated the assessment of pain interference with intrinsic brain activity measured with resting state functional magnetic resonance imaging (rs-fMRI). In contrast to mTBI in the civilian population, post-911 Veterans and SMs who have sustained an mTBI have a high prevalence of comorbid PTSD and depression which may affect FC of the DMN. The focus of this study was to begin investigation of FC of the DMN in relation to pain interference in the CENC cohort of Veterans and SMs who sustained mTBI. In this initial report, we present cross-sectional data on the relation of pain interference to FC of the DMN in the mTBI group. Pending collection of longitudinal data and imaging post-911 Veterans and SMs without mTBI as controls, we view the findings presented here as preliminary.

Methods

Design and subjects

This observational study evaluated the relation of self-reported pain interference with everyday activities on the TBI-QOL (6) to brain FC and cortical thickness in 65 post-911 Veterans and SMs who were diagnosed to have sustained an mTBI. The CENC observational study population is comprised of Operation Enduring Freedom (OEF; Afghanistan)/Operation Iraqi Freedom (OIF; Iraq)/Operation New Dawn (OND)-era Veterans and SMs who experienced combat situation(s) and a subgroup who had one or more mTBIs during deployment (in combat and/or non-combat situations), or prior to or following deployment. This report is limited to those participants who had at least one mTBI, were enrolled at a CENC centre which acquired imaging, whose data had been double checked at the time of analysis, and who were able to successfully complete the MRI scan without excessive movement. All study activities were approved by and conducted in accordance with all relevant Institutional Review Boards and other regulatory committees required by the VA and Department of Defense. Table 1 summarizes the demographic and clinical features of this sample.

Procedure

Measurement of pain interference

Pain interference items from the TBI QOL (6) were administered to the participants via the NIH Toolbox on the same day

Table 1. Study demographics

Characteristic	Total sample size (N = 65)
Age at Baseline	
Median	42.0
Min, Max	26, 59
Gender	
Male	53 (81.5%)
Female	12 (18.5%)
Race	
White	36 (55.4%)
African-American	25 (38.5%)
Other	4 (6.2%)
Ethnicity	
Not Hispanic or Latino	60 (92.3%)
Hispanic or Latino	4 (6.2%)
Not Sure	1 (1.5%)
Education	
High school graduate	3 (4.6%)
Some college	28 (43.1%)
College Graduate	34 (52.3%)
Service Branch	
Air Force	5 (7.8%)
Army	42 (65.6%)
Marines	12 (18.8%)
Navy	5 (7.8%)
DRRI-2 Combat Exposure[1]	
Median	34.0
Min, Max	17, 66
Total Number of mTBIs	
Median	2.0
Min, Max	1, 7
TBI with PTA	
Only TBI without PTA	20 (30.8%)
TBI with PTA	45 (69.2%)
TBI with LOC	
Only TBI without LOC	29 (44.6%)
TBI with LOC	36 (55.4%)
Years since Last mTBI	
Median	9.4
Min, Max	0, 44
TBI-QoL Pain Interference[2]	
Median	21.0
Min, Max	10, 50

[1]DRRI-2 = Deployment Risk and Resilience Inventory; Higher scores indicate greater combat exposure.
[2]TBI-QOL = TBI Quality-of-Life; Higher scores indicate greater pain interference

as imaging. Most of the items of the TBI-QOL Pain Interference short form were taken from the Patient Reported Outcome Measurement Information System (PROMIS) (6, 22) based on their validation in a sample of 590 persons with TBI (6). This 10-item bank measures the extent to which pain interferes with everyday activities, including cognitive, physical, recreational and social domains. Each item asks the participant to rate the severity of pain interference with a specific activity over the past 7 days. The ratings of interference used a five-point Likert-type scale, with higher scores indicating more severe pain interference. A sample item is "Over the past 7 days, how much did pain interfere with your day to day activities?" The anchors for each item are 1 (Not at All) and 5 (Very Much). The derived T score has a population mean of 50 and a standard deviation of 10. The TBI-QOL Pain Interference short form correlated with the PROMIS Pain Intensity scale, $r = 0.77$ in a general population sample ($n = 794$) (22). However, the Pain Intensity short and full forms were not included in the TBI-QOL. The TBI-QOL Pain Interference short form has good psychometric properties, including a Cronbach alpha estimate of 0.99, correlations of short forms with the full form ranging from 0.68 to 0.89 and strong evidence for its unidimensionality (6). Cella et al. reported high correlations of the Pain Interference short form with legacy measures of pain in a general population sample (22).

Functional connectivity

During the resting state acquisition, the MRI technologist instructed the participants to lie still and to keep their eyes open and fixated on a marker affixed to the top of bore and within their line of sight. Following the rs-fMRI sequence, participants were queried to assess their wakefulness. None of the participants included in the analysis were determined to have been sleepy or had fallen asleep during the imaging session.

Image data acquisition

To minimize issues related to site-related differences, we confined the analysis reported here to subjects at a single data collection site. Whole brain imaging was performed using a 32-channel head coil on a Philips 3 T Ingenia system (Philips, Best, Netherlands) at the Collaborative Advanced Research Imaging facility (CARI), Wright Center for Clinical and Translational Research, Virginia Commonwealth University. Regular quality assurance (QA) testing was performed throughout the course of the study, and no issues were detected. BOLD T2*-weighted echo-planar images (EPI) were acquired as 200 volumes with 48 axial slices of 3.3 mm thickness with a 0 mm gap, using a 212-mm field of view (FOV), 64 × 64 matrix, repetition time (TR) of 3000 ms, echo time (TE) of 30 ms and an 80-degree flip angle. A set of three dimensional (3D) high-resolution T1-weighted images were also acquired in 170 sagittal slices of 1.2 mm thickness (no gap) with 240 mm FOV, 256 × 256 matrix, TR of 6.78 ms, TE of 3.16 ms and a 9.0-degree flip angle.

Statistical analysis

Demographic and behavioural data

Characteristics of the sample are summarized by mean and standard deviation for continuous variables, median and minimum/maximum for non-normally distributed continuous variables, and frequency and percentage for categorical variables. Statistical analysis of imaging data is further described below.

FC image processing and analysis

The Functional Connectivity Toolbox (Conn) (23) within Statistical Parametric Mapping (SPM) SPM8 (Wellcome Department of Cognitive Neurology, University College, London, UK) implemented in Matlab (Mathworks Inc. Sherborn MA, USA) was used to process and analyse data. Functional images of each subject were realigned, co-registered with each subject's high resolution anatomical image, normalized to the Montreal Neurological Institute (MNI) template, and smoothed using a 6 mm full width-half maximum (FWHM) Gaussian filter. Anatomical landmarks in the normalized high resolution anatomical and functional data were visually checked and compared against the MNI template for each subject. Each subject's anatomical image was segmented into grey matter, white matter (WM) and cerebrospinal fluid (CSF) masks. Physiological noise was addressed by using WM and CSF masks as covariates. Realignment parameters and their first-order derivatives were also covaried. The Artifact Detection Toolbox (23) was used to repair artefact due to frame-by-frame head movement and correct global drift. Outlier time points were defined as exceeding 0.5 mm or three standard deviations from the mean image intensity of the complete resting state run. Outliers were included as regressors in the first level general linear model (GLM) along with motion parameters. Data were band-pass filtered between 0.008 and 0.09 Hz, the default frequency range in the SPM Conn toolbox. The high-pass value was selected to approximate both SPM's default value (0.0078 Hz) and a 2 min value suggested as a standard (0.0083 Hz) (24). The low-pass value approximates the frequently reported 0.08 and 0.10 Hz values and SPM's haemodynamic response function cut-off frequency of 0.091 Hz. FC was measured with single seeds in the following regions of the DMN: (1) MPFC, (2) posterior cingulate cortex (PCC), (3) left lateral parietal lobe (LLP) and (4) right lateral parietal lobe (RLP) (Fox 2005). Seeds were made available by the Conn software package and were 10 mm spheres centred around the following MNI coordinates MPFC: -1 49 -5; PCC -6 -52 40; LLP -46 -70 36; RLP: 46 -70 36.

A GLM was used to estimate the correlation between the seeds and the whole brain on a voxel-wise level for individual participants (first level). Pearson correlation coefficients were then transformed into z-scores using Fisher's method followed by group (second level) random effects analyses, and mean-centred pain interference scores of each subject were regressed onto the *z*-scores representing FC. In SPM, significant clusters are determined by two thresholds, one that is applied to individual voxels (the voxel-level threshold) and another that is applied to the voxels that survive that

threshold and occur spatially contiguous with other voxels (cluster-level threshold). Significance was defined by a voxel (height) threshold of $p < 0.001$(25), uncorrected, recommended for control of inflated cluster extent (26), and a cluster threshold of $p < 0.05$, false discovery rate (FDR) corrected for multiple comparisons across the whole brain. The Bonferroni method was further used to correct for the number of tests (4 seeds × 2 tails = 8; $p = .05/8 = 0.00625$) in the FC analysis. As an exploratory post-hoc analysis of the effect of TBI frequency, the sample was separated into two subgroups of subjects based on the number of TBIs they reported (1–2 or >2). Regressions of pain interference scores onto FC were then carried out in each group separately.

Cortical Thickness Analysis

An exploratory analysis of cortical thickness was undertaken using the automated post-processing software, FreeSurfer® (http://surfer.nmr.mgh.harvard.edu/) (27), version 6.0. Following initial automated analysis, a manual inspection of the accuracy of post-processing steps, including cortical parcellation, was performed. Identifiable errors were corrected through the FreeSurfer® toolbox. Following manual inspection and any necessary edits, each subject was reprocessed through the automated pipeline to account for manual intervention. Once the automated pipeline and manual editing were adequately completed, the FreeSurfer Query, Design, Estimate and Contrast (QDEC) analysis tool was used to fit between-subject GLMs for those study participants with minimal pain interference reporting in contrast to those with the highest levels. To arrive at the lowest and highest levels of pain interference in groups of equal numbers, the total number of subjects, 65, was divided by three to create groups of approximately 21 subjects each. A group of 21 subjects who reported the lowest pain interference scores (mean = 11.8, standard deviation = 2.0, range 10–16) was contrasted to a group of 21 subjects with the highest pain interference scores (mean = 39.0, standard deviation = 6.6, range = 30–50). The intermediate group of 23 subjects was not examined. For all analyses, each subject's image was first smoothed with a 10 mm FWHM Gaussian kernel followed by application of the GLM analysis for each hemisphere independently. FDR was set at 0.05 where significant differences were shown on an 'inflated' cortical surface map that displays cortical thickness not only at the crest of a gyrus but also deep within the sulcus.

Table 2. Study demographics for subgroups

Characteristic	Study groups: Low pain (*N* = 21)	High pain (*N* = 21)	Total (*N* = 42)
Age at Baseline			
Median	37.0	47.0	43.0
Min, Max	28, 56	30, 58	28, 58
Gender			
Male	20 (95.2%)	14 (66.7%)	34 (81.0%)
Female	1 (4.8%)	7 (33.3%)	8 (19.0%)
Race			
White	11 (52.4%)	8 (38.1%)	19 (45.2%)
African-American	9 (42.9%)	11 (52.4%)	20 (47.6%)
Other	1 (4.8%)	2 (9.5%)	3 (7.1%)
Ethnicity			
Not Hispanic or Latino	20 (95.2%)	20 (95.2%)	40 (95.2%)
Hispanic or Latino	1 (4.8%)	1 (4.8%)	2 (4.8%)
Education			
High school graduate	1 (4.8%)	1 (4.8%)	2 (4.8%)
Some college	13 (61.9%)	8 (38.1%)	21 (50.0%)
College Graduate	7 (33.3%)	12 (57.1%)	19 (45.2%)
Service Branch			
Air Force	2 (9.5%)	1 (5.0%)	3 (7.3%)
Army	12 (57.1%)	15 (75.0%)	27 (65.9%)
Marines	5 (23.8%)	3 (15.0%)	8 (19.5%)
Navy	2 (9.5%)	1 (5.0%)	3 (7.3%)
DRRI-2 Combat Exposure[1]			
Median	35.0	34.0	34.0
Min, Max	20, 66	17, 48	17, 66
Total Number of mTBIs			
Median	2.0	2.0	2.0
Min, Max	1, 5	1, 5	1, 5
TBI with PTA			
Only TBI without PTA	6 (28.6%)	5 (23.8%)	11 (26.2%)
TBI with PTA	15 (71.4%)	16 (76.2%)	31 (73.8%)
TBI with LOC			
Only TBI without LOC	9 (42.9%)	7 (33.3%)	16 (38.1%)
TBI with LOC	12 (57.1%)	14 (66.7%)	26 (61.9%)
Years since last mTBI			
Median	10.0	9.4	9.8
Min, Max	5, 44	0, 37	0, 44
TBI-QoL pain interference[2]			
Median	11.0	39.0	22.5
Min, Max	10, 15	30, 50	10, 50
PTSD from MINI			
No	17 (81.0%)	7 (33.3%)	24 (57.1%)
Yes	4 (19.0%)	14 (66.7%)	18 (42.9%)
Depression from PHQ-9			
No	16 (76.2%)	5 (25.0%)	21 (51.2%)
Yes	5 (23.8%)	15 (75.0%)	20 (48.8%)
Total % service connected disability			
Median	60.0	90.0	65.0
Min, Max	0, 100	0, 100	0, 100

[1]DRRI-2 = Deployment Risk and Resilience Inventory; Higher scores indicate greater combat exposure.
[2]TBI-QOL = TBI Quality-of-Life; Higher scores indicate greater pain interference.

Results

Pain interference

The mean pain interference score was 24.06, standard deviation = 12.1, minimum = 10, maximum = 50 (Table 1). For values associated with subjects grouped on high and low pain, please see Table 2.

Functional connectivity

Twenty-two percent of the subjects showed excessive motion in greater than 50% of the volumes/time points and were excluded. This percentage was roughly the same in both the subgroup with one to two mTBIs and the subgroup with more than two mTBIs, 21% and 23%, respectively, and no subjects fell asleep. In the analysis with all subjects, a significant negative relation was found between pain interference scores and FC between the MPFC seed and three clusters that were both within and outside of the DMN, i.e., greater pain interference was associated with less FC ($t(1,63)=3.22$, voxel (height) threshold =.001 uncorrected, $r^2=0.14$). The largest cluster encompassed a DMN area–the PCC and precuneus, and included bilateral lingual gyrus (cluster threshold $p < 0.0000001$, FDR corrected, beta = −0.01, 90 % CI [−0.005, −0.011]), while another cluster also associated with the DMN was located in right middle and inferior temporal gyri and temporal pole (cluster threshold $p < .0002$, beta = −0.01, 90% CI [−0.00, −0.10]), and the last cluster was located in right lateral occipital cortex and angular

gyrus (cluster threshold $p < .0003$, beta = −0.01, 90% CI [−0.006, −0.011]). No other seeds were significant. A beta of −0.01 indicates that a negative regression was observed, and the slope (beta = −0.01) of the regression line between the FC *z*-score and the pain interference score indicates that each increment of 0.1 for the Fisher-transformed *z* is associated with a change of 10.0 points for the pain interference score. Please see Figures 1 and 2 and Table 3. Table 3 summarizes the results of the four seeds that were tested.

When we explored whether TBI frequency might affect the relation of pain interference scores to FC of the DMN, we once again found significant effects with only the MPFC seed. The group with one to two mTBIs demonstrated a significant negative regression between pain interference scores and FC between the MPFC seed and one cluster which was located in the right superior lateral occipital cortex ($t(1,40) = 3.31$, voxel (height) threshold = .001 uncorrected, cluster threshold $p < .001$, FDR corrected, r^2=0.22, beta = −.01, 90% CI [−0.007, −0.014]). The group with more than two mTBIs demonstrated a significant negative regression between pain interference scores and FC between the MPFC seed of the DMN and one cluster which was located in the left hippocampus and parahippocampal gyrus ($t(1,21)$=3.53, voxel (height) threshold = .001 uncorrected, cluster threshold $p < .003$, FDR corrected, r^2=0.37, beta = −0.01, 90% CI [−0.008, −0.014]).

Cortical thickness

Please see Figure 3. Higher reported pain scores were associated with increased cortical thickness in the left cuneus, right anterior temporal pole and parietal (including precuneus) and insular cortices, and bilateral frontal lobes including the anterior cingulate cortex (ACC). Greater thickness of the anterior insular cortex was associated with the top third of participants reporting the highest levels of pain.

Discussion

We found a negative relation of pain interference severity with FC of brain regions within the DMN; higher pain interference with performing daily activities was related to lesser FC of mesial prefrontal cortex with posterior regions of the DMN, including PCC, precuneus and lateral temporal lobes. When subjects were divided into subgroups based on number of mTBIs, the subgroup with the greater number of mTBIs (>2) demonstrated a significant negative relation with another posterior area of the DMN, the hippocampus and parahippocampal gyri. This relation is consistent with findings in civilian patient groups representing three different causes of chronic pain; all three groups showed decreased connectivity of MPFC to the posterior constituents of the DMN (21). In

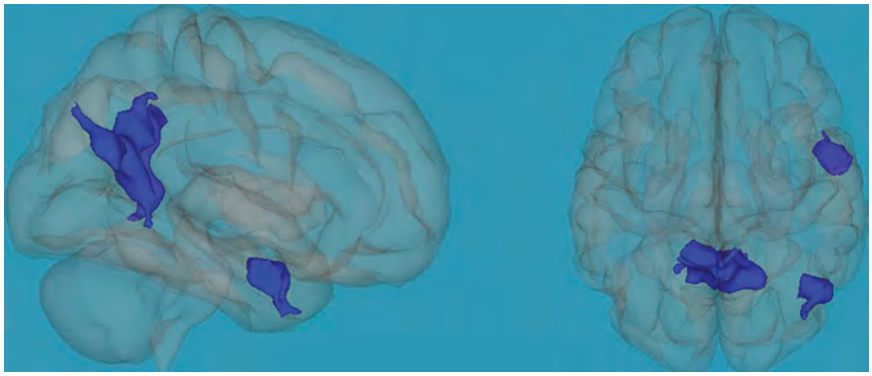

Figure 1. Overlay representing the significant negative relation of Pain Interference scores on the TBI-QOL(6) and functional connectivity between the medial prefrontal cortex seed of the default mode network and three clusters involving the (1) bilateral posterior cingulate cortex, precuneus, lingual gyri; (2) right middle and inferior temporal gyri and temporal pole; (3) right lateral occipital cortex. Right side of brain is on right side of image.

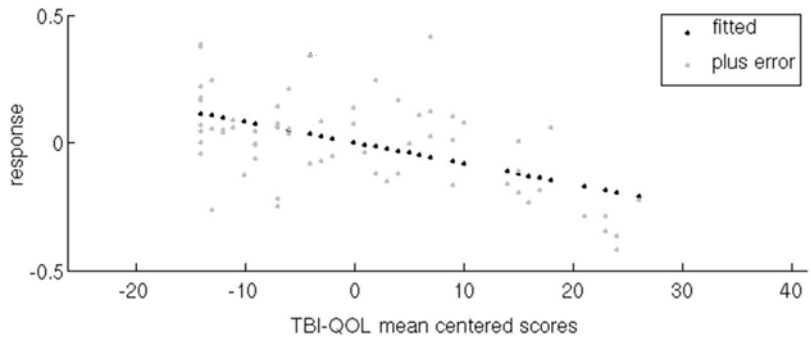

Figure 2. Negative relation between the Pain Interference score in the TBI-QOL measure (6) and functional connectivity of the default mode network between the medial prefrontal cortex (seed) and the cluster incorporating posterior cingulate cortex and precuneus. *X*-axis represents mean-centred scores. Dark circles represent fitted response, while light dots represent residuals.

Table 3. Results from the regression analyses relating QOL Pain Interference scores onto the functional connectivity of 65 Veterans with mTBI. The four seeds of the default mode network and any associated significant clusters are listed.

Cluster-Level *p* Value (corrected) [a]	Cluster Size (k)[b]	Most Significant Coordinates[c] (x y z)			Location
a. Posterior cingulate cortex seed					
Positive Regression					
NS					
Negative Regression					
NS					
b. Medial prefrontal cortex seed					
Positive Regression					
NS					
Negative Regression					
0.0000001	1720	-10	-48	8	Precuneus, Posterior Cingulate Gyrus, Bilateral Lingual Gyrus
0.000193	404	58	-4	-28	R Middle Temporal Gyrus, R Temporal Pole, R Inferior Temporal Gyrus
0.000321	357	50	-66	24	R Lateral Occipital
c. Right lateral parietal seed					
Positive Regression					
NS					
Negative Regression					
NS					
d. Left lateral parietal seed					
Positive Regression					
NS					
Negative Regression					
NS					

[a]Probability at the cluster level of significance after random field theory family-wise error correction over the whole brain search volume. Cluster probability also survives Bonferroni correction for four seeds and two directions ($p = 0.05/8 = 0.00625$).
[b]Number of voxels within a cluster.
[c]Negative values along the x-axis are defined to be in the subject's left hemisphere.

contrast to Baliki et al.'s finding that increased pain was also negatively related to FC between mesial prefrontal cortex and the insula, we could not confirm this relation in Veterans and SMs with chronic pain following mTBI. Other MRI-based techniques including arterial spin labelling have also been used to assess the relation between increased evoked clinical pain and changes in the connectivity of the DMN with the insula or ACC (28). Altered FC of regions within the DMN and with the insula in patients with chronic pain have been interpreted from the perspective of neuroplasticity, implying that neural transmission associated with chronic pain alters the connectivity of brain regions (21).

Regions outside the DMN that were found to be negatively related to FC of mPFC and pain interference scores are the lingual gyrus and lateral occipital cortex. When subgroups were created based on number of mTBIs, the negative regression between pain interference scores and FC from the MPFC to occipital regions was significant only in the subgroup who had fewer (one or two) mTBIs. The lingual gyrus was reported to be active during spontaneous thought in a meta-analysis of mind wandering studies and was attributed to possible involvement in visualising events (29). Although the role of lateral occipital cortex is less clear, it has been linked to semantic processing during the perception of scenes and objects (30) and being impacted by threat during fear conditioning (31). Lateral occipital cortex was also reported during FC in another paper involving this population (20), suggesting the possibility of negative arousal in Veterans and SMs thinking about threatening events while at rest.

In the current study, those with self-reported higher levels of pain had thicker cortical thickness that was most prominent in left cuneus and anterior cingulate and right parietal (including precuneus) and insular cortices as well as right anterior temporal lobe. At a cortical level, the parietal, cingulate and insular cortices have long been known to be associated with pain processing (32-34). Previous reports have also indicated grey matter alterations in the PFC, insula, and ACC in patients with chronic pain. Apkarian et al. (11) found that grey matter density of DLPFC was inversely related to severity of chronic low back pain, including intensity, duration and the affective dimension of pain (11). PTSD severity was reported to be inversely related to cortical thickness of the postcentral and temporal gyri and subgenual ACC of post-911 Veterans who had sustained mTBI. Although our results are inconsistent with these studies, the latter study did not investigate the effect of pain (12). Further, as reviewed by Borsook et al. (35), both increased and decreased thickness findings have been observed in association with pain, and increased cortical thickness is consistent with other studies (36-39). MRI-derived regional differences in cortical thickness are likely related to a host of factors, including pain mechanism, presence of PTSD, symptom chronicity and whether co-morbid physical conditions exist. For example, whether the pain is post-traumatic in origin, migrainous, associated with headache or more with neck-back regions, body or internal pain, may make a difference (39-42). This initial analysis of interim, cross-sectional imaging and pain interference data from the ongoing CENC was not designed to specifically examine other

variables that may be contributing to pain interference and cortical thickness; instead we addressed whether there were differences in FC of brain regions within the DMN and in cortical thickness between those with the highest and lowest levels of pain interference as reported by the subjects. We note that several individuals in the group reporting a high level of pain interference were also those with the lowest levels of cortical thickness in the sample (see Figure 3). This observation is likely fitting with the conclusion that chronic pain is a multiplex problem associated with diverse factors and the potential to affect brain structure and function in complex ways. Future studies reporting longitudinal imaging and pain interference data will hopefully begin to unravel these complex factors associated with pain.

It is notable that some of the regions implicated in the relation of pain interference to FC and to cortical thickness were the same, in particular, precuneus and right anterior temporal lobe, both part of the DMN. Further, the anterior cingulate, a region of the DMN with a high rate of connections, which was found in the cortical thickness analysis is close in proximity to the MPFC seed in the FC analysis. Increased pain interference was associated with both decreased FC and thickened cortex. Future studies will investigate the mechanistic relation between FC and cortical thickness.

Limitations and future directions

This initial study reports cross sectional data and lacks a control group of Veterans and SMs who had been deployed, exposed to combat, but without any history of mTBI. The mean post-injury interval greater than 9.0 years also raises the possibility of intervening events, such as disease, injury and stress, contributing to our findings. As the CENC's data collection proceeds, we will have sufficient follow-up data and data collected from a control group to address these limitations.

This study also did not address sex-related differences in the relation of chronic pain to FC. There is strong evidence for the existence of sex differences both in the prevalence of chronic pain and in the neurobiology of pain. Results from imaging studies of civilians with pain indicate more prominent primary sensorimotor structural and functional alterations in female chronic pain patients compared with male chronic pain patients as well as differences in the nature and degree of insula alteration (with greater insula reactivity in male patients), differences in the degree of anterior cingulate structural alteration and differences in emotional-arousal reactivity (43).

Strengths of this initial study of FC and cortical thickness in relation to pain interference include the results of functional and structural imaging in Veterans and SMs, a population in whom co-morbidities of PTSD and depression complicate clinical management and often lead to a general decline in physical and mental health (5). We also used the TBI-QOL Pain Interference short form which has good psychometric properties including reliability, validity, unidimensionality and a high correlation with the full form score (6,22).

Future studies will also utilize additional neuroimaging techniques as well as more detailed investigation of the relation between PTSD, depression and chronic pain. In

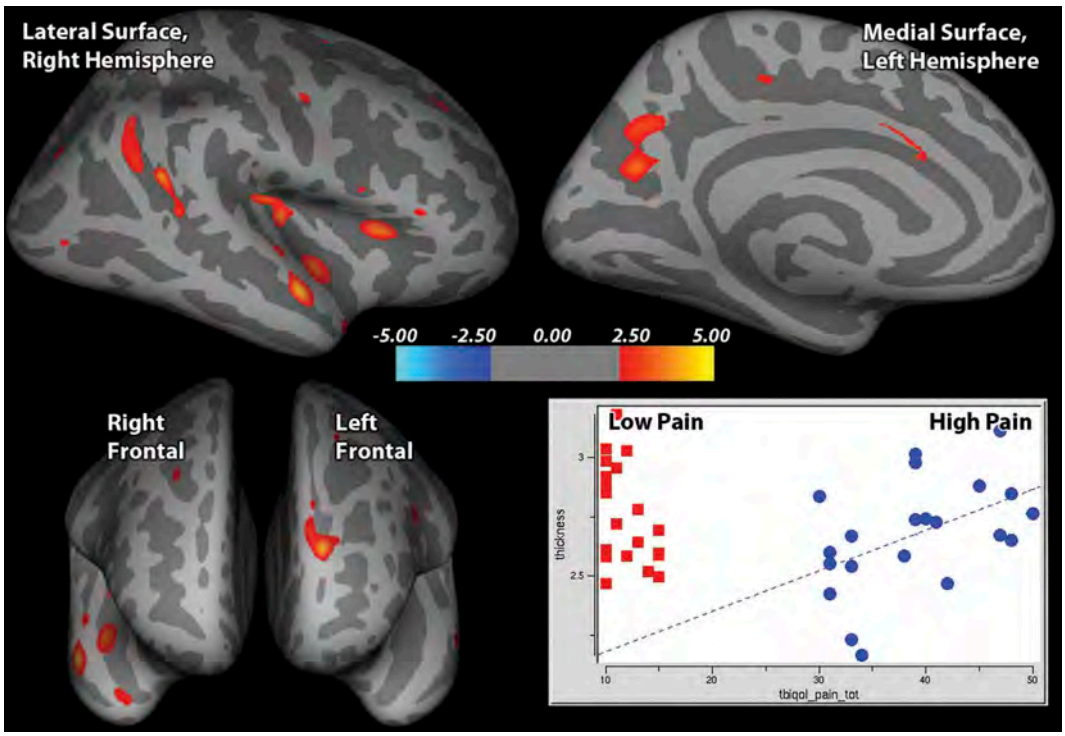

Figure 3. Regions where greater pain reporting was associated with increased (warm red-to-orange colours) cortical thickness are depicted on inflated brain images where the most substantial QDEC findings that include the right lateral surface (top left), medial surface of the left hemisphere (top right) and a bilateral view of the frontal lobes (lower left). Bottom right reflects the scatter plot from the anterior insular cortex exhibiting greater thickness in the top third of participants reporting the highest levels of pain.

addition to the nociceptive underpinnings of pain, a significant body of research indicates that pain constitutes a multidimensional experience that incorporates psychobiology, attentional processes and expectations of pain resulting from past and learned pain experiences. Expectations of pain, and the anxiety caused by these expectations, are suggested as a possible source of the increased pain perception seen in chronic pain patients (44-46). Brain regions involved in processing cognitive and affective states such as the dorsolateral prefrontal cortex, pre- and sub-genual cingulate and amygdala have been implicated in imaging studies examining brain regions which may modulate pain (47-49), and there is some evidence for overlap in certain brain regions involved in networks for both "physical" and "psychological" pain (50,51).

Conclusion

Pain interference with daily activities by Veterans and SMs who had chronic mTBI was negatively related to FC of the mesial prefrontal cortex with posterior regions of the DMN, a network that is activated by intrinsic cognitive and affective processes. Exploratory analysis also showed a positive relation of cortical thickness in left cuneus and anterior cingulate and right parietal (including precuneus) and insular cortices as well as right anterior temporal lobe to severity of pain interference in this sample. However, we acknowledge that the cross-sectional design of this initial study precludes inferences about causality regarding the relation of pain interference to FC of regions in the DMN and cortical thickness. Longitudinal investigation is indicated to characterize changes in the DMN and cortical thickness in relation to chronic pain, other co-morbidities of mTBI and individual differences in this population.

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Declaration of interest

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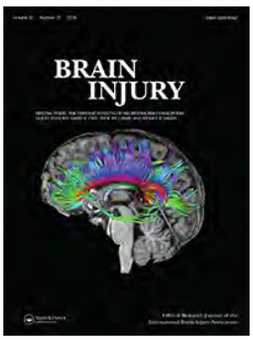
Appendix 11

Recruiting for a multicentre DoD and VA longitudinal study: lessons learned



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Recruiting for a multicentre DoD and VA longitudinal study: lessons learned

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ABSTRACT

Primary Objective: The primary objective of the study is to identify and delineate effective recruitment practises in a large, multi-site, longitudinal, observational study employing both military service members and Veterans.
Setting: Four Chronic Effects of Neurotrauma Consortium sites.
Design: A descriptive study.
Results: Overall and cohort-specific recruitment increased with the addition of focused recruitment strategies and a military/Veteran-centric recruitment director.
Conclusion: Use of site-specific strategies aligned with local Institutional Review Board procedures and emphasizing awareness of service member organizational allegiances was the key to effective recruiting. Adding a recruitment director with background similar to study participants coincided with significantly improved overall participant numbers and specific subpopulations of research subjects, thus adding to the value of the study.

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Longitudinal studies enhance the understanding of the recovery patterns of health conditions over time but can be logistically challenging to initiate, maintain, and complete (1). A major challenge is recruiting the requisite number of study participants to adequately power the study to achieve the study goals (2–4). Longitudinal studies often contend with potential study participants' reluctance to volunteer due to the lengthy time commitment frequently involved, both in terms of actual clinic time and the months to years of follow-up required, expenses associated with travel and missing work, and disruption to their daily lives (5). Identifying effective participant recruitment strategies for longitudinal studies that are efficient, non-coercive and yield participants representative of the target population of study is vital to successful study completion.

This paper examines the recruitment lessons learned from the ongoing DoD/VHA Chronic Effects of Neurotrauma Consortium (CENC). The centerpiece study of CENC is the multicentre *Observational Study on Late Neurologic Effects of OEF/OIF/OND Combat*. The Observational Study aims to establish a large cohort (>1100) of US Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn (OEF/OIF/OND) Veterans and service members (SMs), most of whom (80%) were exposed to at least one mild traumatic brain injury (mTBI), with the remainder having no TBI during their lifetime (unexposed), and to follow them long term to assess changes in their physical and mental health. The longitudinal study addresses an important research gap by identifying and characterizing the late effects of mTBI and assessing the influence and interaction of the many potential risk factors for neurodegeneration, in particular, early dementia (for complete details, see https://cenc.rti.org/).

In general, longitudinal studies have relied on a number of recruitment techniques including mailing letters, piloting procedures with mock participants, emphasizing participant convenience, distributing explanatory brochures, providing telephone call-in options using a dedicated phone line, and using a primary language questionnaire format. But, results have been hampered by reports of both participant's lack of interest and lack of time (6,7). Multiple other projects/registries have gathered longitudinal, multicentre data from individuals with varying degrees of brain injury (8–10) from an array of settings. One such ongoing research effort, the Traumatic Brain Injury Model Systems National Data Base, has identified the primary barriers to participant recruitment as (1) lack of transportation and time, (2) turnover of clinical staff responsible for enrolment, and (3) lack of time on the part of clinical staff to recruit and enrol (11). Bush et al. (12) highlighted several other barriers related to military culture and environment, including the fact that the promise of personal health benefits and improved access to care, which often motivates research participation in civilian populations, is less pertinent for both veterans and active military personnel, who already have access to free quality health care as a function of their prior service or active military duty. Furthermore, stringent health screening prior to admittance into the military theoretically produces a healthier population that is less interested in novel medical interventions than an older, more chronically ill population. Active Duty personnel may also be burdened by the effort and inconvenience involved in research participation, because they are often

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stationed far away from study sites without easy access to motor vehicles, and/or may face decreased support from military supervisors due to work demands and mandatory training requirements. Military service is often transitory and mobile and sometimes reassignment occurs with short notice, thereby further hindering SMs' participation in research studies. Additionally, SMs are subject to heightened regulatory protections, including restrictions regarding financial compensation for their time and participation unless off-duty, and limits on full-fledged endorsement of participation by the chain of command. Lastly, SMs may feel particularly strained by recent conflicts and multiple deployments, as well as recruitment requests from other military health research studies, and thus may be more reluctant to volunteer for another research study.

Like Active Duty SMs, recruitment challenges may also be amplified for Veteran participants (13). Studies (14,15) have cited geographical distance from a VA facility, lack of awareness of available health care through the VA, stigma related to reporting symptoms, perceived quality of VA health care, and having private health insurance as barriers to Veterans utilizing VA medical centres for care. Consequently, Veterans not utilizing VA medical centres for care are less likely to be aware of research projects and may be less inclined to participate even if aware. Additionally, time constraints may play a role. Many Veterans of recent conflicts are of working age with younger families and may be reluctant to take time off work or from family responsibilities for research participation. Some have noted that older Veterans may be more prone to chronic health conditions with accompanying episodic exacerbations that may impede ongoing research participation (16,17). Gender also potentially affects the utilization of VA facilities with women generally using outpatient services less frequently than males (18). Reasons for this have been reported as lack of awareness that the VA provides services for women, concern over potential insensitivity to women's issues, and environmental concerns (19) leading to a general sense of discomfort. In sum, the factors cited above can combine to make SMs and Veterans less accessible for research participation. Limiting recruitment efforts to the VA facility may cause inability to reach enrolment goals and may also unintentionally cause sampling bias and limit generalizability.

Although the above studies highlight general difficulties and barriers unique to engaging Veterans and SMs with scientific research, only a few directly address these concerns in the context of longitudinal studies that require participants to spend hours in neuropsychological testing, giving biospecimen samples and in biophysiological measurement. We anticipated that these challenges were likely to be magnified when participation requires follow-up visits that can span years. This paper contributes to the current literature by describing the experiences of recruiting Veterans and SMs in the CENC Observational Study, with an emphasis on the strategies found to be most effective. The unique elements of recruitment associated with the specific interventions employed to enhance recruitment are identified. We plan a future paper on the techniques found effective in retaining participants.

Lessons learned in recruitment

The CENC Observational Study has trialled and refined its recruitment methods over a 3-year period. On the path to optimizing recruitment strategies, the CENC staff learned to appreciate several overarching considerations related to the study design and to the target population. Keeping the following considerations at the forefront of planning and implementing multicentre longitudinal studies, especially studies of Veterans and SMs, can help ensure successful recruitment.

Considerations related to study design

From the outset, staff embraced not only the longitudinal research considerations noted above but also those related to the study design. While currently funded for 5 years, the study is forecasting 20 years or more duration. This time span is greater than most longitudinal studies and presents challenges to both recruitment and retention. For a study of this duration, it is crucial to clearly explain this commitment at the point of enrolment, to ensure that participants understand the potential 20-year study duration, in efforts to minimize future attrition. Second, an emphasis was placed on building and maintaining trusting relationships between the research team and participants to facilitate smooth follow-up.

The nature of a multicentre study encompassing private, military, and federal institutions is such that regulations vary between institutions. A stumbling block in the VHA system we consistently encountered was the variation in regulations and approvals of the identical study protocol from one VA site to another. For example, in instances where the Institutional Review Board (IRB) deferred to a Privacy Officer (PO) or Information Security Officer (ISO) to decide about a recruitment strategy based on interpretations of regulations outside the scope of research, POs and ISOs rendered decisions that differed from one VA site to another. These layers of oversight within different institutions, including safety committee and affiliate IRB reviews, also challenged the timeline and study implementation. This created varying recruitment strategies across sites. Similarly, we found that when obtaining site-specific IRB and VA approvals to access VA site lists of OIE/OEF Veterans to create mailing lists for recruitment letters, flexibility of approach was important. At some locations, IRB approval of the concept was required before acquiring a list, while at other locations, we had to first acquire the list before the IRB would approve the process of sending mailers to people on the list. These scenarios typify the detailed level of attention and energy that is required to

move forward with a major recruitment technique across multiple sites within a (likely any) large bureaucratic structure. Thus, multicentre endeavours must factor in the additional time and flexibility needed to address such inevitable differences when undertaking such a study.

Considerations related to target population

Military personnel and Veterans, especially those from recent conflicts, are fairly young, mobile, and interested in continuing their military careers or commencing their post-military lives. Consequently, it is essential that recruitment efforts be sensitive to the commitment required of participants and efforts be flexible enough to maintain effective communication with this population. For example, utilization of mobile technologies and social platforms needs to be maximized to the extent possible under regulatory restraints. In our view, traditional, staid recruitment efforts such as newspaper advertisements and flyers likely will be progressively unsuccessful as time passes, and more of a social media outreach model should be employed.

Suggested steps

Based on these lessons learned, we review the following general steps critical to our success in recruiting >1100 Veterans and SMs. More granular suggestions are also provided (see Table 1).

Create and document a comprehensive recruitment plan for each site

It was essential that all recruitment procedures be formally documented. While this step is a considerable time investment, having these procedures specified helped ensure uniformity across sites. Documented methods of procedures and standard operating procedures for recruitment also facilitated the onboarding process for new sites added after study initiation. Furthermore, such documentation aided in training new personnel hired over the long duration of the study as well as refreshing existing personnel in protocol requirements. Formal documentation of recruitment procedures is also crucial for replicability in future studies.

Table 1. Suggested steps for recruiting Veterans and service members.

Objective	Important steps
Create a comprehensive site-specific plan	• Conduct extensive in-person visit(s) to each site to gain perspective of challenges, opportunities and meet face-to-face with site personnel • Set site-specific goals • Codify study-wide MOP and SOP • Make available for new sites and personnel to use as template • Conduct biweekly phone conferences to discuss problems • Modify per site due to regulatory or administrative factors
Recruit from multiple avenues at each site	• Determine which clinics most likely to have desired target population • Meet with key clinic staff and other key influencers • Determine what community-based national organizations exist with target population (traditional vs. new) • Determine what local organizations exist with target population • Meet with organization staff to determine best recruitment techniques available
Develop relations with informatic and administration staff	• Face-to face meetings vital • Learn the culture at the facility • Identify key personnel with interest/abilities • Determine capability and enthusiasm for data mining by staff
Hire an overall recruitment director	• Experienced in target population culture • Medical/Science background is beneficial but not critical • Sensitivity to research with human subjects • Able to work with wide array of individuals
Continuously monitor site progress	• Establish and enforce site-specific goals • Create dashboard to display progress • Allow all sites to see site and overall progress • Produce and distribute metrics for tracking progress and compliance and make publically available • Develop remediation plan for failures to maintain goal progress
Use an empirically informed tiered contact approach	• Establish methods of contacting potential participants • Identify available site-specific participant pools • Determine what strategies are permissible at each site per regulatory constraints • Identify which contact methods yield best results
Employ a multipronged approach to leverage traditional and non-traditional recruitment sites	• Stratify participant pool lists by geographic distance to study site • Utilize military service organizations, both traditional and newly formed online organizations • Utilize resources of university Veterans and Military Service Member offices • Utilize the Reserve Component forces (National Guard and Reserve) within each state to extend reach to participant pools • Utilize other traditionally Veteran/service member events as recruiting events

A comprehensive recruitment plan was also formulated for each study site, incorporating techniques found in the literature along with adjustments for this study's needs. These needs were identified through in-person site visits and numerous teleconferences to assess for site-specific recruitment practices, opportunities, and shortcomings as well as staffing levels, expertise, commitment, and enthusiasm. After weighing findings from these site assessments alongside the first year recruiting data, a comprehensive recruitment plan was formulated.

Key in our comprehensive plan was to build within staff an awareness of 'military culture' to strengthen recruitment and retention efforts. We were aware that a universal characteristic of the military culture is adherence to a clear and well-defined mission. Both Veterans and military personnel have been exposed to and are accustomed to continual teamwork and personal sacrifice to accomplish a larger mission. We believe it is helpful to stress that while research participation may not prove ultimately beneficial to a specific participant personally, we are committed to learning about the effects of mTBI over an extended period, which in turn can help their current comrades as well as future SMs. Anecdotally, this thematic message seemed to resonate effectively with many participants.

An important component of each site's recruitment and retention plan was its own specific, individualized mission for each year. Until the end of the first year of recruitment, each site had a comprehensive goal, but not a specific, monthly target. While sites were aware of the overall initial recruitment goal of 1100 (which has since been exceeded) sites did not have specific target contributions to these totals. Site target numbers were initially estimated and were later adjusted based on actual conditions at the sites after study initiation. The revised site-specific plans were informed by factors such as participant population pool, throughput capacity, study protocols variations at each separate location, availability of outside diagnostic equipment (e.g. MRI facilities), study staff size, and personnel capabilities. After a year of operation, we were better able to evaluate these issues and formulate site objectives for the upcoming year. Focusing each site on their own specific mission in support of the overall consortium mission was a major step as it aided sites in focusing on a goal that they helped formulate. Implementing site-specific plans also allowed for flexibility to respond to site needs and to test out strategies that other sites found to be effective.

Recruit from multiple avenues at each recruitment site

The first wave of enrolments was culled primarily from appointment lists at polytrauma clinics likely to have eligible individuals and who were known to and comfortable with the research staff. Over time, it became evident that this pool would not be large enough to sustain recruitment for the numbers of participants needed. An additional problem was that TBI clinics were yielding individuals with diagnosed mTBI, while the enrolment rate of unexposed participants lagged behind the desired 20%, creating a potential power problem in statistically controlling for the effects of mTBI. There was also concern that the mTBI positive portion of our sample might not be representative of the broader military and Veteran mTBI population, many of whom are not suffering late effects and therefore not engaged in TBI clinical care. After the first year of recruiting and enrolling participants, our control subject enrolment was less than half of the desired percentage (7% vs. 20%) and was not trending upward.

We found that expanding recruitment beyond the polytrauma clinics to multiple types of avenues at each VA site was the key to attaining our desired proportions. One avenue was to leverage hospital administrative data to create mailing lists of potentially eligible persons to send recruitment brochures and letters. The available administrative grouping that most closely resembled our target population was any registered patient with a history of OEF/OIF/OND deployment. Although we determined that the hospitals do record OEF/OIF/OND history designation in their administrative database, we encountered numerous administrative and regulatory barriers in trying to obtain a mailing list from these sources, which leads to the third suggestion below. In the years since increasing different avenues, we have increased our control subject enrolment to 18.43% as of December 2017.

Develop professional relationships with key informatics and administrative personnel

Although transferring effective recruitment procedures from one VA to another seemed logical, smooth transition of procedures between VAs was hampered by differences in data management, revealing a need to harmonize efforts across slightly different VA hospital platforms, an often slow and still ongoing process. Key to expediting this effort was to develop professional relationships with crucial informatics and administrative personnel at each site. For example, after staff at one site spent considerable time uncovering the correct query language to extract a list of Veterans deployed during OIE/OEF/OND, the strategy was shared with other sites. However, other sites were unable to duplicate this search strategy because lists were categorized differently at each VA site. Key to overcoming this hurdle was to develop personal relationships at the local level. Having prior face-to-face meetings with specific central personnel at each site induced a familiarity (both with the study aims and with the site procedures) that allowed for improved access and helpful communication when problems arose. Often, a phone call or e-mail was expedited because a face-to-face meeting had occurred, and a comfort level established between central study staff and site researchers.

Appoint an overall director of recruitment

As we surveyed the work accomplished at the 18-month point in the 5-year grant cycle, we determined that a dedicated 'National Director of Recruitment' would be a worthwhile addition. We focused on having a national recruiter with military experience who could relate to recruits, 'speak their language' and who was familiar with the military culture and ethos. We also ideally sought an applicant with medical familiarity who could quickly be certified in human research subjects training requirements. Our search

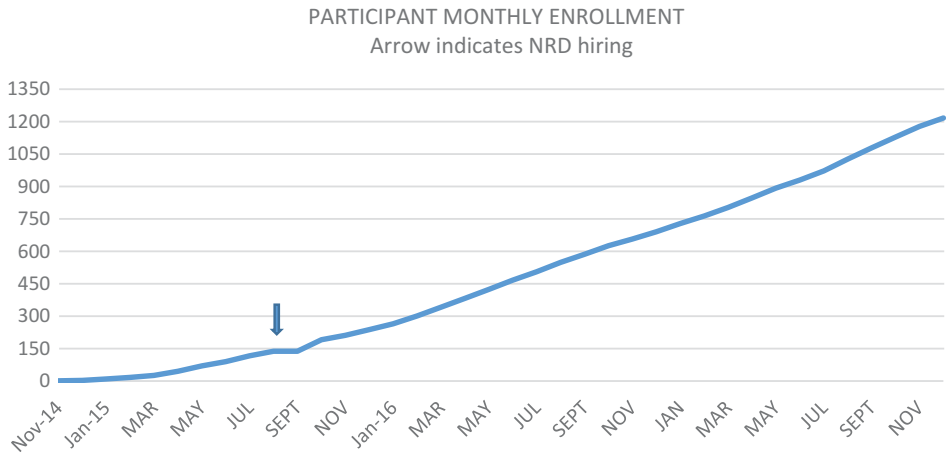

Figure 1. Participant monthly enrolment.

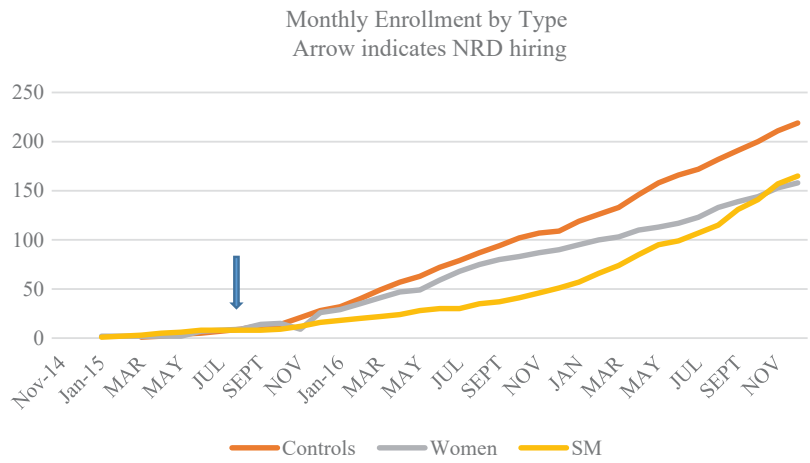

Figure 2. Monthly enrolment by type.

efforts resulted in the fortuitous hiring of a retired US Army Lieutenant Colonel who had significant organizational, medical, and leadership experience. Tasking one individual to oversee recruitment and retention across all sites allowed for a specific and dedicated focus on recruitment and retention while permitting the study PI and co-investigators to concentrate on scientific and related administrative issues. This hiring coincided with observable upticks both in general recruitment (see Figure 1) as well as specific cohorts (Figure 2).

While it is crucial to task an individual with oversight of recruitment, it is equally important to task the right individual. As the Observational Study focuses on OIF/OEF/OND Veterans and SMs, it was logical that the National Director of Recruitment be a military person who has served in OIF/OEF/OND and thus is an insider, to assist in recruiting other members of their community. Uniformed Services University published a guide for researchers entitled *U.S. Army Culture: An Introduction for Behavioral Health Researchers* to help researchers better understand their intended study population (20). This guide concludes that cultural competence is more than just cultural awareness or even a working knowledge of a culture and 'understanding military cultural competence' is the key to successful military research. Equally important, as noted above, is the awareness and sensitivity to the importance of the spirit and the technical regulatory requirements of research with human participants, to include the concepts of respect, beneficence, justice, and confidentiality.

Continuously monitor site and overall progress

Another important practice found to enhance recruitment is to continuously monitor both individual site and overall progress toward preset goals. This allows us to identify which strategies have been effective and thus, should be replicated and which strategies have yielded fewer returns, to consider for modification or elimination.

Another aspect of ongoing monitoring is to provide regular feedback to each site. Site progress in recruitment was operationalized through colour-coded metrics using a green (on target), yellow (target jeopardy), or red (not meeting target) system. We continue to provide weekly written feedback to all sites via e-mail as well as a web-based dashboard that tracks each site's progress in real time and give verbal feedback via bimonthly conference calls to problem-solving challenges.

Monthly scores are also incorporated into the general site feedback communication chain.

Use a tiered contact approach

To ensure efficient use of resources, we developed and followed a tiered approach for contacting potential participants that shaped the timing and method of contact. The approach was informed by data from ongoing analyses of successes and shortcomings. Taking such a national level perspective helped to prevent the process from becoming bogged down by site-specific practices and procedures that were proving problematic. The process is as follows: (1) once appropriate databases are developed, letters are sent to potential participants describing the study mission and its potential value; (2) at this stage, sites await 'free-responders' calling in and making appointments after receiving the letters; (3) after a specified period (2–4 weeks), if letter recipients have not contacted the site, a second letter is mailed. Some sites are also granted IRB approval to pursue follow-up phone contact with mail recipients; and (4) at those sites, if no spontaneous response results from this second mailing, study staff call participants, asking if they received the mailer and whether they have interest.

Metrics were developed to determine the percentage responses of both the free-response phases and the follow-up phone phase. In this way, a sense of the effectiveness of each round of mailings was developed so that staff time could be more effectively utilized. Such an awareness also allows us to roughly estimate timing and volume of recruitment efforts so that a steadier flow occurs, thus preventing a 'push–pull' phenomenon in which participants are actively recruited and then potentially made to wait for appointments. Procedures were then developed to determine when attempting contact with an individual was no longer productive and, in fact, could be counter-productive by creating an unwanted feeling of harassing potential participants.

Employ a multipronged approach to leverage traditional and non-traditional recruitment sites

Basic to our recruitment success has been simultaneous targeting of multiple recruitment sources. We used the VA's lists of OEF/OIF/OND Veterans to create hospital-based mailing lists for recruitment. From these lists, we were able to filter Veterans by certain criteria to further target segments of this population. For example, we filter by geographic proximity to target Veterans living in closer proximity to the VAs, as this reduces travel time, is convenient for Veterans and consequently increases the likelihood of participation. Targeting Veterans who live closer to the study sites also addressed cost-effectiveness. Although the VA is a logical site from which to recruit participants for the CENC Observational Study, we found it necessary to also target Veterans outside the VA system both to accelerate recruitment and to increase representativeness of our sample.

We targeted traditional Military Service Organizations (MSOs), which include the American Legion, Veterans' of Foreign Wars (VFW), and American Veterans. These respected organizations have been in existence upwards of a century, assisting Veterans and providing a valuable service to the country. While it was a natural thought to turn to these historically significant organizations, we noted a recent *Washington Times* article report that younger Veterans are hesitant to join traditional MSOs, many of which are down in enrolment (21). The VFW peaked at 2.1 million in the 1990s but is only at 1.3 million members today, with an average age of nearly 70 years old. The *Times* article notes that 'more Iraq and Afghanistan Veterans say they are joining groups that allow them to stay active, continue to serve their country and interact with civilians to help reintegrate into society after serving overseas'. Essentially, we found that traditional MSOs do not contain or attract the broader population that CENC seeks, necessitating looking to other organizations.

As a Veteran, our national recruiter was eligible to join several organizations and, in fact, had been a member of several MSOs for years, such as the VFW and the American Legion. However, rather than just the more traditional MSOs, he had also joined several of the newer military-specific organizations such as *Together We Served, Iraq and Afghanistan Veterans of America, Rally Point*, and several others. Instead of attending monthly meetings to reach only handfuls of possible participants, two of the previously mentioned organizations agreed to post information about our study to their website or to include our information in their monthly news e-mail, reaching thousands of possible participants at one time. Rather than totally abandoning our more traditional organizations contacts, we used a multipronged approach that included taking the route most travelled by today's Veterans.

The third prong in our recruitment plan has been through the Military Student Office located at every university and community college across the country. Colleges have historically seen Veterans and currently serving SMs as potential students. Each of our study sites is located adjacent to a major university with a booming military experienced student body presence along with a thriving co-located community college. The challenge has been to access these university systems. Each has specific regulations such as the Family Educational Rights and Privacy Act and Gramm-Leach-Bliley Act among others. Each also has an IRB, meaning that a flyer that has already been approved by a VA IRB must also be approved by each university IRB. To recruit from university campuses, we found that paper literature (i.e. tri-fold flyers, one-page advertisements on bulletin boards) yielded limited returns in potential participants. Instead, e-mails yielded better returns—at one university, the person in charge of the Military Student Office agreed to send out an e-mail version of the tri-fold flyer to all the individuals receiving benefits through the G.I. Bill programme. They were provided with informational basics, such as study information and a point of contact to e-mail if interested. In one day with one e-mail, six possible participants contacted us, whereas we had not had a single contact in the previous 6 months with a paper copy of the same flyer. This method has proven effective on several occasions at two different community colleges, and the response rate has been nearly identical with six from one college and five from the other. We consider these approaches very productive in terms of the effort-to-harvest ratio.

Discussion

Recruiting Veterans and SMs for a longitudinal study is not without its challenges. Our experience sheds light on key barriers, and the strategies we found to be most effective. Our study encountered several primary challenges. The first is related to the long (~20 years) commitment for an observational study involving day-long testing, while the second has to do with a young, busy, and mobile military population. Yet, another challenge involved navigating the varied administrative processes in multiple VA and military facilities. Previous studies have addressed these barriers through efforts such as making participants feel special, informing participants of ongoing findings, and developing an online area for participants to share their experiences. We augmented some of these strategies with others including adopting a comprehensive plan with site-specific goals, recruiting from multiple avenues using multi-pronged approaches, establishing personal site visits and interacting with key personnel, continuously monitoring progress and providing feedback, and employing a tiered approach for contacting potential participants.

Among these strategies, appointing a national director of recruitment helped maximize reach and coincided with the greatest gains—particularly with cohorts of interest (i.e. women, Active Duty SMs). A national director affords study staff a global view that allows nimble navigation through the pitfalls related to site-specific requirements and contradictions among these regulations. Moreover, we found that having a Veteran oversee recruitment was extremely helpful. Other studies have similarly shown that having personnel from a specific community recruit from that same community can be particularly beneficial. For example, studies with individuals with spinal cord injuries have found that including individuals with similar disabilities contribute to recruitment successes. Similarly, a peer-driven initiative with AIDS patients has been utilized (22). We extend those findings to Veteran and SM participation, where individuals share an ethos and identity that can be leveraged to motivate study participation. We also were fortunate to not only recruit a director with military background but also one who was familiar with the medical environment and research personnel and the numerous important regulatory issues surrounding recruitment. This combination of peer background with participants and familiarity with medical/research approaches is optimal.

This description of a successful recruitment effort has inherent limitations. When recruitment began, we were focused on daily operations and analysing recruitment results in an intuitive, non-quantified manner. Only well into the study did we begin to conceive of a paper and then realized that quantifying the results explicitly would lend statistical support to our suggestions. Consequently, systems were established but were put in place too late to inform this paper fully. We plan future efforts with respect to the efficacy of further recruitment strategies as well as retention plans. It could also be argued that a national director without military background would have produced comparable results. We cannot refute this directly, but numerous anecdotal incidents lead us to believe knowledge of the military culture imparted by the recruitment director lent credence and efficacy to our efforts. Finally, while others have described overall conceptual recruitment frameworks (23), ours is one of the few efforts to concretely describe recruitment processes with veterans and SMs in an ongoing, successful study of this size.

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Declaration of interest

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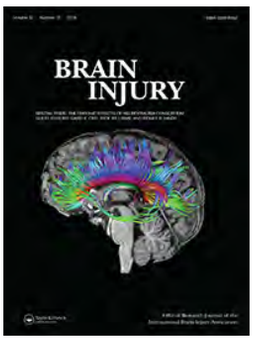
Appendix 12

Sensory dysfunction and traumatic brain injury severity among deployed post-9/11 veterans: a Chronic Effects of Neurotrauma Consortium study



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Sensory dysfunction and traumatic brain injury severity among deployed post-9/11 veterans: a Chronic Effects of Neurotrauma Consortium study

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ABSTRACT

Objectives: To describe the prevalence of sensory dysfunction (i.e. auditory, visual, vestibular, chemosensory and multiple sensory problems) and explore associations with traumatic brain injury (TBI) severity and injury mechanism among deployed Post-9/11 Veterans.

Methods: This retrospective cohort analysis used Departments of Defense and Veterans Affairs diagnostic codes and administrative data.

Results: Among the 570,248 Veterans in this cohort, almost 23% had at least one diagnosis of sensory dysfunction. In the multinomial regression analysis, the odds of all types of sensory dysfunction were greater among those with any TBI relative to those with no TBI. The odds for auditory or multisensory problems were higher among those that indicated exposure to blast. In particular, exposure to quaternary blast injury (e.g. crush, respiratory and burn injuries) was associated with increased odds for auditory, visual, vestibular and multisensory problems.

Conclusions: Sensory problems affect a substantial number of deployed Post-9/11 Veterans and are more common among those with TBI or with exposure to deployment-related blast exposure. Because sensory problems profoundly impact quality of life, their identification and enhanced education and therapy are vital tools to improve prognosis for these relatively young Veterans.

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Introduction

Sensory dysfunction following head injury has been frequently documented. Auditory, visual, vestibular and chemosensory (i.e. smell and taste) problems are more commonly evidenced among those with a history of traumatic brain injury (TBI), particularly those exposed to blast (1–5). While the relationship between blast exposure and injury to the auditory and visual systems are established in the current literature, the rapid change in pressure associated with blast is likely to affect the air- and liquid-filled organs that characterize all sensory systems (1,6–9).

TBI has been described as the signature wound of the Iraq and Afghanistan conflicts. The Department of Defense (DoD) recently reported that more than 375,000 service members have been diagnosed with a TBI since recording began in 2000, with over 82% classified as mild in severity (10). Further, Post-9/11 Veterans, who are counted among all Gulf War era Veterans (i.e. 1990–present), report a staggering number of disabilities for compensation that has eclipsed those of all previous eras. For each of the past 5 years, more than 250,000 Veterans have submitted disability claims from this era, with 2 of the more prevalent service-connected disabilities being tinnitus and hearing loss (11). Importantly, injuries that impact central and peripheral sensory systems are associated with long-lasting and negative consequences on physical, psychological, psychosocial health and community participation (12–14).

While the relationship between sensory dysfunction, brain injury and blast exposure are reported in the literature, meaningful gaps in knowledge remain. First, the prevalence of sensory dysfunction is poorly understood due to assessments frequently being limited to a single sensory modality, specialized care settings and/or small clinical samples. Next, it is not well understood the extent to which TBI type (e.g. closed head or penetrating brain injury) or severity (i.e. mild, moderate or severe) are associated with sensory dysfunction, and if there are differences among Veterans with different TBI classifications. The purpose of this study was to describe the prevalence of sensory conditions and examine their association with TBI severity and injury mechanism in a large cohort of deployed Post-9/11 Veterans who have received Department of Veterans Affairs (VA) care.

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Methods

Data sources and cohort

After obtaining institutional review board approval, we identified deployed Post-9/11 Veterans using the national Operation Enduring Freedom, Operation Iraqi Freedom and Operation New Dawn (OEF/OIF/OND) roster file provided by the VA Office of Public Health and procured their data from the national VA inpatient and outpatient data files located in the Austin Data Repository. Inclusion criteria for deployed Post-9/11 Veterans in this study were (1) entered and received VA care between fiscal years 2002 and 2014 with (2) at least 3 years of care during that period, provided that (3) one or more years of care occurred after 2007 to ensure that the Veteran had been screened for TBI.

Integral to this study was clinically derived data from the VA's TBI screening and subsequent comprehensive TBI Evaluation (CTBIE) (15–17). In 2007, screening for TBI became mandatory among Post-9/11 Veterans utilizing VA care. In order to screen positively for TBI, one must report exposure to TBI as well as post-concussive symptoms immediately subsequent to that injury and within the last week. Once a Veteran screens positive for TBI, she/he is referred for a second, more in-depth clinical interview. The CTBIE queries the patient on the number, type and characteristics of combat exposures, particularly those associated with head injury or persistent post-concussive symptoms.

Outcome groups

In order to describe the full spectrum of sensory dysfunction, we created mutually exclusive outcome groups for each sensory modality included in the analysis using International Classification of Disease, Ninth Edition, Clinical Modification (ICD-9-CM) diagnosis codes wherein diagnosis (as primary or secondary diagnoses) must have been documented in at least 2 separate VA health care visits at least 7 days apart (See Table 1) (18,19). Sensory dysfunction diagnoses were identified at any time during VA care between 2002 and 2015. We categorized diagnoses into auditory (e.g. hearing loss, tinnitus, hyperacusis), visual (e.g. blindness, low vision, photophobia), vestibular (e.g. vestibular dysfunction, dizziness, balance problems) and chemosensory (i.e. smell and taste) problems. We also included the outcome group multisensory problems, which included individuals that had any combination of two or more of the four aforementioned sensory modality dysfunctions. Notably, auditory processing disorders have not been included among the conditions evaluated in this analysis, largely due to concerns with the standardization and interpretation of diagnostic assessments.

Table 1. International Classification of Diagnoses, Ninth Edition, Clinical Modification (ICD-9-CM) diagnosis codes used to identify auditory, visual, vestibular and chemosensory problems in this study.

Sensory dysfunction group	ICD-9-CM codes
Auditory problems	389.X, 388.3X, 382.01, 384.2X, 384.8X, 384.9, 872.6X, 872.7X, 388.42
Visual problems	369.X, 379.99, 368.16, 368.2, 368.41, 368.45, 368.46, 368.47, 368.8, 368.13
Vestibular problems	438.85, 379.54, 386.X, 794.16, 780.4, 781.2, 781.3
Chemosensory problems	781.1

Covariates

Socio-demographics. Socio-demographic characteristics were obtained using VA inpatient and outpatient data and the OEF/OIF/OND roster file. We first used the roster file and then supplemented with VA patient data as it was the most recent and addressed information that may have been missing. Demographic variables included age (at entry to VA care), sex, race/ethnicity (Caucasian Non-Hispanic, Black Non-Hispanic, Asian, Hispanic, Native American/Pacific Islander or unknown) and marital status (married or not married). Because age violated the assumption of linearity in the model, it was categorized into the following age groups: less than 30 years of age, 31–40, 41–50 and 51 or more years as has been used in previous papers describing auditory conditions among Veterans (20,21). Military demographic characteristics from the roster file included component of armed forces (Active or Guard/Reserve), rank at discharge (Enlisted or Officer/Warrant) and branch (Army, Air Force, Navy/Coast Guard, Marine Corps).

TBI severity. We designed an algorithm using both the Department of Defense Trauma Registry (DoDTR) and VA administrative data to identify the severity of TBI recorded among a hierarchy of these sources (See Figure 1) using guidance on TBI severity from both the VA clinical practice guidelines and the Armed Forces Health Surveillance Center (22,23). TBI severity was identified using all available data within the study period. Because coding guidance indicates that each TBI should be coded only once in clinical care, we required only a single inpatient or outpatient diagnosis. Additionally, we used information from the VA's TBI screening and CTBIE to describe the full spectrum of TBI exposure available through the above mentioned data sources. The resultant severities were no evidence of TBI (hereafter, no TBI), historically resolved (i.e. exposure to TBI where the subsequent symptoms were not problematic at the time of screening indicated on the VA TBI Screening), screen positive (i.e. indicated exposure to TBI as well as subsequent and lingering symptoms on the CTBIE, but no additional evidence of a TBI), mild TBI (mTBI), moderate/severe TBI, penetrating TBI (pTBI) and TBI of unclassified severity (hereafter, unclassified TBI) based on the CTBIE.

Injury mechanism. To examine the association between the sensory dysfunction groups and injury mechanism, we included exposure reported by Veterans on the CTBIE (16,17). We included whether Veterans indicated exposure to blunt, bullet, fall, vehicular, or blast trauma while on OEF/OIF deployment ("Yes" or "No"). Among those that reported exposure to blast while deployed, we examined the unique association of each blast injury phase with the sensory dysfunction groups. Primary blast (i.e. blast wave), secondary blast (i.e. rapidly moving debris), tertiary blast (i.e. being thrown onto a stationary object) and quaternary blast (i.e. subsequent environmental hazards such as toxic fumes or falling structures) were the phases included in this analysis ("Yes" or "No").

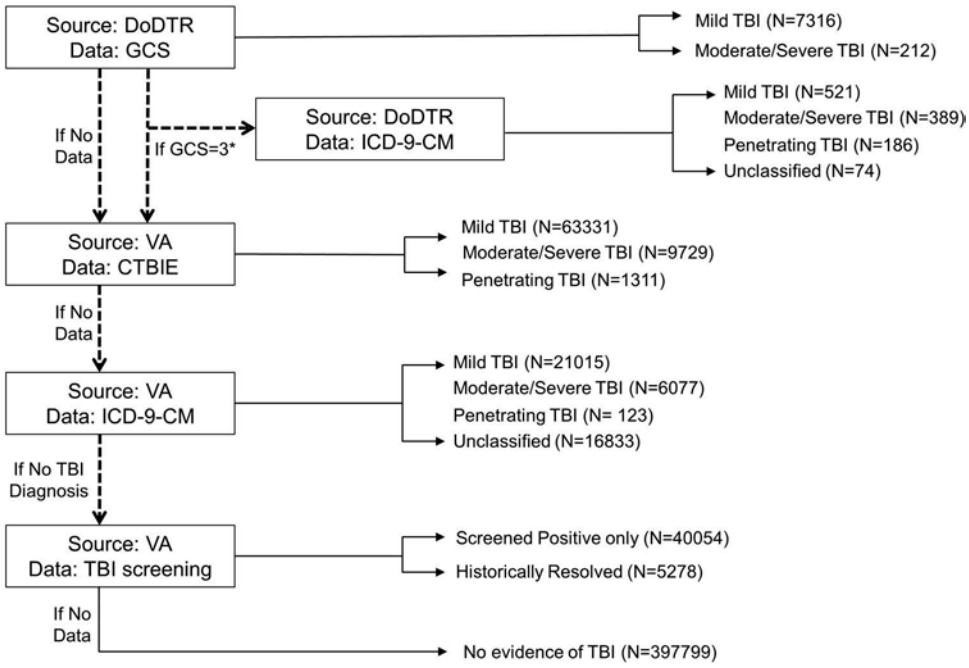

Figure 1. Diagrammatic representation of the algorithm used to categorize traumatic brain injury (TBI) severity. In this algorithm, data from the Department of Defense trauma registry (DoDTR) were first considered. The DoDTR stores Glasgow Coma Scale scores, which range between 3 and 15; an individual with a score of 12 or less would be considered to have a moderate/severe TBI, whereas an individual with a score of 13 to 15 would be considered to have mTBI. Then, if the previously mentioned data source was not available for an individual, self-reported duration of loss of consciousness, alteration of consciousness, and post-traumatic amnesia from the comprehensive TBI evaluation (CTBIE) was used to classify TBI severity based on Department of Defense criteria (22). Then, if the aforementioned data sources were also not available, International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes from VA care were used to classify TBI severity based on coding guidance from the Department of Defense (23). Lastly, if data were not available from all of the above listed sources, responses from the VA TBI screening measure was examined to help identify those that had indicated a history of TBI and reported recent symptomology (Screen Positive). If a Veteran did not have any evidence among these data sources of exposure to TBI, they were categorized as no TBI.

Analysis

We first described the characteristics of those with auditory, visual, vestibular, chemosensory, multisensory problems, and those with no sensory problem diagnoses identified in this study. Based on the standardized residuals from the cell chi-square analysis among each of the factors included in the analysis, $p < 0.05$ was considered statistically significant to indicate groups that had higher and lower than expected rates of each condition. We also used multinomial regression analyses, controlling for socio-demographic characteristics, to determine if TBI severity was associated with any sensory dysfunction group relative to those without sensory problem diagnoses. In a follow-up analysis among those with CTBIE data, we evaluated the association between injury mechanism (blunt, bullet, fall, vehicular or blast trauma) and sensory dysfunction group. Further, among those that indicated exposure to blast while on combat deployment, we examined the unique association between blast injury phase and sensory dysfunction group in this study using a multinomial logistic regression. Although significant differences can be present when confidence intervals overlap, we used a conservative approach and identified significant differences as those conditions for which no overlap occurred (24). All analyses were conducted using SAS® Version 9.2 (SAS Institute, Carey NC). The study was over-powered because of the large cohort size, making statistical significance easy to achieve; we therefore focus our discussion on large effect sizes (adjusted odds ratios; AORs > 2.0 or < 0.5), although smaller effects sizes may still be statistically and practically significant (25).

Results

Prevalence of sensory conditions in the cohort

The resulting overall cohort numbered 570,248 Post-9/11 Veterans. Using the diagnosis codes described in Table 1, 108,106 (18.96%) of this cohort had auditory Problems, 15,414 (2.70%) had visual problems, 19,967 (3.50%) had vestibular problems, 493 (0.09%) had chemosensory problems and 14,370 (2.52%) had multisensory problems. The descriptive statistics for the resultant sensory dysfunction groups are shown in Table 2 for the overall cohort. Among those who completed the CTBIE, 25,728 (25.30%) had auditory problems, 2821 (2.77%) had visual problems, 3109 (3.06%) had vestibular problems, 54 (0.05%) had chemosensory problems and 6771 (6.66%) had multisensory problems.

Socio-demographic characteristics of the cohort

The average age of the sample was 31.68 years with a standard deviation of 9.03 years. The overall cohort was predominantly white (65.12%), male (87.02%), 30 years of age and younger (57.06%) and most recently an enlisted (92.92%) active duty (59.58%) service member in the Army (62.64%). The descriptive statistics of this cohort and the results of the cell chi-square analysis are shown in Table 2.

Table 2. Descriptive statistics of traumatic brain injury (TBI) severity, injury mechanism, socio-demographics, and military characteristics among the 570,248 Post-9/11 Veterans of this cohort by each of the sensory dysfunction groups included in the study.

	None	Auditory problems	Visual problems	Vestibular problems	Chemosensory problems	Multisensory problems
***N* (%)**	441832 (77.48)	94748 (16.62)	8765 (1.54)	10270 (1.80)	263 (0.05)	14370 (2.52)
TBI severity						
No TBI	327817 (82.41)$^{\uparrow}$	55325 (13.91)$^{\downarrow}$	4396 (1.11)$^{\downarrow}$	5429 (1.36)$^{\downarrow}$	163 (0.04)	4669 (1.17)$^{\downarrow}$
Historically resolved	4216 (79.88)	911 (17.26)	55 (1.04)	49 (0.93)$^{\downarrow}$	<5%[a]	45 (0.85)$^{\downarrow}$
Screen positive	30501 (76.15)$^{\downarrow}$	7471 (18.65)$^{\uparrow}$	519 (1.30)$^{\downarrow}$	659 (1.65)	16 (0.04)	888 (2.22)$^{\downarrow}$
Mild TBI	57768 (62.67)$^{\downarrow}$	22878 (24.82)$^{\uparrow}$	2596 (2.82)$^{\uparrow}$	2856 (3.10)$^{\uparrow}$	40 (0.04)	6045 (6.56)$^{\uparrow}$
Moderate/Severe TBI	9340 (56.93)$^{\downarrow}$	4083 (24.89)$^{\uparrow}$	614 (3.74)$^{\uparrow}$	677 (4.13)$^{\uparrow}$	23 (0.14)$^{\uparrow}$	1670 (10.18)$^{\uparrow}$
Penetrating TBI	863 (53.27)$^{\downarrow}$	429 (26.48)$^{\uparrow}$	87 (5.37)$^{\uparrow}$	45 (2.78)	<5%[a]	195 (12.04)$^{\uparrow}$
Unclassified TBI	11327 (67.00)$^{\downarrow}$	3651 (21.59)$^{\uparrow}$	498 (2.95)$^{\uparrow}$	555 (3.28)$^{\uparrow}$	18 (0.11)$^{\uparrow}$	858 (5.07)$^{\uparrow}$
Age						
30 and under	267424 (81.01)$^{\uparrow}$	46649 (14.13)$^{\downarrow}$	4558 (1.38)$^{\downarrow}$	5132 (1.55)$^{\downarrow}$	131 (0.04)	6220 (1.88)$^{\downarrow}$
31–40	97596 (76.59)$^{\downarrow}$	21412 (16.80)	2025 (1.59)	2654 (2.08)$^{\uparrow}$	65 (0.05)	3675 (2.88)$^{\uparrow}$
41–50	63970 (70.61)$^{\downarrow}$	19398 (21.41)$^{\uparrow}$	1811 (2.00)$^{\uparrow}$	2028 (2.24)$^{\uparrow}$	55 (0.06)	3329 (3.67)$^{\uparrow}$
51+	12842 (58.07)$^{\downarrow}$	7289 (32.96)$^{\uparrow}$	371 (1.68)	456 (2.06)	12 (0.05)	1146 (5.18)$^{\uparrow}$
Sex						
Male	378557 (76.18)$^{\downarrow}$	89199 (17.95)$^{\uparrow}$	7607 (1.53)	8194 (1.65)$^{\downarrow}$	225 (0.05)	13115 (2.64)$^{\uparrow}$
Female	63275 (86.26)$^{\uparrow}$	5549 (7.56)$^{\downarrow}$	1158 (1.58)	2076 (2.83)$^{\uparrow}$	38 (0.05)	1255 (1.71)$^{\downarrow}$
Marital status						
Married	186279 (73.94)$^{\downarrow}$	48451 (19.23)$^{\uparrow}$	4202 (1.67)$^{\uparrow}$	4894 (1.94)$^{\uparrow}$	123 (0.05)	7986 (3.17)$^{\uparrow}$
Not married	255553 (80.28)$^{\uparrow}$	46297 (14.54)$^{\downarrow}$	4563 (1.43)$^{\downarrow}$	5376 (1.69)$^{\downarrow}$	140 (0.04)	6384 (2.01)$^{\downarrow}$
Race/Ethnicity						
Caucasian Non-Hispanic	282644 (75.88)$^{\downarrow}$	69026 (18.53)$^{\uparrow}$	4796 (1.29)$^{\downarrow}$	6291 (1.69)$^{\downarrow}$	159 (0.04)	9548 (2.56)
African-American Non-Hispanic	84157 (83.59)$^{\uparrow}$	10074 (10.01)$^{\downarrow}$	2347 (2.33)$^{\uparrow}$	2122 (2.11)$^{\uparrow}$	62 (0.06)	1913 (1.90)$^{\downarrow}$
Asian	11531 (77.26)	2553 (17.11)	217 (1.45)	240 (1.61)	<5%[a]	375 (2.51)
Hispanic	51842 (76.73)	10942 (16.19)	1167 (1.73)$^{\uparrow}$	1408 (2.08)$^{\uparrow}$	29 (0.04)	2179 (3.22)$^{\uparrow}$
Native American/Pacific Islanders	6407 (77.84)	1280 (15.55)	162 (1.97)$^{\uparrow}$	125 (1.52)	<5%[a]	256 (3.11)$^{\uparrow}$
Unknown	5251 (82.23)$^{\uparrow}$	873 (13.67)$^{\downarrow}$	76 (1.19)	84 (1.32)	<5%[a]	99 (1.55)$^{\downarrow}$
Rank						
Enlisted	413507 (77.61)	87726 (16.46)	8294 (1.56)	9596 (1.80)	240 (0.05)	13456 (2.53)
Officer/Warrant	28325 (75.68)$^{\downarrow}$	7022 (18.76)$^{\uparrow}$	471 (1.26)$^{\downarrow}$	674 (1.80)	23 (0.06)	914 (2.44)
Component						
Active	274639 (80.03)$^{\uparrow}$	49456 (14.41)$^{\downarrow}$	5485 (1.60)$^{\uparrow}$	6137 (1.79)	154 (0.04)	7286 (2.12)$^{\downarrow}$
Guard/Reserve	167193 (73.62)$^{\downarrow}$	45292 (19.94)$^{\uparrow}$	3280 (1.44)$^{\downarrow}$	4133 (1.82)	109 (0.05)	7084 (3.12)$^{\uparrow}$
Branch						
Army	275922 (76.46)$^{\downarrow}$	62667 (17.36)$^{\uparrow}$	5807 (1.61)$^{\uparrow}$	6426 (1.78)	158 (0.04)	9906 (2.74)$^{\uparrow}$
Air Force	45302 (79.06)$^{\uparrow}$	8759 (15.29)$^{\downarrow}$	794 (1.39)	1134 (1.98)$^{\uparrow}$	37 (0.06)	1274 (2.22)$^{\downarrow}$
Navy/Coast Guard	60044 (82.59)$^{\uparrow}$	8726 (12.00)$^{\downarrow}$	1056 (1.45)	1516 (2.09)$^{\uparrow}$	31 (0.04)	1332 (1.83)$^{\downarrow}$
Marines	60564 (76.32)$^{\downarrow}$	14596 (18.39)$^{\uparrow}$	1108 (1.40)$^{\downarrow}$	1194 (1.50)$^{\downarrow}$	37 (0.05)	1858 (2.34)$^{\downarrow}$

TBI: traumatic brain injury
[a]Based on Department of Veterans Affairs reporting guidelines, groups of 11 or fewer are not presented.
$^{\uparrow}$Frequency is significantly higher than expected based on standardized residuals in chi-square analysis.
$^{\downarrow}$Frequency is significantly lower than expected based on standardized residuals in chi-square analysis.

Association between sensory conditions and TBI

The cell chi-square analysis shown in Table 2 revealed that Veterans with mTBI, moderate/severe TBI, pTBI or unclassified TBI had higher than expected rates of auditory, visual, vestibular and multisensory problems. Those with moderate/severe TBI or unclassified TBI also had higher than expected rates of chemosensory problems. Veterans classified in the historically resolved and screen positive TBI groups had lower than expected rates of multisensory problems. Separately, Veterans in the historically resolved TBI group had lower than expected rates of vestibular problems, while those in the screen positive group had lower than expected rates of visual problems, but higher than expected rates of auditory problems.

In the multinomial regression analysis controlling for socio-demographic factors in Table 3, Veterans with any TBI severity had increased odds of auditory problems relative to Veterans with no TBI. Further, those in the screen positive, mTBI, moderate/severe TBI, pTBI and unclassified TBI groups were significantly more likely to have visual, vestibular, or multisensory problems relative to Veterans with no TBI. Those in the mTBI, moderate/severe TBI and unclassified TBI groups were significantly more likely to have chemosensory problems relative to Veterans with no TBI. Almost uniformly, TBI of increased severity was associated with elevated odds for each of the sensory dysfunction groups evaluated in this study.

Association between sensory conditions and injury mechanism

In the cell chi-square analysis shown in Table 4, Veterans that reported exposure to blunt trauma had higher than expected rates of vestibular problems. Reported exposure to bullet trauma was associated with higher than expected frequencies of auditory and multisensory problems. Those that reported falls while on deployment were more likely than expected to have vestibular or multisensory problems. Veterans that reported exposure to blast trauma while had higher than expected rates of auditory problems. The multinomial regression analysis controlling for injury mechanism is shown in Table 5. Increased odds for auditory problems were evident among those that endorsed a history of blunt, bullet or blast trauma while deployed. There were increased odds for

Table 3. Results of the multinomial regression analysis controlling for socio-demographic and military characteristics to examine the association of TBI severity and injury mechanism with sensory conditions among deployed Post-9/11 Veterans.

AOR (95% CI)	Auditory problems versus none	Visual problems versus none	Vestibular problems versus none	Chemosensory problems versus none	Multisensory problems versus none
TBI severity					
No TBI	Ref	Ref	Ref	Ref	Ref
Historically resolved	1.29 (1.20–1.39)*	1.06 (0.81–1.39)	0.84 (0.63–1.11)	1.08 (0.27–4.35)	0.86 (0.64–1.16)
Screen positive	1.48 (1.44–1.52)*	1.35 (1.23–1.48)*	1.53 (1.41–1.66)*	1.18 (0.71–1.99)	2.33 (2.16–2.51)*
Mild TBI	2.47 (2.42–2.52)*	3.80 (3.61–4.00)*	3.75 (3.58–3.94)*	1.66 (1.16–2.37)*	9.24 (8.86–9.63)*
Moderate/Severe TBI	2.77 (2.67–2.88)*	5.62 (5.14–6.14)*	5.52 (5.07–6.00)*	5.96 (3.82–9.31)*	16.14 (15.18–17.17)*
Penetrating TBI	3.12 (2.77–3.51)*	8.65 (6.91–10.81)*	4.08 (3.02–5.52)*	2.87 (0.40–20.59)	20.47 (17.41–24.05)*
Unclassified TBI	1.98 (1.90–2.06)*	3.66 (3.32–4.02)*	3.59 (3.28–3.93)*	3.71 (2.27–6.08)*	6.40 (5.93–6.91)*
Age					
30 and under	Ref	Ref	Ref	Ref	Ref
31–40	1.32 (1.29–1.34)*	1.26 (1.19–1.34)*	1.47 (1.40–1.55)*	1.38 (1.00–1.91)	1.70 (1.62–1.78)*
41–50	2.01 (1.97–2.06)*	1.92 (1.80–2.05)*	1.91 (1.80–2.03)*	1.79 (1.24–2.06)*	2.94 (2.80–3.10)*
51+	3.62 (3.50–3.75)*	2.36 (2.10–2.65)*	2.37 (2.13–2.64)*	1.95 (1.02–3.71)*	5.78 (5.36–6.24)*
Sex					
Male	Ref	Ref	Ref	Ref	Ref
Female	0.50 (0.49–0.52)*	1.08 (1.01–1.15)*	1.88 (1.78–1.98)*	1.10 (0.77–1.57)	0.95 (0.89–1.01)
Marital status					
Married	Ref	Ref	Ref	Ref	Ref
Not married	0.89 (0.88–0.91)*	0.93 (0.89–0.98)*	0.93 (0.89–0.97)*	1.02 (0.78–1.34)	0.81 (0.77–0.84)*
Race/Ethnicity					
Caucasian Non-Hispanic	Ref	Ref	Ref	Ref	Ref
African-American Non-Hispanic	0.52 (0.51–0.53)*	1.65 (1.57–1.74)*	1.05 (0.99–1.10)	1.34 (0.99–1.81)	0.70 (0.66–0.73)*
Asian	1.00 (0.96–1.05)	1.17 (1.02–1.35)*	0.93 (0.82–1.06)	1.46 (0.74–2.86)	1.13 (1.02–1.26)*
Hispanic	0.89 (0.87–0.91)*	1.34 (1.25–1.43)*	1.22 (1.15–1.29)*	1.05 (0.70–1.56)	1.28 (1.22–1.34)*
Native American/Pacific Islanders	0.85 (0.80–0.90)*	1.38 (1.18–1.62)*	0.77 (0.65–0.92)*	0.28 (0.04–1.97)	1.07 (0.94–1.22)
Unknown	0.73 (0.68–0.79)*	0.89 (0.71–1.12)	0.75 (0.60–0.93)*	1.01 (0.32–3.18)	0.66 (0.54–0.81)*
Rank					
Enlisted	Ref	Ref	Ref	Ref	Ref
Officer/Warrant	0.86 (0.83–0.88)*	0.80 (0.72–0.88)*	0.89 (0.82–0.97)*	1.22 (0.78–1.92)	0.77 (0.72–0.83)*
Component					
Active	Ref	Ref	Ref	Ref	Ref
Guard/Reserve	1.34 (1.31–1.36)*	0.97 (0.92–1.02)	1.11 (1.06–1.16)*	1.17 (0.89–1.54)	1.48 (1.43–1.54)*
Branch					
Army	Ref	Ref	Ref	Ref	Ref
Air Force	0.94 (0.92–0.97)*	1.02 (0.95–1.11)	1.26 (1.18–1.35)*	1.58 (1.08–2.30)*	1.18 (1.10–1.25)*
Navy/Coast Guard	0.84 (0.82–0.86)*	0.99 (0.93–1.07)	1.34 (1.26–1.43)*	1.04 (0.70–1.56)	1.04 (0.98–1.11)
Marines	1.27 (1.25–1.30)*	0.99 (0.92–1.06)	1.05 (0.98–1.12)	1.32 (0.90–1.93)	1.18 (1.11–1.24)*

TBI: traumatic brain injury; AOR: adjusted odds ratio; Ref: reference group.
*indicates statistical significance at $p < 0.05$

vestibular problems among those who reported blunt, bullet or fall trauma while on deployment. Lastly, increased odds for multisensory problems were found among all injury mechanisms included in the analysis.

In the follow-up analysis among those that reported exposure to blast while deployed, we found in the cell chi-square analysis that Veterans that reported exposure to secondary or tertiary blast were more likely than expected to have auditory or multisensory problems. Veterans that reported exposure to quaternary blast had higher than expected rates of auditory, visual, and multisensory problems. The multinomial regression controlling for blast injury phase revealed that both auditory and multisensory problems were associated with all phases of blast. Increased odds for visual or vestibular problems were associated with exposure to quaternary blast.

Association between sensory conditions and socio-demographics

Based on the cell chi-square analysis shown in Table 2, those younger than 30 years of age were less likely than expected to have auditory, vestibular, visual or multisensory problems. Those in the older age groups were significantly more likely than expected to have auditory problems (41–50 and 51 and older), visual problems (41–50), vestibular problems (31–40 and 41–50) and multisensory problems (31–40, 41–50, and 51 and older). In the multinomial regression analysis shown in Table 3, the older age groups were consistently associated with increased odds of any sensory dysfunction group included in the analysis relative to those 30 years and younger.

In the cell chi-squared analysis shown in Table 2, men more frequently than expected had auditory and multisensory problems and less frequently than expected had vestibular problems while women exhibited the opposite trend. In the multinomial regression analysis shown in Table 3, women were more likely to have vestibular problems but less likely to have auditory problems relative to men. Married individuals consistently had auditory, visual, vestibular and multisensory problems more frequently than expected while their unmarried counterparts had these conditions less frequently than expected. The multinomial regression analysis revealed this same trend.

In the cell chi-square analysis shown in Table 2, Caucasian Non-Hispanic Veterans had lower than expected rates of visual and vestibular problems and higher than expected rates of auditory problems. Conversely, African-American Non-Hispanic Veterans had lower than expected rates of auditory and multisensory problems and higher than expected

Table 4. Descriptive statistics of injury mechanism by sensory dysfunction group among the 101 804 deployed Post-9/11 Veterans in the cohort that had completed the comprehensive traumatic brain injury evaluation (CTBIE).

N (%)	None 63208 (62.18)	Auditory problems 25728 (25.30)	Visual problems 2821 (2.77)	Vestibular problems 3109 (3.06)	Chemosensory problems 54 (0.05)	Multisensory problems 6771 (6.66)
Blunt						
No	44027 (62.57)	17779 (25.27)	1934 (2.75)	2013 (2.86)	37 (0.05)	4577 (6.50)
Yes	19181 (61.24)	7949 (25.38)	887 (2.83)	1096 (3.50)[↑]	17 (0.05)	2193 (7.00)
Bullet						
No	62817 (62.61)	25125 (25.04)	2760 (2.75)	3044 (3.03)	<5%[a]	6535 (6.51)
Yes	2201 (56.89)[↓]	1089 (28.15)[↑]	119 (3.08)	139 (3.59)	<5%[a]	319 (8.25)[↑]
Fall						
No	47367 (62.44)	19407 (25.58)	2065 (2.72)	2186 (2.88)	39 (0.05)	4790 (6.31)[↓]
Yes	15918 (61.34)	6347 (24.46)	761 (2.93)	926 (3.57)[↑]	15 (0.06)	1983 (7.64)[↑]
Vehicular						
No	48837 (62.44)	19733 (25.23)	2166 (2.77)	2352 (3.01)	36 (0.05)	5087 (6.50)
Yes	14447 (61.24)	6021 (25.52)	660 (2.80)	760 (3.22)	18 (0.08)	1686 (7.15)
Blast						
No	15999 (66.53)[↑]	5024 (20.89)[↓]	717 (2.98)	863 (3.59)[↑]	16 (0.07)	1427 (5.93)[↓]
Yes	47291 (60.81)[↓]	20732 (26.66)[↑]	2109 (2.71)	2250 (2.89)	38 (0.05)	5347 (6.88)
Primary blast						
No	4984 (64.44)[↑]	1875 (24.24)[↓]	203 (2.62)	220 (2.84)	<5%[a]	449 (5.81)[↓]
Yes	40889 (60.50)	18151 (26.86)	1844 (2.73)	1959 (2.90)	<5%[a]	4710 (6.97)
Secondary blast						
No	17866 (63.87)[↑]	6877 (24.59)[↓]	735 (2.63)	787 (2.81)	<5%[a]	1696 (3.06)[↓]
Yes	28007 (59.15)[↓]	13149 (27.77)[↑]	1312 (2.77)	1392 (2.94)	<5%[a]	3463 (7.31)[↑]
Tertiary blast						
No	19896 (63.14)[↑]	7967 (25.28)[↓]	820 (2.60)	909 (2.88)	17 (0.05)	1900 (6.03)[↓]
Yes	25977 (59.29)[↓]	12059 (27.52)[↑]	1227 (2.80)	1270 (2.90)	21 (0.05)	3259 (7.44)[↑]
Quaternary blast						
No	34100 (62.59)[↑]	14044 (25.78)[↓]	1400 (2.57)	1540 (2.83)	<5%[a]	3374 (6.19)[↓]
Yes	11773 (56.50)[↓]	5982 (28.71)[↑]	647 (3.11)[↑]	639 (3.07)	<5%[a]	1785 (8.57)[↑]

[a]Based on Department of Veterans Affairs reporting guidelines, groups of 11 or fewer are not presented.
[↑]Frequency is significantly higher than expected based on standardized residuals in chi-square analysis.
[↓]Frequency is significantly lower than expected based on standardized residuals in chi-square analysis.

Table 5. Results of the multinomial regression analysis examining the association between injury mechanism with sensory dysfunction group among deployed Post-9/11 Veterans in the cohort that had completed the comprehensive traumatic brain injury evaluation (CTBIE).

AOR (95% CI)	Auditory problems versus none	Visual problems versus none	Vestibular problems versus none	Chemosensory problems versus none	Multisensory problems versus none
Blunt	1.08 (1.05–1.11)*	1.05 (0.96–1.14)	1.21 (1.12–1.31)*	1.00 (0.56–1.79)	1.11 (1.05–1.18)*
Bullet	1.16 (1.08–1.25)*	1.20 (0.99–1.45)	1.25 (1.05–1.50)*	0.98 (0.24–4.06)	1.25 (1.11–1.41)*
Fall	1.01 (0.98–1.05)	1.09 (1.00–1.19)	1.21 (1.12–1.31)*	1.07 (0.58–1.96)	1.26 (1.19–1.33)*
Vehicular	1.04 (1.00–1.08)	1.01 (0.93–1.11)	1.05 (0.97–1.15)	1.67 (0.95–2.96)	1.09 (1.03–1.16)*
Blast	1.42 (1.37–1.47)*	1.02 (0.93–1.11)	0.94 (0.86–1.02)	0.83 (0.46–1.51)	1.34 (1.26–1.42)*
Primary blast	1.09 (1.03–1.16)*	1.04 (0.90–1.21)	1.04 (0.90–1.21)	1.33 (0.40–4.42)	1.13 (1.02–1.26)*
Secondary blast	1.14 (1.10–1.18)*	1.04 (0.94–1.15)	1.08 (0.98–1.18)	1.58 (0.75–3.32)	1.12 (1.05–1.20)*
Tertiary blast	1.07 (1.04–1.11)*	1.06 (0.97–1.17)	1.01 (0.92–1.11)	0.81 (0.41–1.60)	1.16 (1.09–1.24)*
Quaternary blast	1.16 (1.11–1.20)*	1.30 (1.17–1.44)*	1.17 (1.06–1.29)*	1.08 (0.52–2.28)	1.41 (1.32–1.51)*

AOR: adjusted odds ratio; CI: confidence interval
*indicates statistical significance at $p < 0.05$

rates of visual and vestibular problems. Hispanic Veterans had higher than expected rates of visual, vestibular and multisensory problems while Native American/Pacific Islander Veterans also had higher than expected rates of visual and multisensory problems. Veterans of unknown race/ethnicity were less likely than expected to have auditory and multisensory problems.

In the multinomial regression analysis shown in Table 3, Veterans who were African-American Non-Hispanic, Hispanic, Native American/Pacific Islander or of unknown race/ethnicity were significantly less likely to have auditory problems relative to Caucasian Non-Hispanic Veterans. Conversely, Veterans who were African-American Non-Hispanic, Asian, Hispanic or Native American/Pacific Islander Veterans were significantly more likely to have visual problems relative to Caucasian Non-Hispanic Veterans. Regarding vestibular problems, Hispanic Veterans were significantly more likely and Native American/Pacific Islander Veterans were significantly less likely than Caucasian Non-Hispanic Veterans to have these diagnoses. Lastly, African-American Non-Hispanic Veterans and Veterans of unknown race/ethnicity were significantly less likely, while Asian Veterans and Hispanic Veterans were significantly more likely, to have multisensory problems relative to Caucasian Non-Hispanic Veterans.

Discussion

This article evaluated the prevalence of sensory dysfunction and its associations with TBI severity and injury mechanism among deployed Post-9/11 Veterans. In our relatively young Veteran cohort, nearly 23% had been diagnosed with at least one sensory condition. Our findings affirm that increased odds of sensory dysfunction is associated with any TBI

exposure, with increased severity associated with greater odds of each sensory dysfunction group. Further, we found that exposure to blast while on deployment was associated with increased odds for auditory or multisensory problems, with exposure to quaternary blast associated with significantly increased odds for most sensory dysfunction groups. These findings, combined with consistent trends among socio-demographic traits associated with sensory dysfunction identified in this analysis, can be used to identify those at risk for sensory dysfunction and can enable more targeted, individualized and holistic care to improve long-term quality of life.

Based on our analyses, nearly a quarter of VA care-seeking Post-9/11 Veterans have been diagnosed with at least one type of sensory dysfunction. Because inclusion in this study required at least 2 diagnoses at least 7 days apart, this estimate is likely a conservative one. The prevalence of sensory dysfunction varies based on whether it is evaluated using diagnostic codes or symptom self-report as well as the setting and patient population in which it is measured. Previous reports have estimated that hearing loss and tinnitus affect 20% and 25% of the general US population and 12–58% and 6–75% of Iraq and Afghanistan Veterans, respectively (26–28). Visual impairment in the USA has been previously estimated among 6.4% of the general US population and has been documented among 38% of Veterans receiving care for deployment-related polytrauma (29,30). Dizziness, the most commonly diagnosed condition observed in this study included among those in the vestibular problems group, has been estimated to affect 20–30% of the general population and reported by upwards of 60% of blast-exposed active duty service personnel (31–33). Collectively described as chemosensory problems in this study, problems with smell and taste have been reported among 13.5% and 17.3% of the general US population and 13–25% and 5–7% among those with head injury, respectively (34–36). Some recent analyses of OEF/OIF/OND military and Veteran samples with different TBI severity, although primarily mTBI, have not reported changes in taste or smell as a post-TBI chronic symptom (37). Epidemiological assessments of chemosensory dysfunction are sparse, although studies of literature generally suggests that complaints of this type are more common among those with head injury, much like the other sensory modalities examined in this analysis (34–36,38). Lastly, multisensory problems were evidenced among 2.52% of Veterans in this study, which is generally lower than estimates of 7–21% in a comparable Veteran cohort (39–42). In addition to our conservative method of diagnostic identification, comparison between estimates may be limited by the fact that measurement is frequently undertaken among generally older or specialized clinical samples.

All TBI groups included in this analysis were associated with increased odds of sensory dysfunction, with increased severity associated with significantly higher odds of these conditions. While numerous previous reports have demonstrated this association, most have frequently been limited to a single sensory modality or severity of TBI. (8,35,36,43–45) This article is the first to contextualize the association between the spectrum of TBI severity and a broad gamut of sensory modality dysfunction to provide a more holistic assessment of the scope of sensory dysfunction among Post-9/11 Veterans. Notably, those with mTBI had heightened odds of all sensory dysfunction included in our analyses, which ranged from being 60% more likely to have comorbid chemosensory problems and nearly 10 times more likely to have multisensory problems relative to Veterans with no TBI. These associations were even more dramatic among those with moderate/severe TBI or pTBI for all sensory modalities included in this analysis. Notably, even Veterans in the screen positive group had modestly increased odds for all but chemosensory problems in our analysis. These findings reveal that exposure to head injury of any severity is associated with increased rates of sensory dysfunction.

The inclusion of injury mechanism in this analysis revealed nuanced but informative trends among potentially traumatic exposures commonly experienced by Veterans of this era, such as blast. Much like previous reports, there was a clear association between blast exposure, including its individual injury phases, and auditory dysfunction (46–50). This may be unsurprising, given that the general military environment (e.g. training for explosives, gunfire) is rife with noise exposures that, like blast, are pressure waves with the potential to negatively impact peripheral sensory organs. Veterans that reported exposure to blunt or bullet trauma on the CTBIE were also more likely to have auditory, vestibular or multisensory problems. This finding suggests that the shared peripheral sensory system architecture of the auditory and vestibular systems may be particularly sensitive to jarring physical trauma. It is therefore worrisome that many soldiers often eschew ear protection in the field because of how it limits awareness of the potentially hostile environment (51).

Similar to our findings, previous reports have likewise implicated blast exposure as a risk factor in the development of visual and vestibular dysfunction (48,52–54). However, these effects were limited to those that reported exposure to quaternary blast, rather than blast exposure more generally. However, a modest effect of blast exposure on vestibular dysfunction may be a lack of specificity in diagnostic coding commonly used in clinical care with which to identify it. Histological and electrophysiological studies in humans and animals suggest that the saccule, one of the five vestibular sensory organs, may be particularly susceptible to noise-related damage (55–60). Although the saccular pathway can be assessed clinically using vestibular evoked myogenic potentials, this new clinical procedure is not captured with current diagnostic coding. Likewise, some types of sensory dysfunction may be slowly or poorly identified in the course of typical clinical care due to more pressing conditions commonly exhibited in this population, such as post-traumatic stress disorder or headaches. Clinician education to increase awareness of sensory dysfunction as well as enhanced tools with which to diagnose them could greatly benefit this patient population.

The socio-demographic characteristics included in our analysis also revealed meaningful trends among those more or less likely to report sensory dysfunction among Post-9/11 Veterans using VA care. Most notably, Veterans that were older, married, most recently enlisted and in the Guard/Reserve more frequently received diagnoses of sensory dysfunction in our sample. Consistent with many previous reports, increased age

is associated with all sensory dysfunction groups included in this analysis, which may belie an age-related vulnerability to sensory dysfunction (27,34,61–63). Likewise, men were significantly more likely to receive diagnoses of auditory dysfunction while women were significantly more likely to receive those of vestibular dysfunction (21,26,64,65). In the general population, there is an established male preponderance for hearing loss; however, it is also reasonable to hypothesize that women are less likely to experience auditory dysfunction in this Veteran sample due to differences in hazardous occupational exposures during military service (66,67). The preponderance of auditory problems among males is also likely influenced by a general tendency for women, particularly older women, to have better hearing thresholds than their male counterparts (68). Further, while it is well-established that conditions like dizziness are more common among females, mechanisms underlying that preponderance are poorly understood (32,69,70). These sex-related differences must be interpreted with the caveat that women more frequently report physical symptoms than their male counterparts (71).

Differences in sensory dysfunction by race/ethnicity have been likewise established. In line with this, we found that Caucasian Non-Hispanic Veterans demonstrated the highest odds for auditory problems, while all other race/ethnicities were more likely to be diagnosed with visual problems. Our finding is consistent with numerous reports that African-American Non-Hispanic individuals have greatly diminished odds of hearing loss relative to their Caucasian Non-Hispanic peers, hypothesized to be due to concordant skin and cochlear pigmentation, with darker pigments being more protective (26,27,72,73). Likewise, higher rates of visual dysfunction have been previously noted among these race/ethnicities and have been hypothesized to be due to differences in ocular structure and prevalence of ocular dysfunction, as well as disparities in access to eye care (74). Veterans of Hispanic descent had the highest odds of having two or more sensory modalities affected, a finding that has not been previously reported. These results could enable clinicians to identify and assess Veterans most likely to have sensory dysfunction to better enable timely and holistic care and improve long-term outcomes and quality of life.

This study has several limitations. First, our estimate for prevalence was likely conservative, an artefact due in part to requiring at least 2 outpatient ICD-9-CM diagnoses at least 7 days apart. It is further possible that some of the conditions included in this study are under-identified during the course of clinical care, in part due to more pressing clinical concerns and coding conventions. Our sensory dysfunction groups, several of which combine major health conditions under a single sensory modality, may limit comparisons with other reports that focus on individual conditions. Notably, central auditory processing disorder was not included among the conditions evaluated in this article. This omission is largely because neither the VA nor DoD have standardized approaches for diagnosing or treating such patients. Next, our analyses can only support an association between conditions, because date(s) of incident diagnoses are generally not feasible without linkage between DoD and VA data. Previous experience (see Pugh et al., 2015) has shown that analyses in a temporally refined sample (i.e. verified TBI exposure prior to an epilepsy diagnosis) demonstrated trends identical to those that did not exclude those missing injury date data (75). Further, data were not available to categorize the severity of the unclassified TBI group, which was not independent of the other TBI severity groupings. However, we do not believe this limited our ability to interpret findings. Consistent with the literature that the majority of TBIs are mild, a review of the descriptive data and multinomial regression analysis suggests that the unclassified TBI group most closely aligns with the mTBI group. Further, our measures of injury mechanism and blast injury phase from the CTBIE are both subjective and retrospective. Lastly, the cohort used in this study is limited to Veterans that seek regular VA care and may represent a population of individuals not generalizable to the broader Veteran or civilian population.

Conclusions

The purpose of this work is ultimately to inform clinical practice to improve the identification and effective care of sensory dysfunction. Our findings that comorbid TBI and a variety of socio-demographic characteristics, such as age, sex and military factors, are associated with increased rates of sensory dysfunction may enable clinicians to more effectively identify and provide care for those with sensory conditions. It is of particular clinical importance that sensory issues are swiftly and effectively addressed during clinical care because of their potential to negatively impact patient education or treatment adherence for other, unrelated conditions. This work may indicate that many of these patients with TBI, who become 'professional patients' attending various appointments for their numerous issues, may indeed suffer from a broad spectrum of sensory issues. Evidence such as this may help create more empathy in the patient–provider relationship and/or help a provider assessing a patient with a TBI diagnosis to consider that their behaviour may be influenced, at least in part, by some sensory dysfunction. Early identification and effective rehabilitation may enable more efficient community reintegration and improve long-term outcomes among this relatively young Post-9/11 Veteran cohort.

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Declaration of interest

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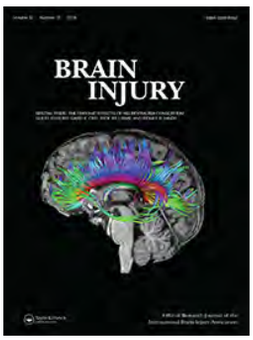
Appendix 13

Is balance performance reduced after mild traumatic brain injury?: Interim analysis from chronic effects of neurotrauma consortium (CENC) multi-centre study



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Is balance performance reduced after mild traumatic brain injury?: interim analysis from Chronic Effects of Neurotrauma Consortium (CENC) multi-centre study

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ABSTRACT

Objectives: Determine if mild traumatic brain injury (mTBI) history is associated with balance disturbances.
Setting: Chronic Effects of Neurotrauma Consortium (CENC) centres.
Participants: The CENC multi-centre study enrols post-9/11 era Service Members and Veterans with combat exposure. This sample (n = 322) consisted of enrolees completing initial evaluation by September 2016 at the three sites conducting computerized dynamic post-urography (CDP) testing.
Design: Observational study with cross-sectional analyses using structural equation modelling.
Main Measures: Comprehensive structured interviews were used to diagnose all lifetime mild traumatic brain injuries (mTBIs). The outcome, Sensory Organization Test (SOT), was measured on CDP dual-plate force platform. Other studied variables were measured by structured interviews, record review and questionnaires.
Results: The overall positive/negative mTBI classification did not have a significant effect on the composite equilibrium score. However, the repetitive mTBI classification showed lower scores for participants with ≥ 3 mTBI versus 1–2 lifetime mTBIs. For repetitive mTBI, pain interference acted as a mediator for the indirect effect, and a direct effect was evident on some sensory condition equilibrium scores.
Conclusion: These findings show that repeated mTBI, partially mediated by pain, may lead to later balance disturbances among military combatants. Further study of CDP outcomes within this accruing cohort is warranted.

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Traumatic brain injury; concussion; balance; pain; veteran; military

Introduction

Deployed US service members (SMs) have been subjected to a high rate of blast exposure in the post-9/11 conflicts [Operation Enduring Freedom (OEF, Afghanistan), Operation Iraqi Freedom (OIF, Iraq) and their follow-on conflicts like Operation New Dawn (OND)]. Explosive munitions are estimated to be involved in up to 78% of the morbidity cases in these post-9/11 conflicts, the highest proportion for any large-scale conflict (1). Traumatic brain injury (TBI) is one consequence of these blast exposures, and is considered the 'signature wound' of post-9/11 combat deployments, with 19% of war fighters estimated to have sustained a TBI (2) and mild TBI (mTBI) accounting for over 80% of TBIs(3). Approximately 20% of those who sustain an mTBI may develop post-concussion syndrome (PCS), a condition of persistent symptoms (≥ 3 months), which may include physical, cognitive and behavioural impairments (4,5). Prevalence rates of PCS are higher among combat and blast-exposed SMs and Veterans (6). One of the symptoms that can persist chronically after mTBI is postural instability or imbalance (7), which has a major impact on functional status, capacity to return to work and quality-of-life (8–10).

Postural stability or balance is defined as the ability to maintain the body's centre of gravity within the base of support with minimal postural sway (11). To achieve balance, input from multiple sensory components, visual, proprioceptive and vestibular, must be integrated and coordinated with the motor system via the central nervous system. In the moderate-severe TBI population, objective impairment of early balance function is ubiquitous, can be measured on routine physical examination, and is predictive of rehabilitation outcome (12,13). Objective balance deficits persisting years after moderate-severe TBI have also been documented on Computerized Dynamic Post-urography (CDP), a method of quantifying balance through body-weight shifts on a force plate (14,15), via lower scores on the Sensory Organization

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Test (SOT) (14). The SOT is part of the CDP protocol that measures information about the integration of the sensory components of balance (visual, proprioceptive and vestibular) under fixed and various sensory feedback conditions to generate a set of 'equilibrium scores' that assesses the overall coordination of these systems to maintain standing posture (16). Scores on the SOT have been shown to correlate with the Dizziness Handicap Inventory, a subjective measure of dizziness, objective measures of postural sway and perceived disability due to imbalance (15).

For persons with mTBI, the evidence for objective long-lasting balance deficits is less compelling than for moderate to severe TBI (17). In the acute (1 week) and sub-acute (1–12 week) periods, multiple small studies have shown static or dynamic balance deficits following sports-related mTBI (18–23). In one investigation, participants with acute mTBI had higher magnitudes of sway when deprived of accurate visual cues, despite having no gross visual or neurologic impairments, leading researchers to comment on the subtle complexity and need for central integration of the multi-sensory contributions to balance (20). Importantly however, these objective findings of imbalance typically resolved within the first several weeks to months (18–23). Until recently, there have been no large scale, well-controlled studies measuring objective balance deficits after mTBI beyond this timeframe in any mTBI sub-populations (19).

Veterans and SMs are posited to be at higher risk than athletes for persisting balance deficits after mTBI due to the additional complexities of blast mechanism and/or common comorbidities such as pain and post-traumatic stress disorder (PTSD) (17). However, there is even less information available for military populations on persisting objective balance deficits after mTBI, even though Veterans and SMs with a suspected mTBI history commonly report chronic (> 3 months) symptoms of imbalance as well as dizziness, vertigo and clumsiness (7,24,25). Published data on objective postural stability are sparse and usually lack non-TBI comparison groups of otherwise similar characteristics. Wares et al (26) recently reported worse balance performance in blast-exposed Veterans/SMs a median 7 months after mTBI accompanied by post-traumatic amnesia (PTA) versus the comparator group, which combined non-TBI participants with participants having mTBI not accompanied by PTA, presumably the less severe form of mTBI. These findings persisted even when statistically controlling for active PTSD, which also correlated with lower SOT scores. A key limitation of this study was that other potential confounders such as pain were not controlled for in the analyses (27). Other limitations included: index mTBI status was confined to the earlier-noted dichotomous variable, other lifetime mTBIs were not considered, and the number of non-TBI comparators was very small.

The current study addresses this research gap via thorough assessment of all lifetime potential mTBI events, CDP testing, inclusion of a host of potential contributors and use of multivariate structural equation modelling in a sample of previously combat deployed SMs and Veterans. It also considers subcategories of mTBI including the accompaniment of PTA, blast causality and repetitive mTBI as well as absence of any lifetime TBI. The primary objective was to determine whether postural stability differs across any of these mTBI classifications. We hypothesized that mTBI classification would have an effect on CDP performance even after considering the following variables into a statistical model: study site, combat exposure level, time since index event, PTSD, depression, anxiety, pain, pain medications, estimated premorbid intelligence, alcohol consumption, as well as age, and gender.

Methods

Design

The study utilized an observational design with cross-sectional analyses using structural equation modelling to test for causal inference.

Setting

This study reports findings of an interim analysis from the Chronic Effects of Neurotrauma Consortium (CENC) Observational Study of the late effects of OEF/OIF deployment. For more information on the background, breadth and overall objectives of the overarching study, see prior publication by Walker et al (28).

Participants

Participants were recruited primarily from mass letter mailing campaigns to registered patients at each hospital and secondarily by advertisements, flyers, community outreach and clinician referrals. The intended population for the overarching observational study is post-9/11 era SMs and Veterans who experienced combat situation(s) and have a varying mTBI history, from none to many. The only exclusion criteria were (1) history of moderate or severe TBI as defined by either (a) initial Glasgow Coma Scale < 13, (b) coma duration > 0.5 hours, (c) post-traumatic amnesia (PTA) duration > 24 hours, or (d) traumatic intracranial lesion on head computerized tomography, or (2) history of (a) major neurologic disorder (e.g. stroke, spinal cord injury), (b) major psychiatric disorder (e.g. schizophrenia) with major defined as resulting in a significant decrement in functional status or loss of independent living capacity. Notably, PTSD and mood disorder were not considered exclusionary.

The intended sample for these analyses are all participants enrolled before October 2016 at the three sites where the CDP SOT was conducted (Hunter Holmes McGuire Veterans Affairs Medical Center (VAMC) in Richmond, VA; Audie L. Murphy VAMC in San Antonio, TX; and James A. Haley VAMC in Tampa, FL) and who were physically able to complete the CDP SOT protocol (n = 322). From there, data exclusions for these analyses were symptom magnification (n = 19) or missing Neurobehavioral Symptom Inventory (NSI) or Mild Brain Injury Atypical Symptom Scale (mBIAS) (n = 2), missing CDP SOT outcome (n = 0), CDP SOT data-collection reliability codes indicating irregular procedure with unreliable results (n = 1), and non-physiologic CDP equilibrium score profile (n = 6; one of whom was

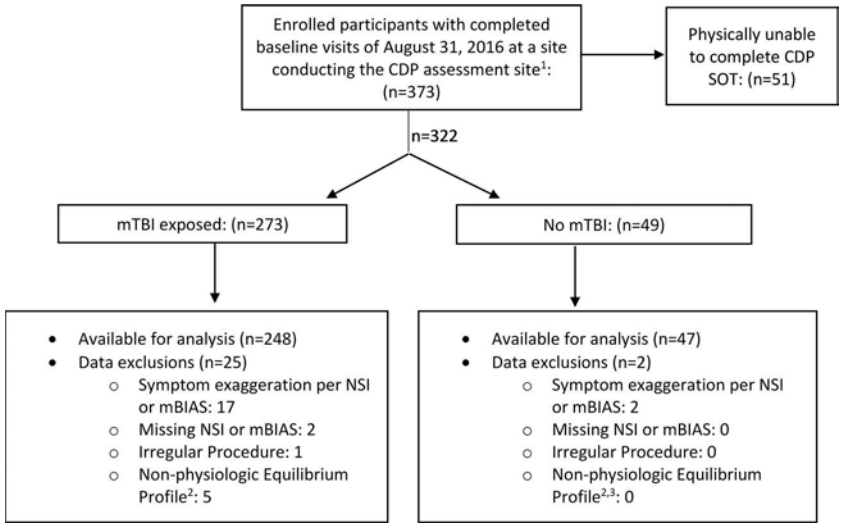

Figure 1. Participant Flow Diagram/Legend: (1) The Houston site did not administer the CDP assessment. As such the CDP analyses exclude all subjects from the Houston site ($N = 119$). An additional 51 individuals did not complete the CDP assessment due to non-tolerance of CDP protocol or technical issues with the machine. (2) Non-credible Effort was assigned if a subject performed poorly on conditions 1 and 2, but performed better on the later, more challenging conditions (3). One subject in the No mTBI group removed due to non-credible symptoms per NSI or mBIAS would have also been removed for non-credible SOT effort.

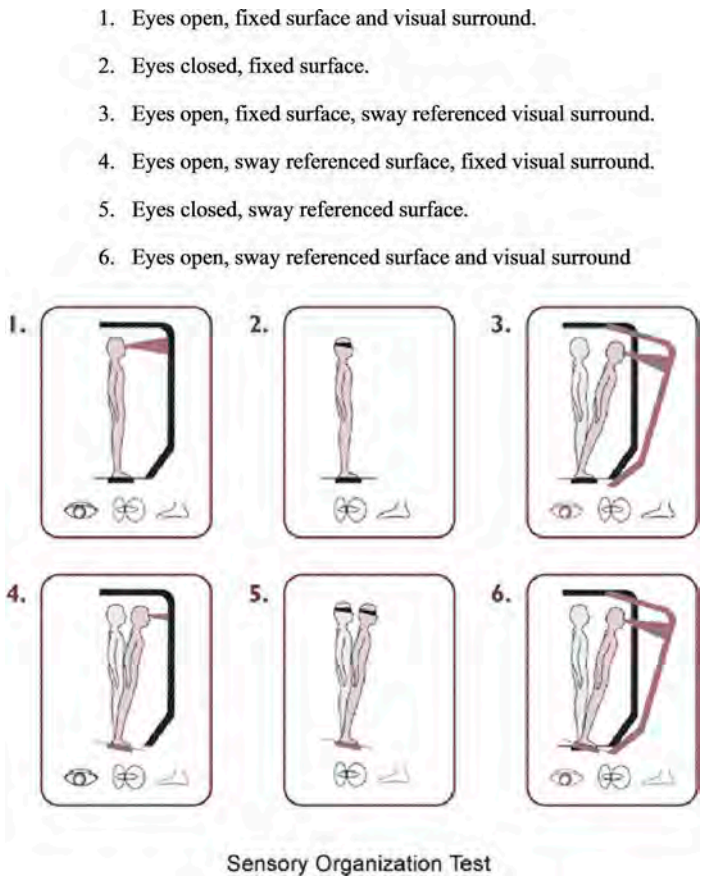

Figure 2. Sensory Organization Test – Six Conditions, courtesy NeuroCom® International, Inc.

already excluded on NSI/mBIAS). Symptom magnification and non-physiologic CDP SOT profile are described in the measures section. After these exclusions, data from 295 participants were available for the multivariate analyses. The participant flow diagram is displayed in Figure 1.

Assessments and measures overview

The full breadth of assessments and data collection measures used in the overarching study are described elsewhere(28). For these analyses, the primary independent variable was mTBI history as determined and measured later.

Potential concussive event identification and TBI diagnoses

This study's in-depth structured interview process entailed screening for all potential concussive events (PCEs) during military deployments and across the entire lifetime, including childhood, using a modification of the Ohio State University TBI Identification (OSU TBI-ID) instrument(29). Each PCE identified is then interrogated to determine whether or not it was a true clinical mTBI via a detailed structured interview, the Virginia Commonwealth University retrospective Concussion Diagnostic Interview (VCU rCDI) (30). Each VCU rCDI renders a preliminary TBI diagnosis of either mTBI with post-traumatic amnesia (PTA), mTBI without PTA, or not mTBI through an embedded algorithm using the structured interview data and based on the DoD/VA common definition of mTBI (31). Every preliminary algorithm TBI diagnosis is reviewed and vetted against the unstructured free text portion of the interview, and against any medical documents recorded in proximity to the event (i.e. first responder, emergency department or in-theatre documentation). Using this process, the site principal investigator confirms or overrides every preliminary algorithm mTBI diagnosis to yield the final diagnosis. The event is also assessed for TBI severity to ensure eligibility (any severity greater than mild excluded from this study). If any doubt remains on TBI diagnosis, the event is adjudicated by a central diagnosis committee consisting of national experts in TBI. Further details on PCE and TBI mapping are reported in an earlier publication that focused on this study's development and methods (28).

mTBI groups (independent variable)

The lifetime mTBI diagnostic process described above led to two main mTBI groups, positive versus negative history. Positive mTBI histories were further classified in several ways, as follows: (1) at least one mTBI with PTA versus only mTBI(s) without PTA, (2) at least three mTBIs versus only one or two mTBI (referred to as Repetitive TBI in results) and (3) at least one mTBI due to Blast Exposure versus only mTBI(s) without Blast Exposure (referred to as Blast mTBI in results).

Outcome measure

Postural stability was measured using the SOT protocol on the NeuroCom Smart Balance Master (NeuroCom; NeuroCom International, Inc, Clackamas, OR). Using dual-plate force platform, the SOT generates equilibrium scores that compare the largest anterior-posterior movements of the subject over the trial to a theoretical limit for six sensory condition tasks. The sensory conditions follow: (1) eyes open with a fixed surface and visual surroundings; (2) eyes closed with a fixed surface; (3) eyes open with a fixed surface and sway referenced visual surroundings; (4) eyes open with a sway referenced surface and fixed visual field; (5) eyes closed with a sway referenced surface and (6) eyes open with a sway referenced surface and visual surroundings (Figure 2.). Evaluators at each site were trained and certified by an expert vestibular physical therapist; certification entailed assessing videotape of the evaluator performing the SOT on a staff volunteer with further corrective training as needed until performance was deemed satisfactory. Each subject performed three trials on the Balance Master for each of the six sensory conditions, resulting in 18 equilibrium trial scores, ranging from 0 (touching a support surface, shifting feet, or falling) to 100 (little or no sway). Average equilibrium scores were generated for each of the six conditions by averaging the three trial scores. The overall composite equilibrium score was calculated as a weighted average of these 6 scores (conditions 1 and 2 are weighted 1/3 as much as conditions 3 through 6).

Non-credible balance performance (exclusion criterion)

As described by Cevette and colleagues (32), SOT equilibrium score profiles were considered non-credible if the average scores on condition 1, 2 or 3 (easier conditions) were higher than on condition 5 or 6 (more challenging conditions), with those participants excluded.

Non-credible symptoms (exclusion criterion)

The mBIAS is a brief (five-item) questionnaire measure developed for symptom over-reporting in OEF/OIF SMs with post-concussive complaints (33). The developer recommended cut-point was used (≥8).

NSI Validity-10 scale. The NSI is a 21-item assessment of post-concussive symptoms with a three-factor structure (somatic/sensory, affective and cognitive) (34). The NSI Validity-10 scale is an embedded measure of distorted symptom profile, and the developer recommended cut-point was used (≥23)(35).

Candidate variables for planned structural equation model (SEM) statistical approach

We selected numerous candidate variables that theoretically might influence this study's outcome measure (CDP SOT) and/or its relationship to the independent variable (mTBI history). In SEM framework, such variables are classified as either a Mediator, Covariate, Moderator or Confounder based

on the nature of their interaction. These candidate variables are described later under our a priori conceptualized SEM classifications.

Candidate mediators

Current PTSD. The Mini-International Neuropsychiatric Interview (M.I.N.I.) is a short structured diagnostic interview, developed jointly by psychiatrists and clinicians in the United States and Europe, for DSM and ICD psychiatric disorders (36). A version of the PTSD module was modified by the developer for DSM-5 and used here.

Current Depression. Patient Health Questionnaire Depression Scale (PHQ-9) is a nine-item self-administered tool that is half the length of many other depression measures, has comparable sensitivity and specificity, and consists of the actual nine criteria upon which the diagnosis of DSM-IV (and DSM-5) depressive disorders is based (37).

Current Anxiety. The Anxiety Short Form from TBI Quality-of-Life (QOL) measurement system was used. TBI-QOL is part of a multisite NINDS-funded project that developed a clinically relevant and psychometrically robust health-related quality of life (HRQL) assessment tools (38).

Current Pain. The TBI-QOL(38) Pain Interference Short Form measures the extent (using a five-point scale) to which pain interferes with everyday activities, including cognitive, physical, recreational and social domains over the past 7 days. Higher scores indicate more severe pain interference.

Mental Health History. A self-report of "Ever Treated for Mental Health Condition" was used.

Current Analgesic and Non-Analgesic Pain Medication Use. The active medication list from electronic medical records was reconciled against participant self-report.

Candidate covariates

Time since index event

Based on responses from the PCE and TBI structured interviews, an index key event and date were established for every participant. Given the military focus of this study, if any diagnosed mTBI was sustained during combat deployment, the most severe one is considered the index event. If no TBIs occurred during combat deployment, then the most severe post-deployment mTBI becomes the index event. Alternatively, for those with neither deployment nor post-deployment TBI (e.g. entirely TBI negative or positive only for pre-deployment mTBI), the self-identified most severe PCE during combat deployment was assigned as the index event so that a militarily relevant event/date could serve for comparisons with rest of the cohort.

Age at evaluation

Age in years at this initial evaluation.

Alcohol consumption

Alcohol Use Disorders Test-Consumption (AUDIT-C), is a widely used brief (three-item) screening tool for heavy drinking or active alcohol abuse/dependency(39). A cut-point of ≥5 was used to define hazardous drinking (40).

Learning disability

A self-reported history of any learning disability reported by the participant in review of medical history.

Estimated premorbid intelligence

The Test of Premorbid Functioning (TOPF) provides an estimate of premorbid intellect, and it is co-normed with the Weschler Adult Intelligence Scale 4th version (WAIS-IV) (41). To account for potentially biased demographic sampling, we used the higher of normed score versus demographic-only index.

Candidate moderators

Gender

Self-identified gender was collected from each participant using a demographic questionnaire.

History of Arthritis. This item was collected as queried in the CDC Behavioral Risk Factor Surveillance System (BRFSS), the nation's premier system of health-related surveys that collect data about US residents regarding their health-related risk behaviours and chronic health conditions (42).

Candidate confounders

Evaluation site

Richmond, San Antonio or Tampa.

Combat exposure intensity

The Deployment Risk and Resiliency Inventory, Version 2, Section D; Combat Experiences (DRRI-2-D) is a 17-item self-report measure that assesses wartime stressors experienced by combatants (43). Respondents are asked to respond based on their exposure to various combat situations. The DRRI was developed to update the Combat Exposure Scale (CES) (44) to include modern wartime experiences.

Number of Months Combat Deployed. This information was abstracted from the Certificate of Release or Discharge from Active Duty (DD 214 form), and supplemented, when needed, by self-report.

Statistical methods

Unadjusted analyses

Characteristics of the sample, stratified by mTBI positive versus negative, were summarized for continuous variables by a mean and standard deviation versus median and inter-quartile range depending on the distribution of the variable, and for categorical variables, by frequency and percentage. Unadjusted comparisons were made using the Student's *t*-Test for normally distributed continuous variables, Wilcoxon Rank Sum test for non-normally distributed continuous variables, Chi-square test for categorical variables and a Negative Binomial test for over-dispersed count variables.

Preliminary models

Site-adjusted analyses were performed to assess the relationship between each characteristic of interest and the various balance performance outcomes. These relationships were

assessed using linear regression methods appropriate for each variable's distribution. These same regression models were fit a second time, including an interaction between the characteristic and the mTBI classifications. Covariate or moderator interactions with $p < 0.1$ were considered for inclusion in the full multi-variable models.

Multivariate model reduction

The relationships between mTBI classifications and the balance outcome measures were analysed using two multi-variable approaches: standard covariate adjusted regression (CAR) and structural equation modelling (SEM). CAR provided a traditional linear regression analysis accounting for covariates, confounders, and potential moderators (45). SEM allowed for the addition of potential mediators of the relationship between mTBI classification and balance outcome measures, calculating the direct, indirect and total effect of mTBI on balance outcome measures (46). Both CAR models and SEMs were originally fit as fully populated models, then underwent ad-hoc model reduction, removing one variable at a time and refitting all models (CAR and SEM, all SOT balance outcomes, and all mTBI classifications).

The CAR and SEM model reduction process removed insignificant factors in the following order: covariate and potential confounder with mTBI interaction terms, followed by covariate, confounder, and moderator main effects. Main effects were not considered for exclusion if the interaction with mTBI was significant; however, any potential moderator with an insignificant interaction term was effectively reclassified as a covariate. SEMs underwent an additional stage of model reductions for the potential mediators. Mediators that did not have significant association in the model with exposure nor outcome were removed first, followed by mediators that consistently only displayed a partial mediating effect (either association with exposure or outcome, but not both). Influential factors for any outcome were retained in all models for consistency. Note that study site, age and gender were identified as key model factors and were retained in the final models regardless of statistical significance. All analyses were performed at the 0.05 level of statistical significance using the SAS/STAT statistical software, Version 9.3 (Cary, NC).

Results

Unadjusted analyses

The characteristics of the final analysis sample are displayed in Table 1, including demographics and all independent variables considered in the model. Compared to the non-mTBI participants, those with a positive mTBI history had a greater proportion of PTSD (32.0% vs. 10.6%), arthritis (51.0% vs. 34.8%) and non-analgesic pain medication use (35.2% vs. 13.0%), while also having higher combat intensity exposure (36.0 vs. 26.0), anxiety (22.0 vs. 18.0) and pain interference (22.0 vs. 15.0).

The unadjusted comparisons of balance performance between mTBI positive and negative groups are displayed in Figure 3, including the CDP SOT composite equilibrium score and the six sensory condition equilibrium scores. Mean equilibrium scores for the mTBI positive participants were significant lower for sensory Condition 2 (87.5 ± 8.1 vs. 89.9 +/- 3.7, $p = 0.0026$) and Condition 3 (87.6 +/- 8.4 vs. 89.6 +/- 3.6, $p = 0.0081$). The remaining sensory conditions and the overall composite scores were not significantly different.

Preliminary models and multivariate model reduction

Based on findings from adjusting for site alone in the preliminary models (results not shown), Mental Health Ever Treated (mediator), Learning Disability (covariate), Combat Duration (confounder) and Combat Exposure Intensity (confounder) were chosen for removal.

Among the covariates, interactions of mTBI exposure with hazardous alcohol use and age showed significance at $p = 0.1$ and warranted exploration in the full multi-variable models. Interactions with learning disability (covariate) were not considered due to the unbalanced nature of learning disability in the sample (91% negative vs. 9% positive). Note that all potential moderator interactions were considered in the full multi-variable models (both CAR and SEM) to assess the accuracy of a moderating role.

Initial multi-variable CAR models included main effects for all covariates, confounders and moderators as well as interaction terms for mTBI classification with Hazardous Alcohol (covariate), Age (covariate), Gender (moderator) and Arthritis (moderator). Exploratory SEMs were fit at the same time, with the addition of mediators. These initial CAR and exploratory SEMs underwent model reduction steps, as described in the Statistical Methods section. This led to the removal of Combat Duration (confounder), Learning Disability (covariate), Hazardous Alcohol Use (covariate; main-effects retained), Age (covariate; main-effects retained), Mental Health Ever Treated (mediator) and Analgesic Pain Medications (mediator) as well as reassigning both Gender and Arthritis from moderator to covariate roles.

After these steps, the final models would include confounders (Site and Combat Exposure Intensity), covariates (Time Since Index Date, Age, Hazardous Alcohol Use, TOPF Reading IQ, Gender, and Arthritis) and mediators (PTSD, Depression, Anxiety, Pain Interference, and Non-Analgesic Pain Medications). Results from CAR and SEM largely agreed, and SEMs were selected as the primary analysis due to significant mediating effects.

Final SEM results

The final model parameter estimates and p values for the total, direct and indirect effects on the CDP SOT composite equilibrium measure are shown in Table 2. Nearly all mTBI classifications had significant indirect effects: mTBI vs. No mTBI ($p = 0.0125$), Repetitive mTBI ($p = 0.0044$) and mTBI with Blast ($p = 0.0212$), but only the Repetitive mTBI model had a significant total effect as well ($p = 0.0046$). In this model, those with 3 or more mTBIs showed a 4.98 lower mean composite equilibrium score compared to having 1–2 mTBIs. The indirect portion of the effect for Repetitive mTBI

Table 1. Baseline demographics by mTBI classification (Positive vs. Negative lifetime history).

Characteristic	Study group: mTBI (*N* = 248)	Study group: No mTBI (*N* = 47)	*p* value
Age at baseline[W]			
Median	41.0	46.0	0.2834
Min, Max	26, 69	24, 68	
Gender[C]			
Male	219 (88.3%)	37 (78.7%)	0.0753
Female	29 (11.7%)	10 (21.3%)	
Race[C]			
White	167 (68.7%)	33 (70.2%)	0.9430
Black or African American	57 (23.5%)	10 (21.3%)	
Other	19 (7.8%)	4 (8.5%)	
Ethnicity[C]			
Hispanic or Latino	54 (22.0%)	14 (29.8%)	0.2436
Not Hispanic or Latino	192 (78.0%)	33 (70.2%)	
Service branch[C,(1)]			
Army	174 (70.4%)	33 (71.7%)	0.4895
Marines	33 (13.4%)	4 (8.7%)	
Air Force	26 (10.5%)	4 (8.7%)	
Navy	14 (5.7%)	5 (10.9%)	
Years since index date[W]			
Median	9.5	9.8	0.5813
Min, Max	1, 47	2, 29	
Total combat-related exposure(DRRI-2)[W]			
Median	36.0	26.0	<.0001
Min, Max	17, 89	16, 54	
Total number of months combat deployment[N]			
Median	18.0	14.0	0.0339
Min, Max	0, 102	0, 51	
PTSD (M.I.N.I.)[C]			
Yes	79 (32.0%)	5 (10.6%)	0.0030
No	168 (68.0%)	42 (89.4%)	
Depression (PHQ-9)[C]			
Yes	94 (38.2%)	12 (26.1%)	0.1165
No	152 (61.8%)	34 (73.9%)	
Other mental health, ever treated (PIHQ)[C]			
Yes	48 (19.4%)	8 (17.0%)	0.7084
No	200 (80.6%)	39 (83.0%)	
Anxiety (TBI-QOL)[W]			
Median	22.0	18.0	0.0150
Min, Max	10, 48	10, 38	
Pain interference (TBI-QOL)[W]			
Median	22.0	15.0	0.0005
Min, Max	10, 50	10, 43	
Analgesic pain medications[C]			
Yes	139 (56.3%)	16 (34.8%)	0.0073
No	108 (43.7%)	30 (65.2%)	
Non-analgesic pain medications[C]			
Yes	87 (35.2%)	6 (13.0%)	0.0030
No	160 (64.8%)	40 (87.0%)	
Arthritis (BRFSS)[C]			
Yes	126 (51.0%)	16 (34.8%)	0.0432
No	121 (49.0%)	30 (65.2%)	
Hazardous alcohol use (AUDIT-C)[C]			
Yes	70 (28.2%)	15 (31.9%)	0.6086
No	178 (71.8%)	32 (68.1%)	
Prior learning disability[C]			
Yes	23 (9.3%)	3 (6.4%)	0.5215
No	225 (90.7%)	44 (93.6%)	
TOPF reading IQ[T]			
Mean (Std)	99.7 (11.6)	99.7 (11.9)	0.9911

C = Chi-square test; T = T-Test; N = Negative Binomial Regression; P = Poisson; W = Wilcoxon Rank-Sum Test.

NOTE: Due to exclusion of missing data, the number of mTBI cases and No mTBI cases within each variable may not add up to the full number of mTBI and No mBI cases.

was also significant, but not the direct effect, even though it was nominally larger (direct = 2.84 vs. indirect = 2.15).

Total, direct and indirect SEM parameter estimates for equilibrium scores on each SOT sensory condition are shown in Tables 3 and 4 for conditions 1–3 and 4–6, respectively. As with the composite measure, only the Repetitive mTBI models showed significant total effects, which were observed in Conditions 2 [eyes closed, fixed surface] (p = 0.0025), 3 [eyes open, fixed surface, sway referenced visual surround] (p = 0.0020), 4 [eyes open, sway referenced surface, fixed visual surround] (p = 0.0161) and 5 [eyes closed, sway referenced surface] (p = 0.0022). In each of these models, those with 3 or more mTBIs had a range of 3.28–7.71 lower mean equilibrium scores compared to those with 1–2 mTBIs. Significant indirect effects were observed in the Repetitive mTBI models for conditions 1, 2, 3, 5 and 6, and significant direct effects were observed in Conditions 2 and 3.

Across the six sensory conditions for the Repetitive mTBI classification scheme, Condition 5 [eyes closed, sway referenced surface] showed the nominally largest total effect (−7.71, p = 0.0022), and Condition 6 [eyes open, sway referenced surface and visual surround] showed the nominally largest indirect effect (−4.10, p = 0.0014).

Full SEM results with all independent variables

Full results of the SOT composite equilibrium score SEMs for mTBI positive/negative and Repetitive mTBI classifications are shown in Figures 4 and 5, respectively. These figures provide the parameter estimate and significance level for each independent variable effect included in the final multivariable SEMs. In both mTBI classification models, pain interference as measured in TBI QOL was observed as the key mediator, driving the indirect effect. The effect of mTBI classification on pain interference, and the effect of pain interference on the composite equilibrium score, were both significant. Compared to a negative mTBI history, a positive history increased pain interference measures by a mean 5.11 points (p = 0.0042), and in turn each point increase in pain interference decreased the composite equilibrium score by a mean 0.25 points (p = 0.0003). In the Repetitive mTBI model, having 3 or more lifetime mTBIs compared to 1 or 2 lifetime mTBIs resulted in a mean 5.48 point increase in pain interference (p = 0.0001), and in turn each point increase in pain interference decreased the composite equilibrium score by a mean 0.27 points (p = 0.0006). The only other variable having a significant interaction with the outcome was TOPF premorbid IQ estimate. For the mTBI positive/negative classification model, each 1-point increase in TOPF T-score was associated with a 0.16 point increase in composite equilibrium score; for the Repetitive mTBI classifications the per unit increase was 0.17 points. Regarding other independent variables, in both of these models the candidate mediators, anxiety and non-analgesic pain medication use, showed significant effects from mTBI classification, but did not significantly affect the outcomes. Similarly, in the mTBI positive/negative model, those with mTBI had a 21% increased risk of PTSD (p = 0.0059), but PTSD did not significantly affect the outcome. In the Repetitive mTBI model, PTSD had no significant interactions. The other candidate mediator, depression, had no significant interactions in either model. No candidate covariate besides TOPF had a significant effect. The candidate confounder, combat exposure intensity, had a significant

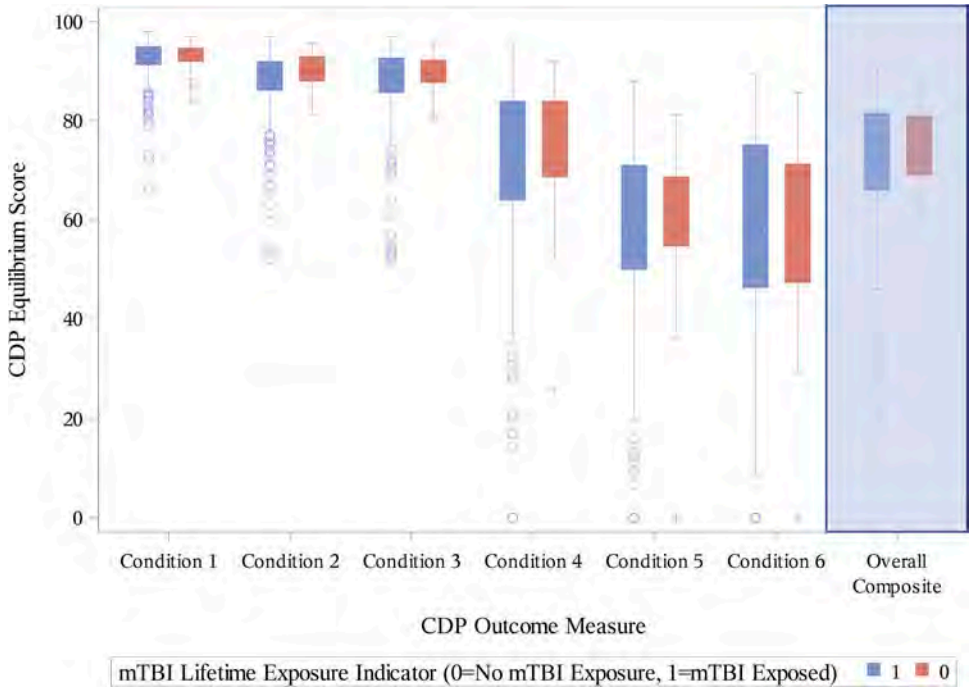

Figure 3. Computerized Dynamic Post-urography (CDP) Sensory Organization Test (SOT) unadjusted equilibrium scores by Positive versus Negative mTBI history classification.

Table 2. SEM parameter estimates for SOT composite equilibrium score.

CDP SOT composite equilibrium score	mTBI vs. No mTBI	mTBI with PTA[1]	Categorical repetitive mTBI[1]	Blast mTBI[1]
Total effect				
Parameter estimate	−1.7300	1.6194	−4.9842	−1.7477
p value	0.4222	0.4015	0.0046*	0.3783
Direct effect				
Parameter estimate	0.5203	2.9190	−2.8352	−0.0596
p value	0.8133	0.1234	0.1134	0.9761
Indirect effect				
Parameter estimate	−2.2504	−1.2996	−2.1490	−1.6881
p value	0.0125*	0.0722	0.0044*	0.0212*

* indicates significance at $p = 0.05$.
[1] mTBI subgroup structural equation analyses were subset on mTBI positive.

effect on Repetitive mTBI classification, but not on the composite equilibrium score.

Full model effects for the other mTBI classifications (blast versus non-blast, with vs. without PTA) with regards to the SOT composite equilibrium score are available online; detailed results for the individual sensory conditions and each mTBI classification are available upon request.

Discussion

This study addresses a research gap by analysing the relationship between mTBI history and balance performance on CDP using SEM in a large cohort of Veterans and SMs with post-9/11 combat exposure. Although SOT equilibrium scores were not different between participants with positive and negative mTBI histories, significant effects were found in the models using the repetitive mTBI classification. On the composite equilibrium outcome, participants with ≥ 3 lifetime mTBIs scored lower than those with 1–2 mTBIs by an estimated 5.8 points on the 100-point scale. Regarding the nature effect, only the indirect component was significant. However, the parameter size for direct effect was nominally higher at 3.66 versus 2.14 for indirect respectively, suggesting a power limitation.

The SEMs of the equilibrium scores across the various SOT sensory conditions provided further characterization of the differences in balance performance between repetitive and non-repetitive mTBI. A significant total effect of repetitive mTBI was found on conditions 2 through 5, with the largest parameter size for condition 5. Condition 5, eyes blinded with sway referenced platform or surface, had been implicated in a prior study of post-acute blast mTBI as being particularly sensitive to chronic mTBI effects (26). This condition is typically implicated for problems arising from the peripheral or central vestibular apparatus. The overall pattern of findings suggests an overreliance on the visual system, potentially due to deficits in vestibular feedback or integration.

This study adds to mounting evidence of a link between historical mTBI and chronic balance decrements. More specifically, the findings suggest that Veterans and SMs with repetitive mTBI are at heightened risk for later life balance deficiencies. This vulnerability is further supported by evidence from preclinical research. For example, Mountney and colleagues recently demonstrated that rodent models of repeated concussions exacerbate sensorimotor dysfunction and prolonged gait abnormalities compared to single concussion, with balance disturbance associated with molecular changes including neuroinflammatory markers and up-regulated glial fibrillary acidic protein (GFAP) (47).

Contrary to the prior study by Wares and colleagues in a different military blast-exposed sample (26), the classification mTBI with PTA versus without PTA did not show a

Table 3. SEM parameter estimates for CDP SOT equilibrium scores on conditions 1–3.

	mTBI vs. No mTBI	mTBI with PTA[1]	Categorical repetitive mTBI[1]	Blast mTBI[1]
SOT condition 1				
Total effect				
Parameter estimate	−0.5381	0.5658	−0.9412	0.2319
p value	0.4537	0.3793	0.1111	0.7254
Direct effect				
Parameter estimate	−0.1400	0.9043	−0.4247	0.5399
p value	0.8480	0.1538	0.4802	0.4165
Indirect effect				
Parameter estimate	−0.3981	−0.3385	−0.5165	−0.3079
p value	0.1949	0.1509	0.0401*	0.1975
SOT condition 2				
Total effect				
Parameter estimate	−1.3195	−0.4893	−3.2755	−2.2966
p value	0.3144	0.6835	0.0025*	0.0603
Direct effect				
Parameter estimate	−0.3510	−0.1249	−2.2984	−1.5371
p value	0.7933	0.9158	0.0377*	0.2112
Indirect effect				
Parameter estimate	−0.9686	−0.3644	−0.9770	−0.7595
p value	0.0784	0.4092	0.0317*	0.0868
SOT condition 3				
Total effect				
Parameter estimate	−1.5495	−0.1714	−3.3987	−1.5905
p value	0.2440	0.8880	0.0020*	0.2013
Direct effect				
Parameter estimate	−0.2297	0.6872	−2.3483	−0.6192
p value	0.8652	0.5650	0.0358*	0.6197
Indirect effect				
Parameter estimate	−1.3198	−0.8586	−1.0504	−0.9713
p value	0.0201*	0.0604	0.0270*	0.0352*

* indicates significance at $p = 0.05$.
[1] mTBI subgroup structural equation analyses were subset on mTBI positive.

Table 4. SEM parameter estimates for CDP SOT equilibrium scores on conditions 4–6.

	mTBI vs. No mTBI	mTBI with PTA[1]	Categorical repetitive mTBI[1]	Blast mTBI[1]
SOT condition 4				
Total effect				
Parameter estimate	−3.3296	0.3806	−5.8570	−0.4900
p value	0.2579	0.8866	0.0161*	0.8580
Direct effect				
Parameter estimate	−1.2838	2.2078	−4.3498	0.8035
p value	0.6711	0.4026	0.0795	0.7709
Indirect effect				
Parameter estimate	−2.0459	−1.8272	−1.5072	−1.2934
p value	0.0882	0.0564	0.1454	0.1870
SOT condition 5				
Total effect				
Parameter estimate	−2.2817	1.9071	−7.7110	−4.5484
p value	0.4684	0.4927	0.0022*	0.1108
Direct effect				
Parameter estimate	0.6033	3.0925	−4.8375	−2.2202
p value	0.8523	0.2607	0.0614	0.4402
Indirect effect				
Parameter estimate	−2.8850	−1.1854	−2.8735	−2.3282
p value	0.0230*	0.2317	0.0060*	0.0219*
SOT condition 6				
Total effect				
Parameter estimate	−0.4427	5.1451	−4.8983	−1.2533
p value	0.9038	0.1070	0.0977	0.7043
Direct effect				
Parameter estimate	3.3099	7.0667	−0.7950	1.6404
p value	0.3774	0.0242*	0.7908	0.6202
Indirect effect				
Parameter estimate	−3.7526	−1.9215	−4.1033	−2.8937
p value	0.0133*	0.1074	0.0014*	0.0180*

* indicates significance at $p = 0.05$.
[1] mTBI subgroup structural equation analyses were subset on mTBI positive.

significant effect on equilibrium scores. Additionally, the blast versus non-blast TBI classification did not show differences. Instead, the current study findings suggest that the number of mTBIs is a more important risk factor for chronic balance deficits than the type of mTBI, at least in terms of clinical subtypes. Future research should consider if biologic markers may offer better mTBI subtype stratification.

Regarding the effects of other independent variables examined, pain interference had a mediating effect, and TOPF had a covariate effect. The mediating effect of pain was such that TBI history led to more pain, which in turn led to lower equilibrium scores. Lower estimated premorbid intellect as measured by the TOPF also led to lower equilibrium scores. These significant interactions were found in both the mTBI positive/negative and repetitive mTBI classification models.

The influence of pain on postural stability has received minimal attention in the literature. Investigators in one small study demonstrated postural instability in older adults with idiopathic neck pain compared to controls (48). Two small studies of patients with chronic low back pain showed impaired postural stability during standing tasks that involved increased complexity and removal of visual information (49,50). Proposed mechanisms for balance deficits with spinal pain include altered proprioception (48), altered spinal muscle activation patterns (51), and/or splinting/guarding to protect or minimize pain (48,50). It is also reasonable to expect that lower extremity pain will reduce postural stability. When considering comorbid TBI, a neurocognitive model of chronic pain posits that TBI diminishes attentional resources for ongoing tasks and that pain typically has priority access and is a distracter (52,53). A prediction of this neurocognitive model is that training to reduce engagement of attention to pain related stimuli would result in improved performance on balance tasks in at least a subgroup of patients. Taken together with results from the present study suggest that addressing and managing pain is an importance component of the treatment program for balance difficulties after mTBI.

The significant covariate effect of TOPF was not unexpected. In prior unpublished work, some in our group have found a similar relationship. The literature indirectly supports this association through findings in other populations. Lower balance performance has been shown for developmentally delayed cohorts including intellectually impaired Special Olympic competitors (54), and patients with dyslexia (55) as well as elderly patients with low cognition (56). Reduced or inefficient sensory feedback is a potential explanation for

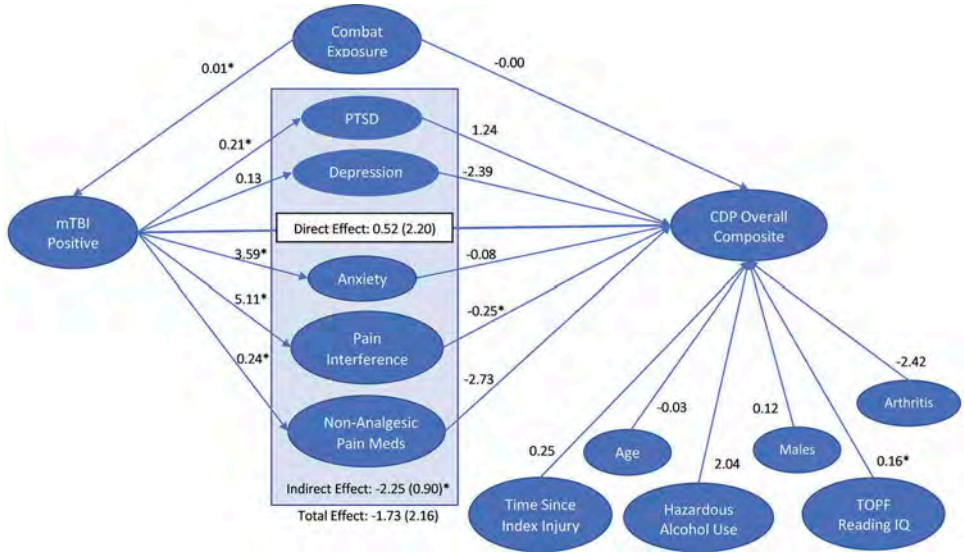

Figure 4. Parameter estimates for pathway analysis of mTBI positive versus mTBI negative history on CDP SOT Composite Equilibrium Score/Legend: Arrows show the direction of assumed effects with estimates of associated parameters presented. For total, direct and indirect effect of mTBI, standard errors are shown in parentheses. * denotes a significant parameter estimate (p value < 0.05). Parameter estimates of 0.00 are < 0.004 and do not represent true zeroes.

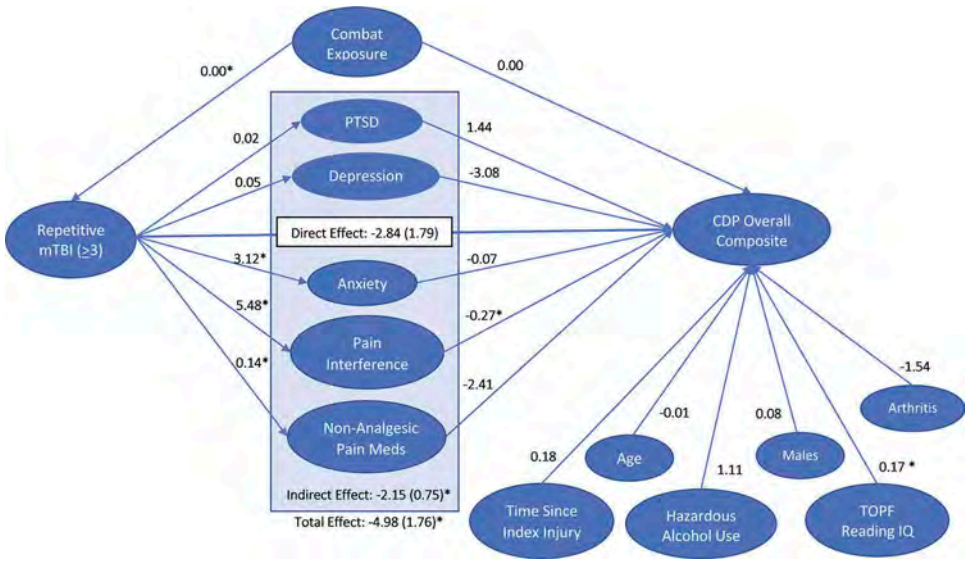

Figure 5. Parameter estimates for pathway analysis of Repetitive (> 3 lifetime) mTBI vs. 1–2 mTBI on CDP SOT Composite Equilibrium Score/Legend: Arrows show the direction of assumed effects with estimates of associated parameters presented. For total, direct and indirect effect of mTBI, standard errors are shown in parentheses. * denotes a significant parameter estimate (p value < 0.05). Parameter estimates of 0.00 are < 0.004 and do not represent true zeroes.

these findings, as is the previously mentioned neurocognitive model of reduced attentional capacity.

Notable variables not associated with equilibrium scores in the final SEMs were anxiety, PTSD and combat exposure. Although combat exposure intensity had an association with TBI, it did not have a separate effect on equilibrium scores. Our findings for PTSD conflict with the previously mentioned study by Wares and colleagues (26), where PTSD had a separate and additive effect to TBI, most notably on conditions 3 and 6 of the SOT. This disparity may be due to differences in the cohorts and/or differences in statistical methods because the current study used more comprehensive multivariate SEM versus the earlier study's use of simple TBI and PTSD group-wise comparisons without factoring other variables such as pain. Other anxiety states have been implicated in past research as lowering postural stability (57,58). In our study, mean values were in the expected direction of TBI leading to higher anxiety, in turn leading to lower equilibrium score, but neither relationship reached significance. A contributing factor to this disparity may be that somatization was better measured in the current study by including pain interference; possibly some of the effect of 'pain' represents somatized anxiety captured as pain in our study, thereby reducing the effect of the other mental health variables. Regardless of the specific mechanism, such an overlap of pain and psychiatric conditions is consistent with previous reports of higher levels of current pain in Veterans with PTSD and depression symptoms (59).

Strengths of this study include a larger sample size than most similar observational studies, non-TBI comparators drawn from same cohort using the same eligibility criteria and recruitment pathways, and the exclusion of subjects with non-credible symptom or balance performance profiles. Other strengths were the rigorous standardized approach to mTBI diagnoses for all lifetime PCEs including combat PCEs, and the analysis of mTBI sub-classifications including repetitive mTBI. Additionally, this study used causal inference statistical methods with SEM to account for many potentially relevant mediators, moderators, confounders and covariates. Although not a controlled experiment with causal design, causal inferences can be made from observational studies using SEM.

Limitations of this study included the retrospective identification of the main insult of interest, mTBI, which is unavoidable given the high incidence of mTBI during childhood, adolescence and young adulthood. Nonetheless, our careful, structured interview process represents a significant improvement over much of the existing literature. Other limitations included lack of information on possible peripheral vestibular pathology that may have been contributing to balance performance, the use of pain interference rather than pain intensity measure, and lack of information on location of pain. Additionally, because the cohort was entirely Veterans and SMs, this study's findings may not generalize to females and/or civilian mTBI populations including athletic concussions.

Conclusion

This study implicates a history of repetitive mTBI (≥ 3) in reducing balance performance among previously combat-deployed Veterans and SMs. Although a direct effect of repetitive mTBI was present in some sensory conditions, only the indirect effect was significant on the composite equilibrium score, with pain acting as a mediator. These findings have important implications for the screening and identification of persons with mTBI histories who may benefit from balance assessment and interventions. They also highlight the importance of assessing for physiological damage to the central and/or peripheral vestibular pathway, and the importance of incorporating pain management strategies into mTBI balance treatment programs. Further research in this area is warranted.

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Conflicts of interest

The authors report no conflicts of interest. The views, opinions and/or findings contained in this article are those of the authors and should not be construed as an official Veterans Affairs or Department of Defense position, policy or decision, unless so designated by other official documentation.

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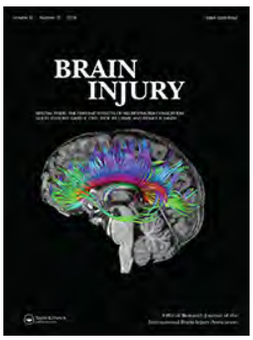
Appendix 14

Assessment of quantitative magnetic resonance imaging metrics in the brain through the use of a novel phantom



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Assessment of quantitative magnetic resonance imaging metrics in the brain through the use of a novel phantom

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ABSTRACT

Objective: Multisite and longitudinal neuroimaging studies are important in uncovering trajectories of recovery and neurodegeneration following traumatic brain injury (TBI) and concussion through the use of diffusion tensor imaging (DTI) and other imaging modalities. This study assessed differences in anisotropic diffusion measurement across four scanners using a human and a novel phantom developed in conjunction with the Chronic Effects of Neurotrauma Consortium.

Method: Human scans provided measurement within biological tissue, and the novel physical phantom provided measures of anisotropic intra-tubular diffusion to serve as a model for intra-axonal water diffusion. Intra- and inter-scanner measurement variances were compared, and the impact on effect size was calculated.

Results: Intra-scanner test–retest reliability estimates for fractional anisotropy (FA) demonstrated relative stability over testing intervals. The human tissue and phantom showed similar FA ranges, high linearity and large within-device effect sizes. However, inter-scanner measures of FA indicated substantial differences, some of which exceeded typical DTI effect sizes in mild TBI.

Conclusion: The diffusion phantom may be used to better elucidate inter-scanner variability in DTI-based measurement and provides an opportunity to better calibrate results obtained from scanners used in multisite and longitudinal studies. Novel solutions are being evaluated to understand and potentially overcome these differences.

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The Chronic Effects of Neurotrauma Consortium (CENC) was created to study the long-term impact of mild traumatic head injury on military Service Members and Veterans, including sequelae that may be detectable via neuroimaging. With specific regard to imaging, human participant magnetic resonance imaging (MRI) data are collected at 11 imaging centres, including MRI scanners within VA, active military and academic sites. A focus of CENC clinical research has been to acquire common data across projects, with attention to (1) similarities across participant samples and variables utilized (including inclusion/exclusion criteria, use of common variables for demographic, medical history and injury data), (2) outcome assessment (including use of common standardized measures) and (3) imaging acquisition and analysis methods (including a core set of pulse sequences with similar parameters, common quality assurance and data acquisition procedures, centralized analysis for each imaging modality). Although differences exist across projects (e.g. some projects include additional study-specific imaging sequences or perform additional post-processing on subsets of data or additional outcome measures to address different research questions), these attempts at consistency facilitate data sharing across studies and enable more global examination of one of the largest existing imaging datasets of active duty Service Members and Veterans to date.

Despite efforts to promote uniformity and consistency in neuroimaging data collection, there remain well-recognized issues related to variability in quantitative imaging data collected across sites and across time (1,2), even after rigorous quality control efforts and relatively standardized acquisition methods and parameters. Variability in quantitative measurement in MRI within multisite studies has been demonstrated in many different MR modalities (3,4) but has been particularly notable in diffusion imaging (5–7). Variations in diffusion tensor imaging (DTI) measurements show coefficients of variation (CoV) of a troubling scale (e.g. 7–29%) (8). For

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instance, in a study by Teipel and colleagues, participants were divided into two groups: (1) those scanned first on one scanner and then on a second scanner a year later and (2) those that were scanned at a 1-year interval on a single scanner. DTI data were analysed using a tract-based spatial statistics and a voxel-based analysis. The effect of inter-scanner variability on asymmetries of fractional anisotropy (FA) and mean diffusivity was measured by comparing interhemispheric differences on longitudinal scans in the two groups. The study revealed a number of brain regions in which significant longitudinal differences were found among subjects imaged on different scanners compared to individuals imaged on the same scanner. These findings were taken to indicate substantial inter-scanner variability in DTI measurements. Evidence of intra-scanner variability in acquisition of DTI data can be seen in another study, in which FA values obtained in the same individuals' images twice on the same 3T scanner at a 2-week interval showed substantial variation (9).

As the earlier statements indicate, it is widely recognized that diffusion imaging data can differ even in the same subject on the same scanner over a short period of time due to substantial changes in centre frequency, receiver gains and voltages, so-called 'scanner drift'. Nonetheless, few comprehensive studies of this phenomenon have been published. Changes in MR scanner hardware and software can also affect reproducibility of DTI data on a single scanner. For instance, one study found significant effects of scanner software upgrade and, even, changes in head position as well as substantial scanner bias, as evidenced by significantly different results on two MR scanners of the same model and software (10).

The lack of standardization in quantitative diffusion imaging poses significant obstacles in the interpretation of imaging data from multicentre studies and consortia, and complicates longitudinal assessment. This lack of standardization has a profound impact on clinical use of DTI, which at this point in time, may be considered unreliable and fraught with error that could lead to misdiagnosis. Enhancing measurement stability across sites and instruments is also essential in providing normative data that could be applied in clinical diagnosis, and the use of phantom objects may advance this effort considerably.

The use of phantoms in MRI-based experiments has a long history. Phantoms have been used in imaging experiments to provide a ground truth (or 'gold standard') for various mathematical imaging models (11–15) to evaluate, analyse, and test the performance of imaging systems (16–20), and to evaluate and calibrate multimodal MR signals from various MR pulse sequences. They are also used to test scanner performance and to validate MR-derived metrics at many imaging centres (21). A formal testing mechanism and validation framework for reproducibility and reliability of MR metrics (22,23) is provided by Quantitative Imaging Biomarkers Alliance and American College of Radiology. The goal of any imaging phantom in the field of MR is to provide reproducible quantitative results from imaging methods for multivendor, multisite and test–retest assessments (24–26). Finally, physical and digital reference objects may play a role in evaluating and optimizing imaging protocols and in creating reproducible analysis pipelines.

Investigators in the CENC Neuroimaging Core have endeavoured to decrease quantitative variability in imaging data acquisition and analysis. Their work has included efforts to evaluate and improve a novel, modular phantom to facilitate calibration and reference measurement across sites. This phantom provides a means to assess several quantitative MRI metrics in a comprehensive manner. While other research groups and consortia, such as the Transforming Research and Clinical Knowledge in traumatic brain injury (TRACK-TBI) consortium have also utilized isotropic diffusion phantoms and human phantoms as part of a comprehensive quality assurance systems (27), the phantom described in this study also include novel components to examine anisotropic diffusion. We report here initial results of both the physical phantom and a traveling human phantom on a subset of the CENC-utilized scanners to assess within-site and cross-site variability in one such metric, DTI-derived FA.

The use of both human and physical phantom measurements is important because both complement one another by providing a real-world case to compare to an object under ideal, controlled conditions, with known parameter values. The human measurement provides tissue values of FA, which, in theory, would allow discrimination of abnormal tissue by virtue of measuring FA values which fall outside an expected range. However, a number of limitations of use of a human phantom are evident. First, a human phantom lacks ground truth DTI values because the ultimate diffusion characteristics of living tissue cannot be known. Second, use of a human phantom at multiple sites is the impractical and expensive. Finally, any individual brain is expected to change as a result of various physiologic states (e.g. hydration status, hormonal fluctuation, etc.), even over short periods of time (28,29). Alternately, a physical phantom enables measurements of several DTI-derived metrics (e.g. tract size and density), has properties and configurations which can be manipulated to isolate effects (e.g. effects due to change in intra- and extra-axonal water), can be mass-produced so that many sites may have matched measurement scales, can remain motionless for unlimited hours to map out the parametric space of MR measurement on a specific device, does not have biological variation and could practicably be used for frequent QA across sites.

The goals of this report are to (1) explore the use of a novel anisotropic phantom which allows measurement in human range of anisotropic diffusion; (2) examine imaging sensitivity, repeatability, systematic error, effect size and CoV for human and phantom measurements across a limited sample of scans across four sites; (3) compare the effect sizes of human tissue and phantom fibre samples; (4) quantify inter- and intra-site/acquisition measurement error and (5) gain perspective on the extent of variation and how it might be quantified and improved in current and future multisite or multivendor studies.

Methods

Human phantom description

As part of the initial site qualification and ongoing quality control efforts in place for the CENC, the same healthy female (age 43–45 years at the time of scanning) human phantom travelled to each scanner involved in the consortium to undergo imaging, with repeat imaging performed at approximately annual intervals

over time. However, scanner upgrades occurring at multiple sites during the period of this investigation preclude direct comparison of data collected from all sites. For the sake of simplicity and ease of data presentation, data from only four sites are presented. Platforms intentionally differed across the sites and included only 3T scanners (1 Siemens Trio, 1 Siemens Verio, 1 GE 750, and 1 Philips Ingenia). Depending on the scanner, 20–32 channel head coils were used. The phantom individual was scanned twice on each scanner for measurement of intra-site reproducibility.

Phantom description

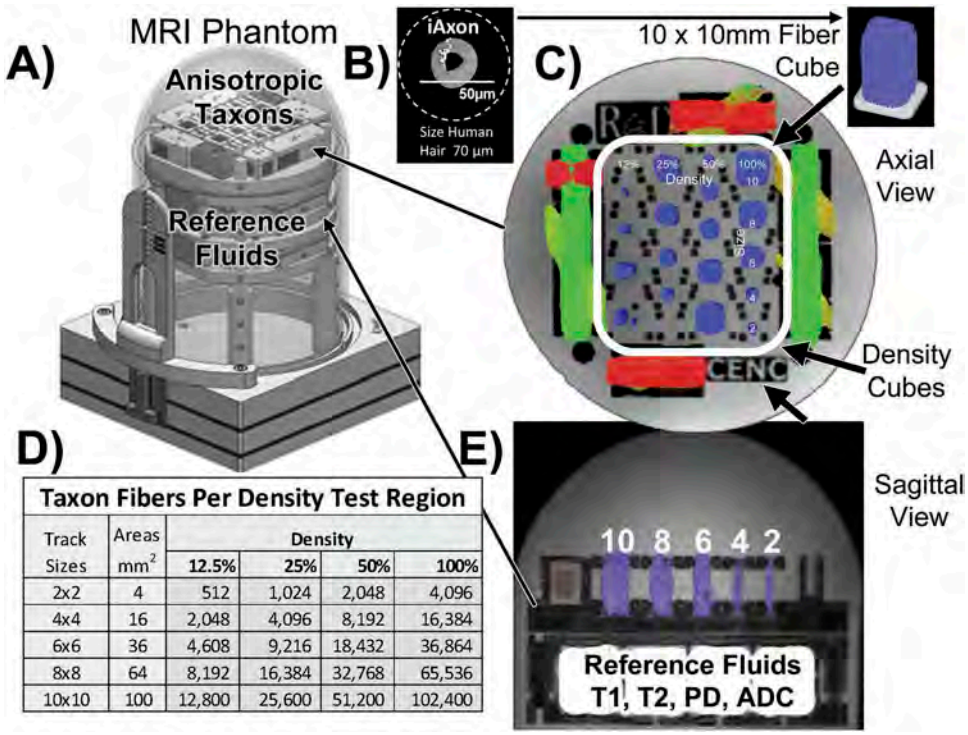
In this study, we utilized the Taxon Anisotropic Brain Imaging Phantom (TABIP) created by the Phantom Metrics division of Psychology Software Tools. This phantom (patent pending (30)) uses polymer textile hollow fibres called Taxons™ that mimic the scale and shape of human axons and offer control of the textile fibre diameter, packing density, and fibre crossing geometry. These fibres have consistent inner and outer diameters (12 μm inner diameter, 32 μm outer diameter), interdigitated fibre crossings at controlled angles, variable fibre packing density, and the ability to be filled with water, generating hindered and restricted spaces. Figure 1 illustrates the phantom and its components.

Varying the fibre density in the phantom simulates fibre loss associated with diffuse axonal injury. In the phantom design, we had 20 test regions with four different densities of Taxons (i.e. 12.5%, 25%, 50% and 100% of the maximal packing density, which is 1024 Taxon tubes per mm^2). These were configured into tracts of different size ranging from 2, 4, 6, 8 and 10 mm on a side. In addition, there were reference fluid test regions to quantify isotropic measures (T_1, T_2, proton density, apparent diffusion constant). More details of the phantom are provided in related publications (31).

Collection of phantom data

The human phantom was scanned with a tightly matched set of parameters across four sites (using the same scanners and head coils as listed above in the description of the human phantom data collection) currently used for collecting data in CENC clinical studies, with TE ranging from 80–94 ms, TR 9000–9050 ms, b = 1300 s/mm^2, 64 diffusion directions and using 20–32-channel head coils. In these protocols, slice thickness ranged from 1.36 to 2.7 mm with an in-plane resolution of 2.2–2.7 mm.

Phantom scanning parameters are included in Supplementary Table 1. Due to ongoing protocol optimization and evolution of sequence parameters for the phantom scanning at different sites, a range of TR (2000–13000 ms) and TE values were collected with three shells using b = 1000, 3000 and 5000 s/mm^2 and using a range of 30–128 directions. However, intra-site parameters were not varied between the first and second scans.



Taxon Fibers Per Density Test Region

Track Sizes	Areas mm^2	Density 12.5%	25%	50%	100%
2x2	4	512	1,024	2,048	4,096
4x4	16	2,048	4,096	8,192	16,384
6x6	36	4,608	9,216	18,432	36,864
8x8	64	8,192	16,384	32,768	65,536
10x10	100	12,800	25,600	51,200	102,400

Figure 1. CENC version 2 MRI axonal diffusion calibration phantom. (A) Image of bell jar phantom with top layer of anisotropic idealized axon (iAxon) fibres and two layers of reference fluids. (B) Scanning electron microscope (SEM) image of iAxon hollow textile tubes filled with water to match the MRI diffusion signal of axons. (C) Axial MRI image of phantom with colour overlap of the anisotropic fibre diffusion tractography in standard convention with blue indicating fibres coursing in an superior-inferior direction, red indicating fibres coursing left to right, and green reflecting fibres oriented in an anterior posterior direction. The density increases from 12.5% to 100% left to right in the centre density region. The tract size 2, 4, 6, 8 and 10 mm on a side changes anterior to posterior (flipping order each column low to high then high to low). The upper right image shows the 10 × 10 mm cube from oblique view. The red, green and yellow show crossing fibre areas. (D) Table of fibre densities in the phantom. (E) Sagittal view of phantom shows the density cubes by size in a sagittal side view. The reference fluids provide reference measurement of standard MRI metrics including the T1, T2 of the tissue, proton density and apparent diffusion coefficient.

Post-processing of phantom data

For the phantom, we examined a water region representing a 0% density (no Taxons) and then the fibre compartments of 12.5%, 25%, 50% and 100% of the maximum Taxon packing density (see Figure 1). FA was evaluated for each fibre compartment using a diffusion tensor model and automated region of interest (ROI) placement. FSL (32) DTIFIT reconstruction was performed on each DTI series to fit a diffusion tensor model at each voxel and produce FA maps. A template was constructed using a b_0 image from a previous phantom scan. ROIs were hand-drawn as rectilinear volumes on the template for each of the 20 fibre anisotropic compartments while referencing phantom manufacturing diagrams and specifications. Each phantom scan was aligned to the template using the non-linear registration tool FNIRT (33,34) on a b_0 image to account for differences in distortion.

The aligned regions were used to extract voxels for each fibre compartment from the FA maps. The set of voxels for each compartment was restricted to the centre 9 voxels within the region in order to reduce partial-voluming effects at the edges. We acquired either 1 or 3 slices; the resulting volumes-of-interest (VOIs) had either 9 or 27 voxels in each fibre compartment. Summary statistics (mean, standard deviation, minimum, maximum) were computed across the voxels for each VOI. We generated plots of FA as a function of position for the VOI and surrounding voxels in order to visually verify the drop-off at the region edges.

Post-processing of human phantom data

Three white matter regions were selected based upon their demonstrated reproducibility using quantitative tractography, importance in studies using DTI in mTBI and as regions of known difference, but that span typical FA values in the human brain (from lowest to highest): the uncinate fasciculus, the genu of the corpus callosum and splenium of the corpus callosum. For the sake of comparison, we also collected a representative measure of cerebrospinal fluid (CSF) and grey matter (head of the caudate). The diffusion data from each acquisition site were processed using a ROI approach using DSI Studio (http://dsi-studio.labsolver.org). A standard cubic seed was placed in the centre of each of the following regions using an axial slice of the FA colour map: (1) right anterior horn of the right lateral ventricle and (2) right head of the caudate. Uncinate fasciculus and corpus callosum (genu and splenium) measures were also derived using standard seed placements (see Figure 2) and a deterministic fibre tracking algorithm (35).

Quantitative reporting and statistical analysis

We compared the aforementioned ROIs using paired sample *t*-tests to compare homologous regions (i.e. four magnets, two observations of a series of ROIs). We used a criterion of $p < 0.05$ (two-tailed tests). We also calculated effect sizes (Cohen's *d*, or the mean difference in FA divided by the average standard deviation [SD]). For intra-scanner SD, we used the SD of the two sample runs per scanner. For the inter-scanner comparisons, we used the square root of the between-scanner variance of the means of the two runs and the variance of the runs within scanner for a given cubic ROI. To mitigate partial volume effects, in particular for small tracts, we used the centre nine voxels of each cube. CoV were also calculated.

We sought to compare the effect size of different brain regions because previous investigators have suggested that the degree of inter-scanner difference varies according to the brain region studied. For instance, Marenco et al. (36) found that the CoV for FA values substantially differed according to the brain region studied. Similarly, Pagani et al. (37) found that the mean FA value and, importantly, the standard deviation of the mean, substantially varied across centres according to the specific brain region investigated.

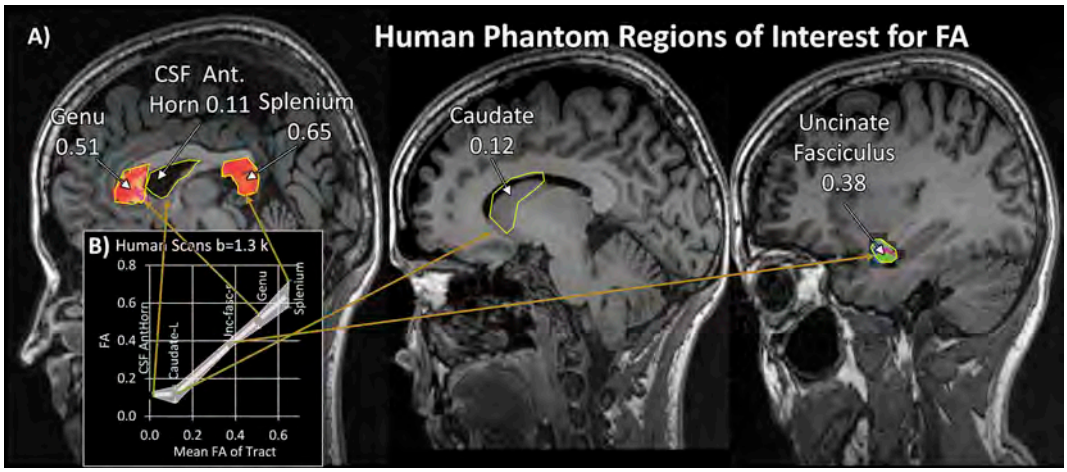


Figure 2. Human phantom scan indicating the location of regions of interest (ROIs) indicated with plot of data across four sites. A) Structural MRI images with overlay of the ROIs of each reference region of expected differential degree of anisotropy. The anterior horn measured cerebral spinal fluid (CSF), and the head of the caudate was used as a measurement of grey matter. The uncinate fasciculus, genu and splenium of the corpus callosum provide a graded range of fractional anisotropy (FA). B) Graph insert shows the mean and standard deviation across the sites. The CSF point is plotted at zero, and the other points at the measured FA on the horizontal axis.

Results

Human phantom

The goal of the human imaging in this project was to quantify the sensitivity and reproducibility of measurement of select white matter tracts with increasing axonal density in the same individual across four scanners and tested on two occasions. We quantified the inter- and intra-scanner effect size (ES) to determine if a single FA measurement of a ROI can unambiguously discriminate different tissue areas based on quantitative FA measurement. Table 1 reports the mean FA, as well as the intra- and inter-scanner SD of the measurement. The intra-scanner SD included both samples (acquired at different time points) for a given scanner. The inter-scanner SD includes both the between- (variance of the between site means) and the within- (variance between scans) SD. The average intra-scanner SD was 0.021, the inter-scanner SD was 0.41 and the ratio of the averages was 2.1.

Table 1 includes the intra- and inter-scanners ES for tissue contrasts. In this instance, detection of significance for a one-tailed test at $p < 0.05$ requires a minimum ES of 1.65, and a threshold for an ES large enough for clinical use in a single subject would fall above 3.30 (i.e. for a detection >0.95 and a false positive of <0.05). The CSF to caudate (grey matter) FA contrast was not discriminable (ES < 1.65), as expected. In contrast, the ES of caudate to uncinate fasciculus, and of corpus callosum genu to splenium showed very high intra-scanner (d = 7.7–21.2) and a range of inter-scanner (d = 2.4–10.7) ES. In Table 1, all the intra-site contrasts (caudate and above) had an ES greater than 7, but for the inter-scanner comparison, 2 of the 4 comparisons fell below an ES of 3.30. The ES varied greatly between sites, with the ES of the genu to splenium of being 3.6, 5.6, 11.5 and 20 across sites.

Phantom object

Figure 3 shows the measured FA within the density cubes per position with a 0.8 mm in-plane resolution as a function of tract size (10, 8, 6, 4, 2 mm fibre bundle on a side) and tract density (for 100%, 50%, 25% and 12.5% density). The edge of the curves shows the FA of the anisotropic water that surrounded each cube. There is a sharp rise in FA occurring in 0.8 mm on the edge of the high-density fibre cubes (25–100%) and complete separability at the 50–100% range for all tract sizes, including the 2 × 2 mm tract. Table 2 shows the z-score (defined as the observed mean signal of the tract divided by the SD of the water control ROI) of detectability for the b = 1000 and b = 3000 s/mm^2 shells based on tract size and density. The grey cells show the non-significant (one-tailed z-score < 1.65) points. The 1000 s/mm^2 shell required a higher density or tract size difference than the FA measured in the b = 3000 s/mm^2 and b = 5000 s/mm^2 data sets.

Table 3 provides the phantom ES over the density of the b = 1000 s/mm^2 shell for the 10 × 10 mm density cube. The

Table 1. Comparison of human phantom data across tissue types; analysis of b = 1300 data.

Tissue	Average FA	SD Within	SD Between + Within	Difference Amounts		Effect Size (d')	
R Ant Horn CSF	0.109	0.017	0.019	FA Contrast	FA Diff	Within	Between
L Caudate	0.118	0.037	0.059	R Ant Horn CSF: L Caudate	0.009	0.25	0.16
R UF	0.375	0.012	0.024	L Caudate: R UF	0.257	21.19	10.66
Genu CC	0.517	0.018	0.043	R UF: Genu CC	0.142	8.08	3.28
Splenium CC	0.658	0.018	0.058	Genu CC: Splenium CC	0.141	7.69	2.42
Average Ratio of SD (Between+ Within)/Within = 2.1				R UF: Splenium CC	0.283	12.86	4.48

R = right; L = left; FA = fractional anisotropy; SD = standard deviation; Ant Horn = anterior horn of the lateral ventricle; CSF = cerebrospinal fluid; UF = uncinate fasciculus; CC = corpus callosum. Effect sizes (Cohen's d') for all values excluding the first comparison (CSF to L caudate). The differences in brain regions related to the presumed white matter density were highly significant in terms of z-scores well above the 2-tailed $p < 0.05$. Note that all contrasts are greater than d' = 2.42 (p-value is 0.0155; 2-tailed). Cohen's d' above 0.80 is considered a large effect size.

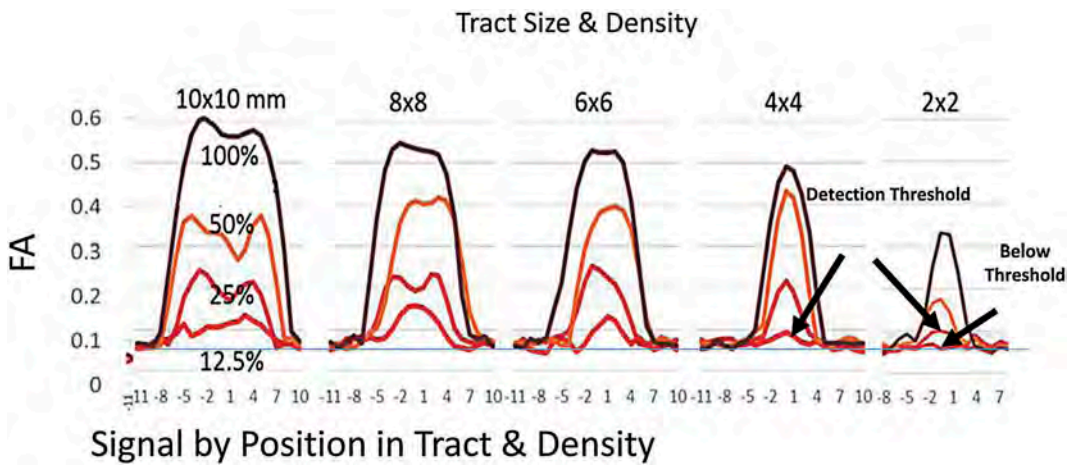


Figure 3. FA measurement of the density cubes by position within the cube for cubes of different sizes (left to right) and densities. The lower right images show detection down to 12.5% of a 4 × 4 mm tract or 25% 2 × 2 mm tract.

Table 2. *Z*-score for tract detection by density size and *b*-value.

		Density *b* = 1000				Density *b* = 3000			
	Cube mm	12.5%	25%	50%	100%	12.5%	25%	50%	100%
Tract Size mm	10	1.25	8.41	12.48	29.98	2.56	21.31	21.31	41.80
	8	2.60	6.99	17.44	21.48	7.66	9.86	25.17	34.73
	6	3.40	10.15	19.13	32.85	3.55	15.82	24.72	36.93
	4	−0.92	1.71	5.78	8.91	3.06	12.14	28.26	33.52
	2	1.28	−0.58	0.41	1.83	−0.02	2.72	8.91	16.76

Note. Values in grey cells are nonsignificant (*z*-scores do not exceed a threshold level of significance). Results are mainly nonsignificant for the smallest tract (2 mm) and at the lower *b*-value (*b* = 1000). However, for the larger tract sizes and those at higher density, the *z*-scores are significant for 2-tailed comparisons. At 2 mm, there is reduction of the FA attributable to partial voluming as the number of tubes and size of the tract dropped below detectable limits.

intra-scanner SDs are small, and in the range of the human observed SD (Table 1), at 0.022. The inter-scanner SDs are larger (0.149). This was expected as the phantom scans had a wider range of variation in parameters as opposed to the parameters used in the human phantom data (see Table A1).

The phantom allows testing of the hypothesis that FA is dependent on Taxonal density (and by extension extra-Taxonal water fraction). That relationship was highly linear at all sites, with correlations between FA and Taxonal density ranging from r = 0.949 to 0.999. Even for the small 2 mm tract, the average correlation was 0.992, showing a strong linear relationship. This demonstration of linearity between FA and fibre density has not been previously reported using similar methods. The observed linearity is likely due to the relationship of FA to the local extra-Taxonal water, where FA approaches 1 as the fraction of extra-Taxonal water goes to zero, as previously demonstrated (38).

Comparison of the human and phantom FA measurement

The human and the phantom object measurements provide complementary metrics to better understand and evaluate FA measurement in diffusion imaging, allowing assessment of measurement bias and reproducibility. These measurements indicate that both the human subject and the physical phantoms were stable over the time period (190 days) of delay between scan sessions (intra-scanner SDs = 0.022). Figure 4 plots the human and the phantom measurements on the same scale for b = 1300, 1000, 3000 and 5000 s/mm^2 shells. We first examine the b = 1300 s/mm^2 and b = 1000 s/mm^2 shells that are most similar. FA values increase linearly with Taxon density and span a physiologically relevant range. Comparison of data collected at different sites in the human phantom range from a mean FA 0.108 (CSF) to 0.666 (splenium), whereas data collected using the phantom increased from FA of 0.062 (CSF) to 0.536 (splenium). Note that the 0% density is based on a volume of free water in the phantom and the 12.5–100% density is based on cubes with fibre densities detailed in Figure 1. The phantom Taxons have a larger diameter than axons (outside diameters of 32 μm vs. 1 μm, inside diameter 12 μm for these Taxons and typically 0.8 μm in axons) (39). To achieve higher FA values, smaller Taxons (or reduction of the extra-Taxonal water) would be necessary.

The range of human and phantom FA are within a range typically reported in the literature (40,41). Based upon existing literature, a typical threshold for the separation of grey matter to white matter in human tissue based is about FA > 0.2; for the phantom, a similar threshold occurred between the fibre density measurements of 25% (FA = 0.168) and 50% (FA = 0.295).

Inter-scanner error was larger than intra-scanner error in both human and phantom measurements. Examining the most anisotropic structures in both (high density splenium in the human and the 100% fibre density cube of the phantom) reveals a range of FA that likely reflects systematic error associated with the scanner. The slope of a linear fit of FA to phantom tract density varied as a function of tract size, and the ratio of the maximum to minimum slope at a given site is not necessarily consistent across sites.

Our initial data revealed that systematic inter-scanner variability was much higher in the phantom assessment than in the human assessment, possibly explained the larger range of pulse sequence variation than the human scans. The inter-scanner SDs of 0.024 for the b = 1300 mm/s^2 shell used in the human phantom study was significantly lower than the SD of 0.24, 0.25 and 0.20 for the b = 1000, b = 3000, and b = 5000 mm/s^2 shells. However, the intra-scanner SDs were similar among the shells, ranging from 0.14 to 0.24. In the b = 3000 mm/s^2, FA measurement of the 100% fibre density cube ranged from 0.276 to 0.669. We note that scan with the highest FA (b = 3000 mm/s^2, site C) also had the highest within-scanner SD, reducing the ES to the lowest. For the b = 3000 mm/s^2 shell, the ES ranged from 1.5 to 16.5 across sites/pulse sequences.

Table 4 provides a comparison of the human and phantom measurement of FA and intra- and inter-site ES. The phantom can provide comparisons with closely matched FA differences. Both human and phantom show high ES ratios of the intra-/inter-scanner ES, suggesting a drop in ES due to high inter-scanner measurement variation. The phantom ESs are substantially lower than the human ESs. The phantom pulse sequences had greater variability and likely are not as optimized as the human scans.

Table 3. Anisotropic phantom data, including effect size comparisons (Cohen d′) at *b* = 1000.

Density	Tubes mm^2	Average FA	SD Within	SD Between+ Within	Comparison	FA Diff	Within (d′)	Between (d′)
0%	0	0.062	0.007	0.145	0:12.5%	0.042	5.56	0.29
12.5%	128	0.103	0.008	0.115	12.5:25%	0.064	7.63	0.56
25%	256	0.168	0.028	0.181	25:50%	0.124	4.47	0.69
50%	512	0.292	0.042	0.154	50:100%	0.244	5.76	1.59
100%	1024	0.536	0.024	0.052	25:100%	0.368	15.67	7.02
Average Ratio of SD (Between+ Within)/Within = 5.9					0:100%	0.474	20.17	9.04

Note: SD = standard deviation. FA = fractional anisotropy. All within-subject effect sizes exceed the threshold for large effect size (d′ = 0.80) and significant two-tailed *p*-values ($p < 0.05$). For the between-subject data, the 0:100% and the 25:100% comparisons represent significant differences with two-tailed testing, though the 50:100% comparison also reflects a large effect size.

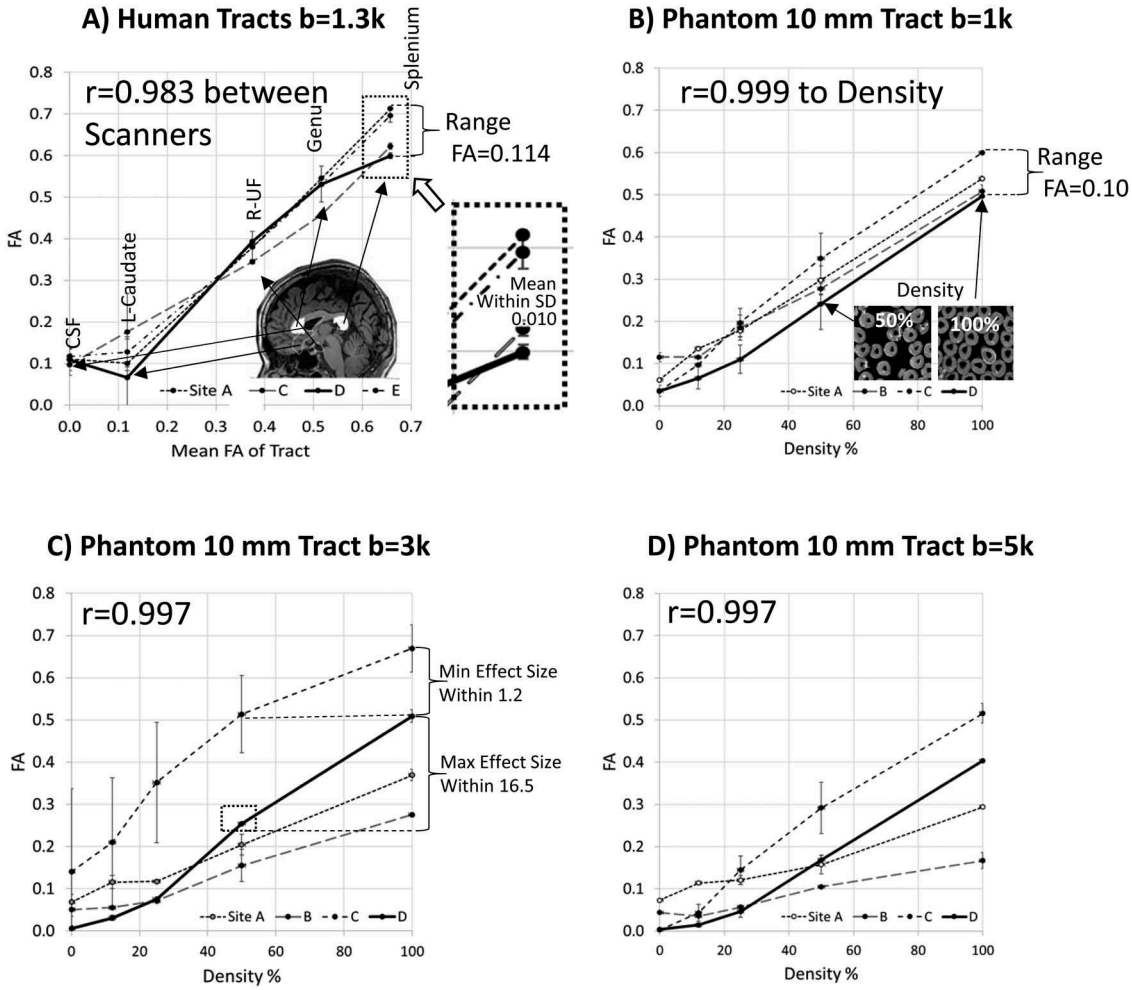


Figure 4. Human and phantom FA measurement across axonal/iAxon densities at representative *b*-values. (A) Human phantom data for five tissues of expected increasing FA. (B–D) Phantom data with measurement of the density of iAxons as a percent of 1024 iAxons per mm^2. The error lines show the intra-scan standard deviation between two runs ranging from same day to years and are small relative to the between scanner deviations at the higher FA values.

Table 4. Comparison of human and phantom FA/effect sizes.

Effect Size (Cohen's d') based on FA Difference of Uncinate Fasciculus and Genu to Splenium CC					
Data Set	Contrast	Δ FA	Effect Size (d') Within Data Set	Effect size (d') Between Data Sets	Ratio of Effect Size Within Data Set to Effect Size between Data Sets
Human Tissue	UF:Splenium CC	0.27	16.7	3.6	4.6
Phantom Density	50% Fibre Density:100% Fibre Density	0.24	5.8	1.6	3.6
Human Tissue	CC Genu:CC Splenium	0.14	14.0	2.0	7.0
Phantom Density	25% Fiber Density:50% Fiber Density	0.12	4.5	0.7	6.5

Note. FA = fractional anisotropy; CC = corpus callosum; UF = uncinate fasciculus. All within-subject effect sizes (d') are highly significant, with a 2-tailed *t*-test *p*-value < 0.00063. For the between-subject comparisons, the only significant 2-tailed contrast at $p < 0.05$ is between the UF –Splenium CC and between the CC Genu: CC Splenium CC. Cohen's d greater that 0.80 is considered a large effect size.

Finally, we calculated CoVs for both human and phantom scanning data (see Table 5). As anticipated, the inter-scanner variation was larger than the intra-scanner variation for both the human and phantom object data.

Table 5. Coefficient of variation for human (*b* = 1300) and anisotropic phantom scan data (*b* = 1000).

Human			Anisotropic Phantom (*b* = 1000; 10 mm tract)		
	Between	Within	Density	Between	Within
R Ant Horn CSF	15%	16%	0%	58%	14%
L Caudate	48%	26%	12.50%	28%	11%
R UF	6%	3%	25%	25%	18%
Genu CC	8%	3%	50%	19%	15%
Splenium CC	8%	3%	100%	10%	5%
Mean exclude 0%	18%	9%	Mean > 0%	20%	12%

Note. R = right; L = left; Ant Horn = anterior horn of the lateral ventricle; UF = uncinated fasciculus; CC = corpus callosum.

Discussion

In this study, we sought to explore MR scanner variability in quantitative analysis of DTI data using a novel phantom that contained properties simulating the complexity of human brain white matter. Specifically, the phantom contained large

numbers of textile-based microtubes arrayed both in parallel and with varying degrees of crossing, but placed in bundles of differing densities. As such, the phantom provided a ground truth measurement of FA values that could serve as a means of determining intra- and inter-scanner variability. We performed multiple scans on each scanner using multiple *b*-values in order to assess the effect of strength of *b*-value on performance characteristics.

Our results can be summarized as follows. First, we found high within-scanner effect sizes and within-scanner repeatability over long testing intervals, with high discriminability for graded tissue contrasts and Taxon density contrasts. Scans were able to detect oriented fibres in a 4 mm tract at a packing density as low as 12.5%. Second, substantial inter-scanner variability across MR scanners leads to lack of reproducibility and error that reduces the ES and the ability to detect both tissue contrasts and Taxon density contrasts. Third, high between-scanner variation was found. For instance, a *b*-value of 1000 s/mm^2, in a 10 mm phantom tract yielded FA values as low as 0.497 on one scanner and as high as 0.600 on another. Fourth, the difference in FA values between these particular scanners greatly exceeds the typical FA value decrease considered to represent evidence of mild TBI in many studies. Fifth, we found similar marked differences in the human scans in some regions (e.g. the splenium of the corpus callosum), even when the acquisition protocols on various scanners were closely matched. This fact has particular significance for combining data from multiple MR scanners; it underscores the importance of making acquisition protocols across sites as similar as possible. Sixth, substantial differences in FA were seen when higher *b*-values (i.e. 3000 and 5000 s/mm^2) were employed. This fact has considerable importance because, apparently along with the advantages of using higher *b*-values comes the disadvantage of decreased reproducibility. Seventh, we found a linear relationship (r = 0.99) for all three *b*-values of large tracts and at all densities. Even the smallest tract, the 2 × 2 mm tract, had an average within site $r > 0.97$ for b = 1000, 3000 and 5000 mm/s^2.

A key goal of diagnostic measurement is to obtain measurements in which the effect size associated with pathology is larger than the systematic measurement error associated with instrumentation. If this condition is not met, inter-site norms are not viable, and norms must be specific to the instrument used for data collection. If the error is systematic and stable, it can potentially be corrected through phantom-based calibration of the measurement values. For FA measurement in TBI using DTI, we seek to discriminate individuals with white matter damage from a healthy population. Using similar samples collected on a single instrument, one can estimate the size of between-group differences from values reported in the literature. For example, Rutgers et al. report a mean FA in the genu of 0.74 and a mean FA in the splenium of 0.82 (40), with a genu–splenium difference of 0.08. This genu–splenium difference in our human subject was 0.15, though this was obtained with different pulse sequence parameters. Rutgers reported the group difference between participants with mild TBI at least 3 months post-injury versus healthy controls in mean FA for the splenium to be 0.02 (Table 3). These differences in mean FA between groups were larger when a group with moderate and severe TBI was used (FA differences of 0.09 and 0.19, respectively, for the splenium, and 0.08 and 0.21 in the genu of the corpus callosum) (Table 2). If we use these numbers to estimate ES for TBI in the splenium, the systematic error we observed in the human phantom is five times the scale of difference in the group of participants with mild TBI, equal to the group with moderate TBI, and half as large as the group with severe TBI.

Our results illustrate both the important capability of current 3T imaging with a stable scanner, but also the hazards of between-scanner and across-time comparisons in the absence of measurement calibration. The high sensitivity and stability within magnets indicates that within-scanner quantification of change is sensitive. However, we recognize that intra-scanner variability may increase with longer time intervals between scans than were employed here (so-called 'scanner drift'). Furthermore, in this study, we did not address the effect of MR scanner upgrades on stability of data, though is likely that changes in MR scanner hardware will affect stability of measurements.

Our findings indicate a significant effect of *b*-values on FA values. This fact makes comparison of FA values between MR scanners fraught with hazard if one ignores such important factors in the imaging protocol for each scanner. However, as our data show, significant differences in FA values are seen between scanners even with a *b*-value of 1000 s/mm^2; at higher *b*-values, the variability is further increased.

We believe that our results are generalizable to the much larger population of MR scanners at academic institutions involved in DTI research. A limitation of this study is the small sample of scanners, which will be addressed in future phantom studies. However, even in this sample of four scanners, we have an order of magnitude difference in the detection of effect size both on tissue and phantom Taxon density contrasts; this suggests caution must be used when comparing DTI data from different institutions. Our findings also indicate that further work is needed to mitigate the differing FA results found on different MR scanners before DTI can be used for clinical diagnosis and monitoring. Additionally, research studies using multiple sites may need to take additional steps to improve data integration and conclusions made regarding clinical outcomes.

Because the intra-scanner measurement is repeatable, it may be possible to estimate the systematic error of inter-scanner measurement and account for inter-scanner differences by use of the phantom. For instance, in one demonstration, we found that by estimating the scanner specific slope, we could report results from different MR scanners by a method that would remove 94% of the systematic error(42), at least in the phantom object data. However, a number of caveats are evident in employment of such a technique. First, the technique must be used prospectively with phantom calibration scans at times near the subject scans (e.g. monthly calibration scans) and before the data on multiple MR scanners is obtained. Stated differently, the technique cannot reasonably be performed retrospectively after MR scanning is performed. As such, if clinical DTI scanning were ever to be meaningfully performed, prospective calibration would be necessary. In addition, careful

coordination of sites by minimizing differences in important imaging characteristics such as field strength, *b*-value, acquisition parameters such as TR and TE, voxel size and slice thickness, and fibre directionality along the *z*-axis would need to be considered.

We were able to employ a technique that, to some degree, allowed FA values between MR scanners to be more easily interpreted. However, it is not clear whether such a technique would be more widely applicable to a larger number of MR scanners, especially if they differed from one another more than those in the relatively homogeneous, and small, population of scanners used in this study (as would be found in a proposed use of DTI for clinical diagnosis). Hence, our study has limitations related to testing of few sites and variation of acquisition sequences on the phantom scans. In future studies, we plan to increase the number of sites and include both standardized, optimally matched pulse sequences and locally used DTI sequences to support a more complete comparison.

Conclusion

Our novel phantom with hollow fibres that mimic the size and scale of axons in the brain provide a means to measure and minimize systematic error in anisotropic diffusion across data collection sites and time. The phantom may be useful in addressing needs of multisite, longitudinal studies utilizing imaging, such as the CENC project.

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Appendix

Table A1.

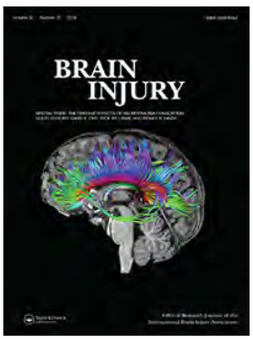
Phantom Scans	TE			TR					
Site	b = 1000	b = 3000	b = 5000	b = 1000	b = 3000	b = 5000	Directions	In plane	Thickness (mm)
A	126	145	167	13200	13200	13200	30	1	2
B	69.4	85.5	95.6	4000	4000	4000	64/64/128	1	2.9
C	98.935	127.74	95.6	2000	2000	4000	64/64/128	1	2.9
D	58.5	75.5	85.9	5100	6100	6700	64/64/128	0.84	2
Human Scans									
Site	TE	TR	Directions	In plane	Thickness (mm)	Directions			
A	94	9000	64	2.7	4.1/2.7	64			
C	94	9000	64	2.7	2.7	64			
D	80.4	9050	71	1.36	2.7	64			
E	94/92	9000	64	2.7	2.7	64			

TE = echo time; TR = repetition time; mm = millimetres.

Table showing image acquisition parameters for the manufactured phantom scans and the human scans used in this study. The term 'in plane' refers to the in-plane resolution and the units are in mm2

Appendix 15

Exploring the factor structure of a battery of neuropsychological assessments among the CENC cohort



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Exploring the factor structure of a battery of neuropsychological assessments among the CENC cohort

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ABSTRACT

Objective: The goal of the Chronic Effects of Neurotrauma Consortium (CENC) study is to explore the effects of concussions among Service Members and Veterans. A factor model was fit to selected neuropsychological measures to identify potentially useful relationships between assessments collected on CENC-enrolled participants.

Method: 492 post-9/11 participants with combat exposure were enrolled across four VA study sites. Participants completed assessments including concussion history, neurocognitive functioning, and self-report questionnaires. Exploratory factor analyses (EFA) using four different methods with varimax and promax rotations were used to analyse the cognitive variables. Final model selection was based on factor loadings towards simple structure.

Results: The scree plot suggested the number of factors to be extracted was between 4 and 5. EFA produced a 5-factor MINRES model with promax rotation that resulted in a factor loading with variables loading on only one factor with a predefined threshold (0.40). Variables loaded on five cognition domains: list learning, working memory/executive skills, cognitive control, fluency, and memory.

Conclusion: These results provide reasonable evidence that data collected from the CENC neuropsychological battery can be reduced to five clinically useful factors. This will enable us to use the factors for further study of the impact of concussion on neurodegeneration.

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Introduction

Most of the literature on the cognitive effects of concussion has come from the civilian sector, particularly athletes. Multiple meta-analyses and research reviews have summarized this literature, with most revealing no long-term effect of a single concussion on cognitive performance, with greater uncertainty following multiple concussions (1–5).

Although there is less literature on the military/veteran populations, the most recent study of military personnel who had sustained a concussion in combat theatre revealed no significant differences in cognitive performance between those with and without a history of concussion (6). Importantly, however, prospective assessment of verbal fluency and premorbid intelligence, as well as symptom reporting and gait performance at 1-year post injury predicted global outcome measures at 5 years post injury. There is concern about the potential later life effects of concussion(s) in terms of possible increased risk for developing dementia or chronic traumatic encephalopathy (CTE). In particular, some have proposed that repetitive head trauma can lead to the pathologic findings associated with CTE, which may represent a degenerative condition that leads to pronounced behaviour and cognitive dysfunction (7). To determine any causal connection between concussion(s) and degenerative neuropathology, large prospective studies that include neuropsychological assessment will remain an important research and clinical endeavour.

The Chronic Effects of Neurotrauma Consortium (CENC) was created to study the long-term impact, including cognition, of concussion(s) on military Service Members and Veterans (8). As computerized collections of tests alone have not yielded consistent results across research studies (9), CENC chose to use a compilation of commonly used neuropsychological measures and International Common Data Elements (CDEs) for concussion (10). These assessments included both paper and pencil tests and computerized cognitive assessment, including the National Institutes of Health (NIH) Toolbox. Though the use of such a large battery provides a wealth of potential information, it can also pose several difficult clinical and research challenges.

First, studying the impact of concussion using such a broad battery of tests produces the statistical challenge of multiple comparisons and potentially inflated Type I error rates. Second, the CENC battery contains tests that may be redundant in nature (e.g. multiple memory measures). This was an intentional part of the design with the idea being that the

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psychometric properties of more common standardized CDEs could be examined relative to newer computerized administered batteries (NIH Toolbox). Regardless, this redundancy poses an important challenge that requires consideration. Related to these challenges is the fact that the lack of a standardized approach among traumatic brain injury (TBI) studies in general complicates the conclusions that can be made when considering this literature at large.

To address these challenges, research groups have relied heavily on statistical methods designed to reduce data dimensionality and discover consistency between measures. One such method includes exploratory factor analysis (EFA), a statistical method used to uncover the underlying structure of a relatively large set of variables. The purpose of this study was to determine the underlying factor structure of the CENC cognitive battery using EFA. This enables the use of factors for further study of the impact of concussions, and to provide a tool for other researchers who may wish to utilize the same standardized battery. Previous studies have incorporated a similar neurocognitive battery, but few have been performed on a large-scale military population with concussion exposure.

Methods

Setting and participants

Enrolment for the CENC Multicentre Observational Study began in September 2014 and a preliminary data snapshot was taken for all subjects completing only their initial in-person visit by 1 September 2016. Enrolled subjects met the following inclusion criteria: (1) history of deployment in Operation Enduring/Iraqi Freedom (OEF/OIF) or related follow-on conflicts, (2) history of combat exposure defined by Deployment Risk and Resiliency Inventory Section D (DRRI-2-D) score > 1 on any item, and (3) > 18 years of age. Individuals were excluded from enrolment if they had a moderate or severe TBI (loss of consciousness greater than 30 minutes or post-traumatic amnesia great than 24 hours), had history of major neurological disorder, or were diagnosed with any major psychiatric disorder. The initial snapshot included 492 participants enrolled across four large Veterans Affairs Medical Centres (VAMCs): Michael E. DeBakey VAMC in Houston, TX, Hunter Holmes McGuire VAMC in Richmond, VA, Audie L. Murphy VAMC in San Antonio, TX, and James Haley VAMC in Tampa, FL. Details regarding CENC's recruitment, enrolment and methods have been previously published (8).

For the current analysis, participants were excluded on the basis of invalid performance on the Medical Symptom Validity Test (MSVT) (n = 41) and/or the California Verbal Learning Test, Second Edition (CVLT-II) (n = 5), or for exaggerated symptom reporting based on scoring above predetermined Neurobehavioral Symptom Inventory and Mild Brain Injury Atypical Symptom (NSI/mBIAS) cutoffs (n = 29) [11,12,13]. Figure 1 displays the study CONSORT diagram, while Table 1 displays the demographic profile among the 417 participants included in the study. A total of 346 (83.0%) participants had at least one lifetime mTBI and the median length of years from last mTBI to enrolment was 8.1 years; however, EFA was not stratified by mTBI exposure. Participants with mTBI exposure in our cohort reported greater neurobehavioral complaints (mean total NSI score of 27.4) compared to those without mTBI exposure (mean total NSI score of 17.4). Additionally, the rate of risk factors and comorbidities was similar between the CENC cohort and the OEF/OIF source population: daily smoker 14% versus 16%, non-prescription drug use 13% versus 10%, low alcohol risk 95% versus 89%, PTSD 29% versus 30%, and major depressive disorder 23% versus, 38%, respectively [14].

Measures

All participants were administered a battery of 18 neuropsychological tests during their initial in-person visit to assess cognitive functioning across multiple domains including memory, attention, language and verbal fluency, executive functioning, processing speed, motor functioning and others selected on the basis of inclusion as recommended elements of the CDEs (10) or their established use in relevant populations. Only raw test scores were considered in the EFA. All neuropsychology test administrators were trained to conduct each assessment following the standardized procedures established by the test developer prior to study enrolment. Annually, administrators were required to submit a video tape of themselves conducting the neuropsychology battery on a test subject to assess assessment fidelity. Additionally, an audit was performed on all neuropsychology data to ensure there were no transcription errors from case report form to database entry. All study activities were approved by and conducted in accordance with all relevant Institutional Review Boards and other regulatory committees required by the VA and Department of Defense. The following assessments were included in the EFA:

Wechsler adult intelligence scale, fourth edition (WAIS-IV)

The WAIS-IV consists of subtests aimed at estimating general intellectual functioning, and inclusion of subtests that specifically target processing speed. For the *Digit Span Forward, Digit Span Backward, Digit Span Sequencing*, and *Letter-Number Sequencing Tests*, the examinee is read a sequence of numbers and/or letters and attempts to recall them in the same, reverse and ascending order, respectively. Participants also complete the *Symbol Search, Coding*, and *Visual Puzzle Tests*. For these tests, the examinee scans a search group and indicates if the symbol matches the target group, uses a key and copies symbols that are paired with numbers, and views a completed puzzle and selects options that would reconstruct the puzzle, respectively (15).

National institutes of health (NIH) toolbox

The CENC protocol includes six NIH Toolbox cognition tests that span various cognitive domains including language, memory, and executive functioning. Previous studies have examined the content, construct, and validity of the NIH Toolbox (16–18). For the *Picture Vocabulary Test*, the examinee selects the picture (from four options) that matches an audio recording of the word, while the *Flanker Inhibitory Control and Attention Test* requires the examinee to focus on a given stimuli while inhibiting attention to the stimuli

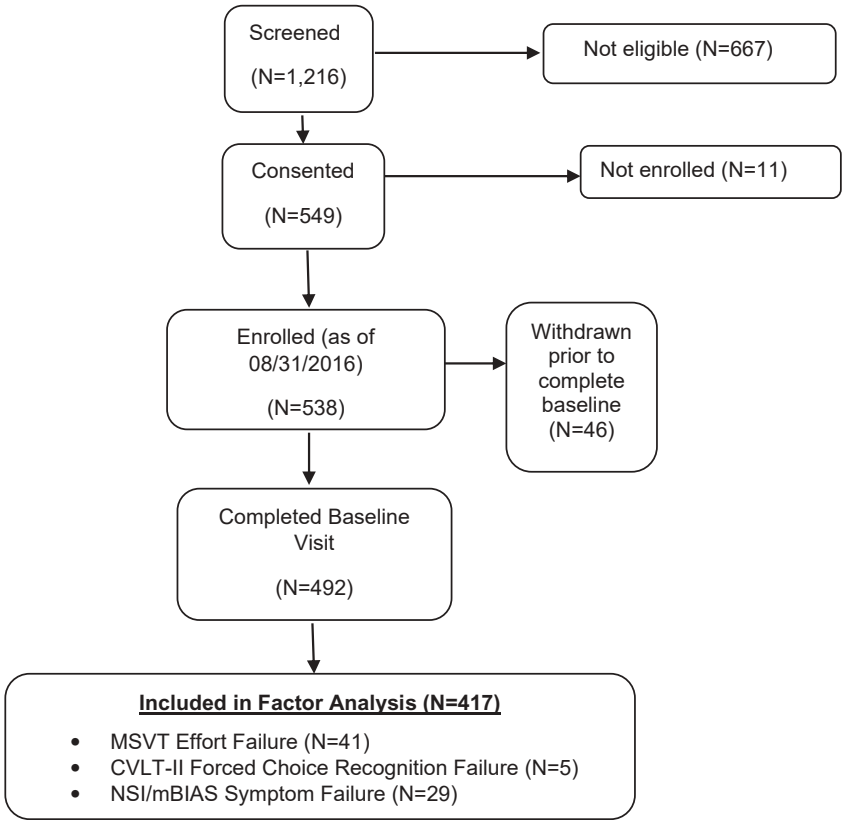

Figure 1. Study CONSORT diagram.

Table 1. CENC baseline demographics.

Demographic characteristics	Total sample size[1] (*N* = 417)
Age at baseline (years)	
Mean (standard deviation)	39.5 (10.3)
Gender	
Male	363 (87.1%)
Female	54 (12.9%)
Race	
White	279 (66.9%)
Black or African American	99 (23.7%)
Other	39 (9.4%)
Ethnicity	
Hispanic or Latino	103 (24.8%)
Not Hispanic or Latino	312 (75.2%)
Currently in military?	
Yes	29 (7.0%)
No	387 (93.0%)
Service rank	
Enlisted	356 (86.0%)
Officer	58 (14.0%)
Education	
College Graduate or Higher	162 (38.9%)
Some College or Technical School	187 (44.8%)
High School Graduate	65 (15.6%)
Some High School	3 (0.7%)
Study site	
Richmond	144 (34.5%)
Houston	96 (23.0%)
San Antonio	74 (17.8%)
Tampa	103 (24.7%)

[1] Does not include missing responses.

flanking it. For the *List Sort Working Memory Test*, the examinee repeats items they are read and shown (either food or animal) in size order (from small to large). The *Dimensional Change Card Sort Test* requires the examinee to match test pictures (i.e. yellow balls and blue trucks) to target pictures, first according to colour and then to shape. The *Pattern Comparison Processing Speed Test* requires the examinee to discern whether two side-by-side pictures are identical. Pairs are presented one at a time and the examinee is given 90 seconds to respond to as many pairs as possible. Last, the *Picture Sequence Memory Test* asks the examinee to recall a series of activities they are presented in the correct order (sequence length varies from 6–18 pictures). Details regarding the scoring of each NIH Toolbox subtest are described in the NIH Toolbox Scoring and Interpretation Manual (19).

Delis-Kaplan executive function system (D-KEFS) verbal fluency test

Participants complete the *Letter Fluency Test* and *Category Fluency Test* from the D-KEFS battery. For each, the interviewer says a letter of the alphabet or a category (e.g. food), and the examinee says as many words as possible that begin with the same letter or fall under the same category within 60 seconds (20). These D-KEFS measures are typically associated with measurement of the executive functioning domain.

California verbal learning tests – second edition (CVLT-II)

For *CVLT-II Trials 1–5*, the interviewer reads a list of 16 words (List A), and the subject is asked to recall as many words as possible in any order (free recall). This is repeated

over five learning trials. For the *Short-Delayed Free and Cued Recall Tests*, the examinee is asked to recall words from List A immediately. In cued recall, the interviewer prompts the participants with the word category. The *Long-Delayed Free and Cued Recall Tests* asks examinees to recall words from List A 20 minutes after originally heard (21). These measures are typically associated with measurement of memory.

Brief test of adult cognition by telephone (BTACT)

The BTACT includes six subtests measuring various cognitive domains, and the telephone call is generally completed 2 weeks after the comprehensive in-person assessment; however, the call window can expand as far as 2 months after the in-person visit. For the *Immediate and Delayed Word Recall Tests*, the examinee is read a list of 15 words and asked to recall as many words as possible in 90 seconds (Immediate Recall). The subject is asked to recall the same words again about 20 minutes later (Delayed Recall). For the *Digits Backward Test*, participants are asked to repeat a string of integers in reverse order, the score being the highest number of integers recalled (from two to eight digits long). For the *Category Fluency Test*, the examinee names as many unique animals as possible in 60 seconds, while the *Backward Counting Test* asks the examinee to count backwards from 100 as fast as possible (within 30 seconds). For the *Number Series Test*, the examinee is read a series of numbers (over five trials) that either increase or decrease in a specific algorithm and are asked to predict the next integer given the pattern. For the *Stop and Go Accuracy Test*, the examinee has 1 minute to accurately respond to the words RED and GREEN with the words 'Stop' and 'Go', respectively, over 20 trials (baseline test). The examinee then completes the reverse and experimental portion of the test, with reverse and mixed meanings of the words RED and GREEN, respectively (22).

Brief visuospatial memory test revised (BVMT-R)

In three *Learning Trials*, the examinee reviews a study key for 10 seconds and then draws as many figures as possible in the same location of the study key (23). The total of the three learning trials was included in the analyses. This measure is typically used to examine memory functioning.

Trail making test (TMT)

For *TMT A*, circles are numbered 1–25 on a response key, and the examinee draws lines to connect the numbers in ascending order. For *TMT B*, circles include both numbers and letters, and the examinee connects numbers and letters in the correct sequence (i.e. 1-A-2-B-3-C). The examinee completes each test as fast as possible, and scoring is based on the time it takes to complete the test (24). This measure is typically used in conjunction with assessment of executive functioning.

Statistical analysis

Data manipulation and EFA were conducted with SAS Version 9.3 (Cary, NC). Initial factor count selection was done in R 3.3.2 using the Parallel function and the nScree function within the nFactors package (25). The nScree function reports several assessments for the number of factors to keep, and we used the optimal coordinates and parallel analysis. Selection of neuropsychological variables into the analysis dataset involved investigating zero or near zero variance and level of missingness (26). Only the BTACT Stop and Go Baseline assessment was removed due to near zero variance, resulting in 31 neuropsychological variables included in the EFA. Among the neurocognition variables (excluding BTACT measures) collected across the 417 participants included in the analysis, 54 participants had at least one measure that was either missing or unreliable. Most missing data was from the NIH Toolbox since not all study sites had software installed at enrolment initiation. Similarly, the small amount of records determined as unreliable were due to technology malfunction during NIH Toolbox administration. For purposes of this EFA, unreliable results were treated as missing data. Although no variables were removed due to level of missingness, all BTACT assessments had between 16.5 and 23.3% missing data. The majority of missing BTACT data is from participants declining to take the assessment or study coordinators being unable to contact participants within the visit window. To impute for missing data, we used multiple imputation and the predictive mean matching technique (based on responses from all other neuropsychological variables) to generate five replicates of the dataset. Correlation analyses on each of the five imputed datasets were used to assess sensitivity of imputations on correlations among variables. Sensitivity analyses on two replicates of the imputed data showed minor effects of missing data imputation on the factor structure.

Multiple methods were used to explore the optimal numbers of factors to extract for the EFA: parallel analysis, Kaiser criteria method, scree plot and number of eigenvalues greater than 1(27). In conjunction with the eigenvalue assessment, the parallel assessment method was used where the selected number of factors was identified by counting the number of factors greater than the mean eigenvalue from a simulated estimate of the eigenvalue distribution using 1,000 replicates (28). We created EFA models based on the following methods: principal components, mean principal components with iteration, maximum likelihood, and least-squares (27). Each modelling method was run with both varimax and promax rotation to limit the number of variables loading highly on more than one factor, thus tending toward simple structure.

Varimax rotation rotates the set of initial factors as a rigid frame to maximize the variance of the squared loadings in each factor (27). In promax transformation, factors are rotated first using varimax rotation and then the orthogonal restriction is relaxed to improve the simple structure approximation allowing factors to be correlated (29). If the promax rotated model displayed uncorrelated factors, then the varimax rotation was preferred. However, promax rotation was given preference if the model displayed correlated factors, as many of the neuropsychological tests overlap in cognitive domain.

Although models with Heywood cases were output to examine the loading structure, they were not considered for final model selection. A Heywood case occurs when the communality is greater than 1, often arising when too many

factors are extracted or the sample size is too small (27). We chose to retain an item on a factor if its loading was 0.40 or higher. A final model was selected that visually displayed the closest approximation to simple structure, namely did not have any variables loading onto two or more factors.

Results

Dataset creation and data analysis were performed as described in Figure 2, and descriptive statistics of the neuropsychological variables included in the EFA are presented in Table 2. As a result of looking at the Scree plot (Figure 3) as well as the optimal coordinates and parallel analysis, EFA models were produced extracting 4, 5, 6, 7 and 8 factors using the modelling methods described above. The five-factor promax transformed minimum residual method (MINRES) model produced the simplest structure and was selected as the final model. Twenty-four of the 31 neuropsychological variables loaded onto an extracted factor. Only the picture sequence memory and picture vocabulary subtests from the NIH Toolbox, Stop and Go reverse and experimental subtests from the BTACT, BVMT-R Total Recall, CVLT-II Trial B and WAIS-IV visual puzzle assessment did not load onto an extracted factor. From the EFA the factors of list learning, working memory/executive skills, cognitive control, fluency, and memory were identified (Table 3). All five CVLT-II measures loaded onto the list learning factor. The working memory/executive skills factor was comprised of the NIH Toolbox list sort working memory, BTACT digit backward, BTACT number series trials, Trail Making B, WAIS-IV digit span forward, backward and sequencing, and WAIS letter number sequencing. Cognitive control consisted of the NIH Toolbox's dimensional change card sort, flanker inhibitory control and pattern comparison subtests, Trail Making A, WAIS-IV coding and WAIS-IV symbol search. The fluency factor included the two DKEFS fluency assessments and BTACT category fluency word count. The two BTACT word recall variables loaded onto the memory factor.

Sensitivity analyses by refitting the model to multiple imputed datasets did not find any effects of imputation on the BTACT loadings. However, although Trail Making B loaded onto the working memory/executive skills factor using the first imputed dataset; it did not load onto any factor for the other two imputed datasets. Similarly, the BVMT-R total raw score did not load onto any factor using the first imputed dataset, but it did load onto the cognitive control

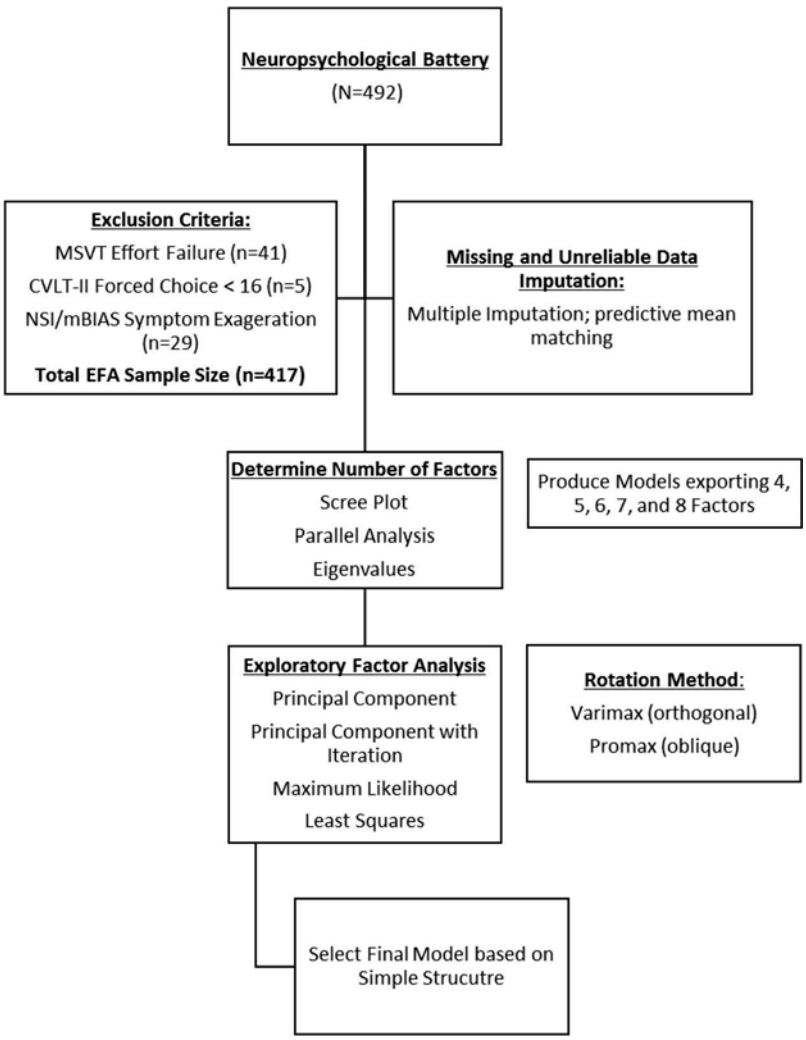

Figure 2. Dataset and exploratory factor analysis structure.

Table 2. Descriptive statistics of neuropsychological variables.

Neuropsychological measure	Mean	Std. Dev.	Median	Q1	Q3
BTACT: Category Fluency Word Count	20.15	4.81	20.00	17.00	24.00
BTACT: Digit Backward	5.04	1.53	5.00	4.00	6.00
BTACT: Stop and Go Experimental	30.57	2.19	31.00	30.00	32.00
BTACT: Stop and Go Reverse	19.28	1.58	20.00	19.00	20.00
BTACT: Number Series Trials	2.63	1.48	3.00	2.00	4.00
BTACT: Word Recall Delay	3.04	2.10	3.00	2.00	4.00
BTACT: Word Recall Immediate	5.46	1.88	5.00	4.00	7.00
DKEFS: Category Fluency	40.89	8.56	40.00	35.00	47.00
DKEFS: Letter Fluency	38.82	10.90	38.00	31.00	45.00
WAIS-IV: Coding	66.14	14.89	67.00	57.00	75.00
WAIS-IV: Digit Span Backward	8.28	2.15	8.00	7.00	10.00
WAIS-IV: Digit Span Forward	9.95	2.30	10.00	8.00	12.00
WAIS-IV: Digit Span Sequencing	8.50	2.21	9.00	7.00	10.00
WAIS-IV: Letter Number Sequence	19.43	2.83	19.00	18.00	21.00
WAIS-IV: Symbol Search	33.18	7.51	33.00	27.00	39.00
WAIS-IV: Visual Puzzle	14.44	4.86	14.00	11.00	18.00
NIH TB: Dimensional Change Card Sort	7.98	1.10	8.07	7.33	8.79
NIH TB: Flanker Inhibitory Control	8.10	1.01	8.11	7.37	8.95
NIH TB: Pattern Comparison	54.47	14.18	53.00	44.00	65.00
NIH TB: Picture Sequence Memory	17.62	7.72	18.00	11.00	23.00
NIH TB: List Sort Working Memory	18.10	2.98	18.00	16.00	20.00
NIH TB: Picture Vocabulary	1722.60	171.27	1725.00	1598.00	1833.00
CVLT-II: Long Delay Cued Recall	10.85	3.22	11.00	9.00	13.00
CVLT-II: Long Delay Free Recall	10.09	3.49	10.00	7.00	13.00
CVLT-II: Short Delay Cued Recall	10.90	3.08	11.00	9.00	13.00
CVLT-II: Short Delay Free Recall	10.06	3.23	10.00	8.00	13.00
CVLT-II: Trial B	5.30	1.97	5.00	4.00	6.00
CVLT-II: Trials 1–5	47.55	10.01	47.00	41.00	54.00
BVMT-R: Total Recall	21.86	7.36	23.00	17.00	28.00
Trail Making A	28.33	11.46	26.00	21.00	33.00
Trail Making B	65.57	25.31	59.00	47.00	80.00

factor for the other two imputed datasets. Despite the small differences, each of these identified neuropsychology tests were very close to reaching the loading threshold (≥ 0.40) for each of the imputed datasets.

The list learning and working memory/executive skills factors were positively correlated with a Pearson correlation coefficient of 0.51. List learning was also positively correlated with cognitive control (r = 0.47), fluency (r = 0.32) and memory (r = 0.33). Only factor 5, memory, was weakly correlated with all other extracted factors, with a maximum coefficient with factor 1, list learning (r = 0.33). The correlation observed between the factors suggested that an oblique factor rotation was appropriate. Since oblique transformation was used, the loading pattern matrix was different than that of the correlations of each variable on the loading factors. Table 4 displays each variable's correlation to the extracted factor. Although each variable was highly correlated with the factor it loaded on, variables also tended to be correlated with extracted factors they did not load on. This is summarized by the moderate correlation observed between the extracted factors (Table 5).

Discussion

We investigated the factor structure of a battery of neuropsychological tests conducted on a cohort of Veterans and Service Members with OEF/OIF combat deployment. Among the EFA models explored in this study, the MINRES promax transformed model was the most adequate for the dataset, producing a five-factor solution with simple structure.

Not unexpectedly, extracted factors had a low to moderate positive correlation between each other. Factor 1, list learning, consists of all CVLT-II subtests and is moderately correlated with factor 2, working memory/executive skills. We would expect a moderate to strong correlation between the working

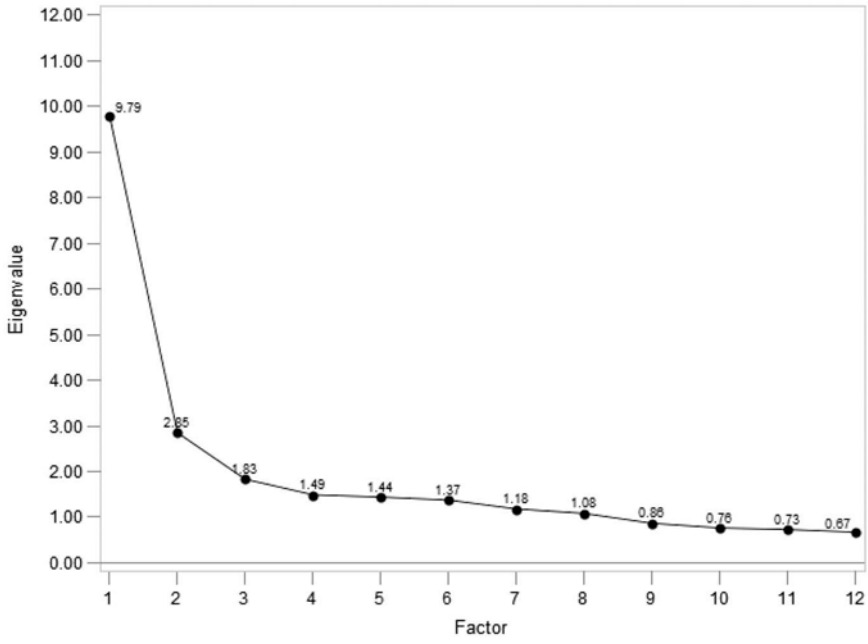

Figure 3. Exploratory factor model scree plot[1].

[1] Two methods used to extract the optimal number of factors were Eigenvalues greater than 1.0 (Rencher, 1995) and the plateau of Eigenvalues (i.e. the 'elbow' in the scree plot).

Table 3. Rotated factor pattern of neuropsychological battery[1,2].

	Factor				
Neuropsychological measure	**1**	**2**	**3**	**4**	**5**
CVLT-II: Trials 1–5	0.82				
CVLT-II: Short Delay Free Recall	0.95				
CVLT-II: Short Delay Cued Recall	0.96				
CVLT-II: Long Delay Free Recall	0.95				
CVLT-II: Long Delay Cued Recall	0.98				
NIH TB: List Sort Working Memory		0.53			
BTACT: Digit Backward		0.60			
BTACT: Number Series Trials		0.53			
Trail Making B		−0.45			
WAIS-IV: Digit Span Forward		0.75			
WAIS-IV: Digit Span Backward		0.68			
WAIS-IV: Digit Span Sequencing		0.63			
WAIS-IV: Letter Number Sequencing		0.80			
NIH TB: Dimensional Change Card Sort			0.78		
NIH TB: Flanker Inhibitory Control			0.78		
NIH TB: Pattern Comparison			0.85		
Trail Making A			−0.43		
WAIS-IV: Coding			0.50		
WAIS-IV: Symbol Search			0.52		
BTACT: Category Fluency Word Count				0.59	
DKEFS: Letter Fluency				0.52	
DKEFS: Category Fluency				0.86	
BTACT: Word Recall Immediate					0.85
BTACT: Word Recall Delay					0.80
	List learning	**Working memory/Executive skills**	**Cognitive control**	**Fluency**	**Memory**
Variance explained by each factor[3]	7.05	7.44	6.51	3.88	2.40

[1] Minimum Residual Method (MINRES) with Promax rotation.
[2] Factor loadings less than 0.40 are not displayed.
[3] Variance explained by each factor ignoring other factors.

Table 4. Neuropsychological variable correlation with extracted factor[1].

	Factor				
Neuropsychological measure	**1**	**2**	**3**	**4**	**5**
CVLT-II: Trials 1–5	0.87	0.47	0.44	0.28	0.36
CVLT-II: Short Delay Free Recall	0.91	0.43	0.40	0.30	0.28
CVLT-II: Short Delay Cued Recall	0.91	0.42	0.38	0.33	0.27
CVLT-II: Long Delay Free Recall	0.93	0.45	0.42	0.25	0.29
CVLT-II: Long Delay Cued Recall	0.94	0.44	0.400	0.29	0.29
NIH TB: List Sort Working Memory	0.48	0.68	0.49	0.41	0.25
BTACT: Digit Backward	0.27	0.55	0.38	0.16	0.20
BTACT: Number Series Trials	0.29	0.53	0.35	0.23	0.15
Trail Making B	−0.35	−0.67	−0.64	−0.41	−0.10
WAIS-IV: Digit Span Forward	0.18	0.61	0.27	0.38	0.15
WAIS-IV: Digit Span Backward	0.34	0.65	0.40	0.326	0.12
WAIS-IV: Digit Span Sequencing	0.36	0.66	0.46	0.35	0.10
WAIS-IV: Letter Number Sequencing	0.42	0.78	0.46	0.43	0.15
NIH TB: Dimensional Change Card Sort	0.36	0.47	0.76	0.28	0.14
NIH TB: Flanker Inhibitory Control	0.29	0.35	0.68	0.23	−0.00
NIH TB: Pattern Comparison	0.24	0.29	0.68	0.29	0.15
Trail Making A	−0.30	−0.59	−0.62	−0.34	−0.11
WAIS-IV: Coding	0.34	0.55	0.64	0.33	0.13
WAIS-IV: Symbol Search	0.34	0.59	0.68	0.37	0.15
BTACT: Category Fluency Word Count	0.27	0.359	0.32	0.62	0.12
DKEFS: Letter Fluency	0.25	0.45	0.35	0.61	0.09
DKEFS: Category Fluency	0.29	0.45	0.37	0.86	0.17
BTACT: Word Recall Immediate	0.26	0.22	0.12	0.20	0.85
BTACT: Word Recall Delay	0.33	0.22	0.19	0.11	0.81
	List learning	**Working memory/Executive skills**	**Cognitive control**	**Fluency**	**Memory**

[1] Minimum Residual Method (MINRES) with Promax rotation.

memory/executive skills and cognitive control factors since they are sub-served by frontoparietal connections and activate the anterior cingulate cortex (30,31). One theoretical view is working memory and inhibition are two fundamental processes of cognitive control which posits the integrative, supervisory role of dorsolateral prefrontal cortex in selecting the most relevant responses in a specific situation or task while inhibiting less relevant approaches (32). We found that the cognitive control factor was moderately correlated with working memory/executive skills, reflecting the demands of tests such as pattern comparison and dimensional change on maintaining the rules of these tasks in short term memory while inhibiting less relevant response alternatives (Table 5). Cognitive control was also correlated with list learning which on the CVLT-II is enhanced by a strategic approach such as semantic clustering (a rule for enhancing learning and recall) while inhibiting alternative approaches such as relying exclusively on working memory which is involved on early trials

Table 5. Neuropsychological factor correlations.

Extracted factor	List learning	Working memory/ Executive skills	Cognitive control	Fluency	Memory
List learning	1.00	0.51	0.47	0.32	0.33
Working memory/ Executive skills	0.51	1.00	0.65	0.52	0.24
Cognitive control	0.47	0.65	1.00	0.40	0.16
Fluency	0.32	0.52	0.40	1.00	0.18
Memory	0.33	0.24	0.16	0.18	1.00

and retaining the first few words presented on each trial. Similarly, the correlation of cognitive control with fluency reflects demands on rule adherence (e.g. words beginning with a specific letter) and inhibition (exclusion of proper nouns in recall and response shifting while performing semantic fluency).

Factor 5, consisting of the immediate and delayed word list-learning trials of the BTACT had relatively low correlations with the other neurocognition factors. Those BTACT tasks might have been expected to have a strong relationship with the CVLT-II, given both are word list-learning tests; however, the BTACT list-learning trials and CVLT-II index scores loaded on different factors. The repetition inherent in the five CVLT-II trials (as well as a lack of time pressure) suggests the possibility that these factors reflect different cognitive processes with the BTACT perhaps reflecting more of an attentional/efficiency aspect. Alternatively, this finding may suggest administration variance (telephone as opposed to in-person administration) played a role in the factor loading (33); however, a study of cognitive function in late onset Alzheimer's disease that used both in-person and telephone assessments found no effects of administration variance (34).

It stands to reason that the neuropsychological variables considered would load differently among the five factors according to the assessments' primary measurement and inherent purpose. Previous studies examining the factor structure of a neuropsychology battery support our findings; however, few studies have used the same source population. A confirmatory factor analytic study, which included the NIH Toolbox in 268 healthy adults, age 20–85 years, disclosed a factor structure that is generally consistent with the present findings (35). The list sorting test loaded on a working memory factor, and there was agreement on the other NIH Toolbox tests (dimensional card sorting, flanker inhibitory control, pattern comparison) which loaded on the cognitive control-executive function factor. Similar to our findings, the factor structure reported by Mungas et al. showed that the WAIS-IV symbol search loaded on an executive function factor which we labelled as cognitive control, while the WAIS-IV letter number sequencing loaded on a working memory factor.

Despite similar findings, our factor structure differed in other areas. Mungas et al. found that the WAIS-IV digit span loaded on the executive function factor, while our model suggests this factor loads better on the working memory/executive skills factor. Additionally, the picture sequence memory and BVMTR tests loaded on an episodic memory factor, whereas these tests did not load on any of the extracted factors we identified. Factor analyses of batteries that include memory and other cognitive tests have demonstrated considerable heterogeneity of factor structure, with some memory tasks loading on a common factor in some studies while in other studies loading with other cognitive tests (36). The influence of differences in test selection between this study and Mungas et al. may explain the differences in factor loadings of memory-related tasks. Alternatively, differences in the source populations (healthy community controls vs combat and mTBI exposed Veterans) may account for this difference in factor structure.

There are numerous validated and accepted cognitive assessments used in today's current neuropsychology research; although there is no consensus on a standardized battery for specific populations, the TBI CDEs encourage a relatively uniform approach depending on the severity and chronicity of concussion. The lack of a standardized battery has made it difficult to study the potential impact of concussion on such a variety of cognitive outcomes. However, since CENC incorporated the use of a broad battery of neuropsychological tests, all in accordance with the TBI CDEs, analysing the underlying factor structure of this test battery allows for more readily interpretable findings between concussion exposure and cognitive decline. Though the literature suggests no long-term cognitive sequelae of concussion (1,2,4,37,38), this study will be following participants for a lifetime in an attempt to gauge any long-term impact of repetitive concussions and/or increased risk of neurodegeneration through causal analysis of the extracted factors from this EFA.

Although our findings are encouraging, there are limitations within our study that must be detailed. Although CENC incorporated a compilation of commonly used neuropsychological measures, extracted factors may not be generalizable to other studies that incorporate different neuropsychology assessments and/or are performed on a different source population. Specifically, the median length of time between injury and enrolment in our cohort was 8 years, limiting the generalizability of our findings to more acute mTBI samples. In addition, the sample included both those with and without concussion history. As multiple meta-analytic studies of concussion have revealed no lasting effect on cognitive performance, this may not be an issue. Nonetheless, a larger sample size will allow for comparisons to evaluate any potential differences in factor structures between these groups. Last, we observed a relatively high amount of missing BTACT data due to participants either declining or being unable to participate in the call. To address the high amount of missing data, we performed multiple imputation with predictive mean matching based on performance on all other neurocognition tests. A sensitivity analysis on multiple imputed datasets suggests no effect of missing data imputation on the BTACT loadings.

In summary, this factor analytic study of neuropsychological performance in active duty and veteran participants revealed five factors. Causal analysis of the five extracted factors will help determine if a specific cognitive domain is more sensitive to the late stage effects of mTBI on neurodegeneration. However, these factors will need to be replicated in confirmatory studies with a larger sample.

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Declaration of Interest

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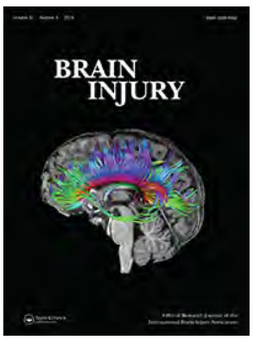
Appendix 16

Chronic Effects of Neurotrauma Consortium (CENC) multicentre study interim analysis: Differences between participants with positive versus negative mild TBI histories



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Chronic Effects of Neurotrauma Consortium (CENC) multicentre study interim analysis: Differences between participants with positive versus negative mild TBI histories

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ABSTRACT

Objectives: Compare characteristics and outcomes of combat-exposed military personnel with positive versus negative mild traumatic brain injury (mTBI) histories.
Setting: Recruitment was from registration lists and ambulatory clinics at four veterans administration hospitals.
Participants: Consented veterans and service members completing initial evaluation by September 2016 (n = 492).
Design: Observational with cross-sectional analyses.
Main measures: Multimodal assessments including structured interviews, record review, questionnaires, neuroendocrine labs and neurocognitive and sensorimotor performance.
Results: In unadjusted comparisons to those absent lifetime mTBI, the mTBI positive group (84%) had greater combat exposure, more potential concussive events, less social support and more comorbidities, including asthma, sleeping problems and post-traumatic stress disorder. They also fared worse on all sensory and pain symptom scores and self-reported functional and global outcomes. They had poorer scores on Wechsler Adult Intelligence Scale-IV coding (processing speed), TMT-B (visual-motor integration and executive function) and two posturography subtests, but were otherwise equal to TBI negative participants on neurocognitive and sensorimotor testing and neuroendocrine levels.
Conclusions: Although differences in characteristics exist which were not adjusted for, participants with historical mTBI have greater symptomatology and life functioning difficulties compared with non-TBI. Performance measures were less dissimilar between groups. These findings will guide further research within this accruing cohort.

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Introduction

Traumatic brain injury (TBI), long recognized as an important source of morbidity in the general population, is considered the 'signature wound' of post-9/11 U.S. military operations (1). Driven by greater use of explosive weaponry by insurgents compared to prior conflicts (2,3), nearly 20% of the more than 2.5 million deployed service members (SMs) since 2003 are identified as TBI survivors (4). As with the civilian sector, the vast majority of these combat-related TBIs are graded as mild TBI (mTBI) or concussion (5).

Up to 20% of concussed individuals experience multiple physical, cognitive, or psychological symptoms that persist beyond 3 months; a condition termed post-concussive syndrome (PCS) (6–8). The prevalence of PCS-like symptoms is especially high among post-9/11 SMs and veterans (9–12). However, the causal pathway between mTBI and PCS remains unclear, confounded by the non-specificity of PCS symptoms and the high rate of comorbidities, with concurrent post-traumatic stress disorder (PTSD) especially common among veterans and SMs (13,14). PCS is poorly understood, and some experts believe it represents misattribution of symptomatology caused by putative factors other than mTBI (13). Later life effects of mTBI are even more controversial, although some evidence points to higher risk of enduring problems with repeated insults (15,16). Concerningly, the effects of mTBIs on recovery from combat and trauma-related comorbidities, on long-term brain functioning, and on risk for developing neurodegeneration, which might include chronic traumatic encephalopathy (CTE), are unknown (17,18). These uncertainties have hindered the advancement of scientifically based treatments to address mTBI late effects.

Limitations in the scientific literature concerning the role of mTBI on long-term health are numerous. Most studies, particularly within military populations, are retrospective and have not adequately addressed the design challenges of valid

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retrospective mTBI identification (19). Documentation from early clinical evaluations, when available, has poor diagnostic accuracy for mTBI (20). Commonly used screening instruments (21,22) are often influenced by other symptoms (23), and have unproven diagnostic accuracy. Individuals may even report illogical, or frankly, contradictory responses, such as endorsing a loss of consciousness but denying a memory gap (24). Unstructured interviews, which could be used to dissect such responses, are limited by the degree of examiner thoroughness, experience, expertise and bias, as well as problems with reproducibility and questionable inter-rater reliability. A range of additional limitations have been noted across studies addressing the question of late effects of mTBI, including small sample size, inadequate comparison groups, and biased sample selection (25). Furthermore, potential confounders and moderators, such as premorbid or comorbid conditions, including substance use, alcohol misuse, chronic pain, PTSD and other psychological/emotional problems, are rarely accounted for adequately (26).

The Chronic Effects of Neurotrauma Consortium (CENC) was established in 2013 via a federal cooperative agreement in response to the National Research Action Plan (27) for improved prevention, diagnosis and treatment of U.S. Veterans and SMs with TBI (see https://cenc.rti.org/). In addition to the centrally coordinated, nationwide, research programming that spans more than 30 academic universities, 15 veterans affairs medical centres (VAMCs) and 3 military treatment facilities (MTFs), the centrepiece of CENC is a multicentre, observational longitudinal study designed to address the research gap of a large, methodologically sound epidemiologic study of SMs and veterans with mTBI history. This study's overarching objectives are: to (1) establish the association of the chronic effects of mTBI, neurodegeneration and common comorbidities, (2) determine whether an mTBI causative effect can be inferred and (3) identify diagnostic and prognostic indicators of neurodegenerative disease and other comorbidities found associated with mTBI. The comorbidities of interest include psychological, neurological (including, memory, seizure, autonomic dysfunction and sleep disorders), sensory deficits (including visual, auditory and vestibular dysfunction), movement disorders, pain (including headache), cognitive and neuroendocrine deficits. The specific objectives of the present interim analysis from this study are to: (1) broadly describe the characteristics (including demographic, military life environment, lifestyle and trait factors) of the initial wave of participants, (2) describe findings on an array of objective and subjective outcomes and (3) explore for differences between the historical mTBI positive and negative groups using univariate statistics to help inform future multivariate adjusted analyses.

Methods

Setting

Combined enrolment and evaluation sites for the CENC multicentre observational study initially included four large VAMCs: Michael E. DeBakey VAMC in Houston, TX; Hunter Holmes McGuire VAMC in Richmond, VA; Audie L. Murphy VAMC in San Antonio, TX; and James Haley VAMC in Tampa, FL. Later, one MTF (Fort Belvoir, VA) was added, and more recently, three additional VAMC enrolment/evaluation sites, in Boston, Minneapolis and Portland were added. Data collected in this report were all from the four original sites. Participants were recruited primarily from mass letter mailing campaigns to registered patients at each hospital and secondarily by advertisements, flyers, community outreach and clinician referrals.

Participants

The intended population is post-9/11 era SMs and veterans who experienced combat situation(s) and have a spectrum of exposure to mTBI, from none to many. Specific inclusion criteria were: (1) history of deployment in operation enduring/Iraqi freedom or related follow-on conflicts, (2) history of combat exposure during deployment as defined by deployment risk and resiliency inventory section D (DRRI-2-D) score > 1 on any item, and (3) > 18 years of age. The deployment risk and resilience inventory-2 (DRRI-2) is a suite of 17 individual scales that assess key deployment-related risk and resilience factors with demonstrated implications for veterans' post-deployment health, with section D containing the 'combat experiences scale' (28). The only exclusion criteria were: (1) history of moderate or severe TBI as defined by either (a) initial Glasgow Coma Scale <13, (b) coma duration > 0.5 h, (c) post-traumatic amnesia duration > 24 h, or (d) traumatic intracranial lesion on head computerized tomography; or (2) history of (a) major neurologic disorder (e.g. stroke and spinal cord injury), (b) major psychiatric disorder (e.g. schizophrenia) with major defined as resulting in a significant decrement in functional status or loss of independent living capacity. Notably, PTSD is not an exclusion criterion. This sample includes individuals who were eligible and consented for the study and completed their initial assessment visit prior to 1 September 2016.

Measures

The following assessments were included in these analyses:

Potential concussive event identification and TBI diagnoses

This study's in-depth structured interview process entailed screening for all potential concussive events (PCEs) during military deployments and across the entire lifetime, including childhood, using a modification of the Ohio State University TBI Identification (OSU TBI-ID) instrument (29). Each PCE identified is then interrogated to determine whether or not it was a true clinical mTBI via a detailed structured interview, the Virginia Commonwealth University retrospective concussion diagnostic interview (VCU rCDI) (30). Each VCU rCDI renders a preliminary TBI diagnosis of mTBI or not mTBI through an embedded algorithm using the structured interview data and based on the DoD/VA common definition of mTBI (31). Every preliminary TBI diagnosis is reviewed and vetted against the unstructured free text portion of the interview and against any found medical documents recorded in proximity to the event (i.e. first responder, emergency

department or in-theatre documentation). Using this process, the site principal investigator (PI) confirms or overrides every preliminary mTBI diagnosis to yield the final diagnosis, mTBI versus not mTBI. If any doubt remains the case is adjudicated by a central diagnosis committee consisting of national experts in TBI. This process is also used to further assess eligibility in terms of whether any PCE was a TBI of greater severity than mild (moderate or severe), in which case the participant was excluded from the study.

Based on responses from the PCE and TBI structured interviews, an index key event and date is established for every participant. Given the military focus of this study, if any diagnosed mTBI was sustained during combat deployment, the worst one is considered the index event. The worst is self-identified by the participant but can be overridden by the site PI if they deem a different combat mTBI as more severe. If no TBIs occurred during combat deployment, then the worst post-deployment mTBI becomes the index event. Alternatively, if both deployment and post-deployment TBI history was entirely negative, then a predefined 'sham TBI' index date is assigned using the self-identified worst PCE during combat deployment (in cases of no PCEs during deployment, the midpoint date of deployment(s) is used). Longitudinal follow-up visits are timed relative to this index date but are not included in these analyses. Further details on PCE and TBI mapping are reported in an earlier publication that focused on this study's development and methods (32).

Primary outcome measure

The National Institute of Health (NIH) toolbox is a standard set of well-validated and nonproprietary neurologic measures intended to represent common currency for use across different health conditions in the range 3–85 years of age (33). Its computerized cognition battery is intended to capture important cognitive constructs sensitive to brain functions, including the effects of TBI, in a highly efficient manner (30 min to administer) (34). Test domains are: vocabulary and reading (picture vocabulary), executive functions and cognitive flexibility (dimensional change card sort), inhibitory control and attention (Flanker inhibitory control and attention test), episodic memory (picture sequence memory test), working memory (list sorting) and processing speed (pattern comparisons). A composite score from the NIH toolbox cognition battery was chosen as the primary outcome for the present study because it is more reliable and sensitive than the individual tests. It is a continuous measure, with a mean of 100 and a standard deviation of 15, with lower scores that indicate reduced cognitive performance.

Secondary outcome measures, comorbidities and covariates

A wide array of questionnaires, examinations and performance tests was selected to sample various neurologic, cognitive and psychological domains. Assessments included: PTSD structured interviews, neurocognitive, neuroendocrine, motor, sensory and vestibular testing and a large battery of questionnaires covering these domains as well as health, well-being and functional status. Secondary outcomes, while focussing on neurobehavioural findings suggestive of a neurodegenerative disorder, such as CTE, are also meant to capture all known and suspected long-term effects of TBI. The number of data collection instruments are extensive, so they are presented in concise table format with covariates, mediators and confounders in Table 1, and secondary outcome measures in Table 2. Most included instruments are part of the TBI common data elements (TBI CDEs) (35). The earlier noted methods paper has references on all measures that are not TBI CDEs (32). Based on purported increased risk for neuroendocrine disorders after mTBI and published screening recommendations, serum testosterone, growth factor and thyroid stimulation hormone were measured (36). Based on firm evidence of abnormal findings acutely but not chronically after concussion (37), balance was measured by computerized dynamic posturography (CDP) using the sensory organization test (SOT) protocol on the NeuroCom Smart Balance Master (NeuroCom; NeuroCom International, Inc, Clackamas, OR). The SOT generates equilibrium scores that compare the largest anterior-posterior movements to a theoretical limit across six sensory condition tasks: (1) eyes open with a fixed surface and visual surroundings; (2) eyes closed with a fixed surface; (3) eyes open with a fixed surface and sway referenced visual surroundings; (4) eyes open with a sway referenced surface and fixed visual field; (5) eyes closed with a sway referenced surface; and (6) eyes open with a sway referenced surface and visual surroundings. Average

Table 1. Synopsis of study independent variables, influencing factors and comorbidities.

Domain	Measure
Health condition of interest: PCE and mTBI history and indexing	
	OSU TBI-ID modified
	VCU rCDI (B & G versions)
	Supplement with DoD or other injury reports if available
Personal fixed factor	
	Demographic: CDC Behavioural Risk Factor Surveillance System (BRFSS)
	Premorbid cognition estimate: Test of Premorbid Functioning (TOPF)
	Educational history: TBI Model Systems Form 1 modified excerpt
	Past health history: BRFSS
Environmental factor	
	Ethnicity: BRFSS
	Military branch and length of service: DVBIC 15-year study
	Combat exposure: Deployment Risk and Resiliency Inventory, Version 2, Section D; Combat Experiences (DRRI-2-D)
	Social support: DRRI-2-Section O, Post-deployment Social Support Scale (DRRI-2-O)
	Disability compensation: VA records and self-report
Modifiable factor	
	Alcohol use: Alcohol Use Disorders Test-Consumption (AUDIT-C)
	Substance abuse: Drug Abuse Screening Test 10 item version (DAST10)
	Effort: Medical Symptom Validity test (MSVT)
	Symptom exaggeration: Mild Brain Injury Atypical Symptoms Scale (mBIAS)
	Resiliency: TBI Quality-of-Life (TBI-QOL) Resiliency Module
	Self-Efficacy: General Self-Efficacy (GSE) Scale
	Tobacco use: BRFSS
	Exercise: BRFSS
Comorbidities:	
	PTSD diagnosis: Mini-international Neuropsychiatric Interview DSM5 version PTSD module (MINI)
	PTSD symptom severity: PTSD Checklist for DSM5 (PCL5)
	Depression: Patient Health Questionnaire Depression Scale (PHQ-9)
	Pain: Toolbox numerical scale, TBI-QOL pain interference module
	Headache: Headache Impact Test Short Form (HIT-6)
	Sleep disorder: Pittsburgh Sleep Quality Index (PSQI)
	Sleep apnoea: Modified STOP-BANG questionnaire
	Medical conditions (HTN, DM, etc.): BRFSS
	BMI/obesity: weight and height measurements

TBI CDE = NINDS TBI common data element.

Table 2. Secondary outcome measures.

Domain
Description/measure
Physiologic
Neuroendocrine disorder: serology (TSH, IGF-1, testosterone)
Symptom scales
Post-concussive syndrome: NSI
Depression: PHQ9
Other psychological distress: TBI-QoL modules (e.g. emotional-behavioural control, anger and anxiety)
Functional Cognition: TBI-QoL modules (e.g. general concerns and executive function)
Neurosensory: Dizziness Handicap Inventory, Hearing Handicap Inventory, Tinnitus Functional Index
Cognitive performance measures
Emerging comprehensive cognitive battery: NIH Toolbox (see primary measure description)
Working memory, processing speed: Wechsler Adult Intelligence Scale 4th version (WAIS-IV)
Visual processing, executive function: Trail Making Test (TMT) Part A&B
Auditory memory and learning: California Verbal Learning Test (CVLT-II)
Visual memory: Brief Visuospatial Memory Test-Revised (BVMT-R)
Verbal fluency: Delis-Kaplan Executive Function System (D-KEFS)
Motor-integrative performance measures
Fine motor; Grooved Pegboard
Gait; NIH Toolbox 4-Metre Walk Gait Speed Test
Motor Examination Index from Unified Parkinson's Disease Rating Scale (UPDRS)
Postural Stability (All sites except Houston): Computerized Dynamic Posturography (CDP)
Sensory Systems Performance
Smell: Brief Smell Identification Test (BSIT)
Central auditory processing: SCAN 3A
Visual acuity: Snellen chart
Verticality: subjective visual verticality test (SVV)
Activity, participation and global outcome
Health care utilization
Economic impact; EuroQol GROUP 5 dimension 5 level version quality-of-life (EQ-5D-5L)
Life participation; TBI-QOL module
Military Participation: Community Reintegration of Injured Service members (CRIS) items
Employment: TBI-MS employment module
Life Satisfaction; Satisfaction with Life Scale (SWLS)

equilibrium scores ranging from 0 (touching a support surface, shifting feet or falling) to 100 (little or no sway) are generated from three trials on each condition. The overall composite equilibrium score is a weighted average of these six scores (conditions 1 and 2 are weighted 1/3 as much as conditions 3 through 6). Additional data collected by the overarching study but not included in these analyses include brain structural and functional imaging, audiometry, computerized eye tracking, biomarkers, salivary cortisol and brain electrophysiology (32).

Statistical methods

These unadjusted analyses explored potential differences in attributes and outcomes between those with and without mTBI. Assessment data identified as unreliable or incomplete by study administrators were removed from all analyses. All cognitive performance scores were considered to be non-credible and were excluded from analyses if the participant did not complete (n = 8) or failed (n = 59) the Medical Symptom Validity test (MSVT) using the developer's recommended cut-point (38). Additionally, if the average equilibrium scores on condition 1, 2 or 3 (easier conditions) were higher than on condition 5 or 6 (more challenging conditions) then effort on balance testing was considered non-credible (39), and those participants were excluded (n = 6) from SOT analysis. Based on data type and distribution, analysis of variance, Kruskal–Wallis, Poisson regression, Chi-square and Wilcoxon–Mann–Whitney tests were used. p-values were calculated to provide a descriptive assessment of potential differences for further exploration, but should not be inferred as conclusive, formal tests of hypotheses. The false discovery rate (FDR) method was used to adjust the criteria to reach statistical significance to correct for multiple significance testing. While other common p-value adjustment methods control the familywise error rate (FWER), FDR controls the expected proportion of erroneous rejections among all hypotheses tested. This method is more powerful compared to other approaches that control the FWER when the number of rejected hypotheses increases (40).

Results

The flow of participants from recruitment until completion of the initial study evaluation is shown in the CONSORT diagram (Figure 1). A total of 1216 combat experienced SMs and veterans were screened for enrolment with 538 individuals enrolled at the end of August 2016. Of the 538, 492 completed their initial visit and are included in this interim analysis.

Among this sample's 492 participants, 1150 VCU-CDIs were conducted and completed, with the TBI diagnosis algorithm confirmed in 98.1% and overridden in only 1.9%. Using the final interview-based diagnostic determinations, 78 participants were totally absent any clinical TBI of any severity during their life and formed the TBI negative group. The remaining participants (N = 414, 84%) all had sustained at least one lifetime mTBI, but no moderate or severe TBI, and constituted the mTBI positive group. This group had a median 2 lifetime mTBIs (range 1–12), and were assessed a median 14.7 years after their earliest mTBI, and a median 8.2 years after their most recent mTBI.

Summary data on demographics, military life environmental factors and health/lifestyle/trait factors are displayed in Tables 3, 4 and 5, respectively, across the two groups considered, namely mTBI positive and mTBI negative. Compared to the TBI negative group, mTBI positive participants had greater combat exposure (DRRI-2-D), more PCEs, and a weaker social support network (DRRI-2-O). The mTBI positive group also contained a greater proportion of individuals leaving the military for medical reasons, having more PTSD (ever treated) as well as a higher prevalence of asthma and poorer sleep pattern (PSQI). While not reaching statistical significance, there was a trend toward more arthritis, underemployment and a greater risk of sleep apnoea (modified STOP-BANG), as well as less resilience and self-efficacy within the mTBI group. Notably, there was no statistical difference between groups on the proportion of invalid symptom reporting (Mild Brain Injury Atypical Symptoms Scale failures) or invalid neuropsychological test effort (MSVT failures). There was also no difference in estimated premorbid

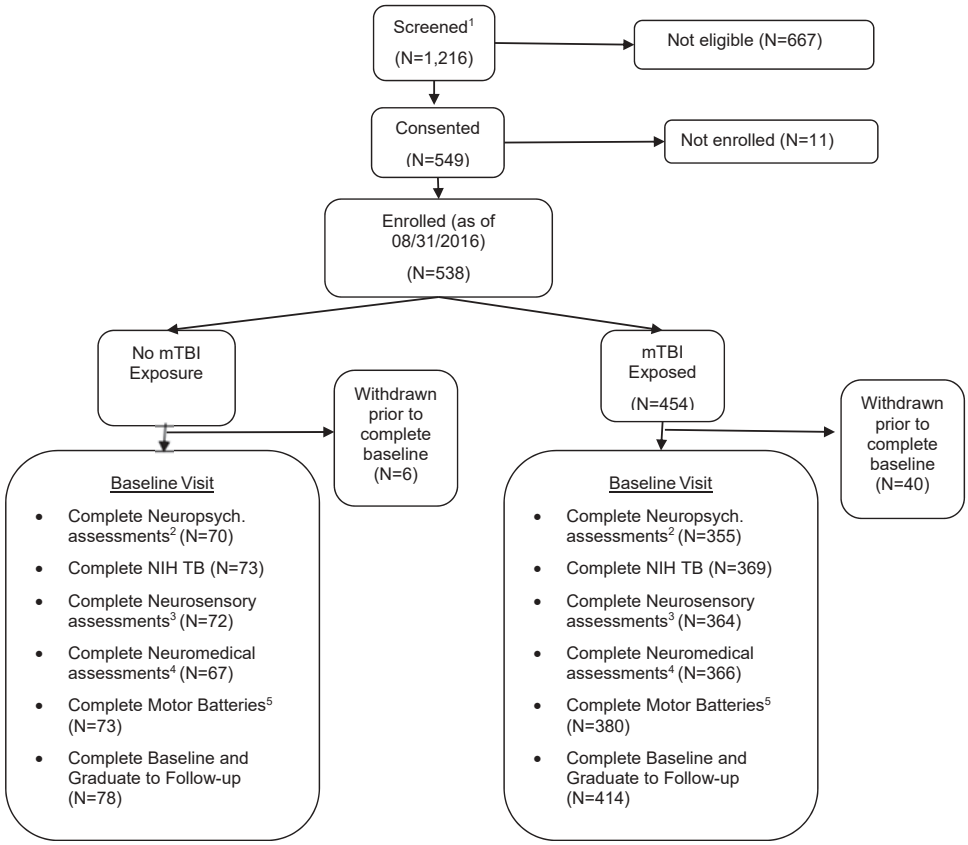

Figure 1. Participant flow diagram.

[1] Screening data collected from all sites starting July 2015;[2] MSVT, BVMT-R, Grooved Pegboard, TMT, WAIS-IV, MSVT, SVV, DKEFS-VF, BVMT-R, TOPF, CVLT-II and BSIT;[3] Visual Acuity, Audiometry and SCAN-3;[4] Vital Signs, Blood and Saliva;[5] CDP, BESS, UPDRS and 4-Metre Walk Gait Test.

cognition (TOPF), self-reported alcohol misuse, drug misuse, tobacco use or learning disabilities.

Most performance measures lacked between group differences. Among the performance tests included in the analyses, differences appeared on only four subtests (Table 6). Specifically, the mTBI positive group had poorer scores within the traditional neurocognitive battery (when comparing demographically corrected norms) on Wechsler Adult Intelligence Scale-IV (WAIS-IV) coding (median scaled score 9.0 vs. 10.0) and trail making test B (median *T*-score 49.0 vs. 51.0), as well as on CDP SOT conditions 2 (eyes closed; mean 87.1 vs. 89.8) and 3 (visual surround sway; 87.2 vs. 89.6, respectively).

No group differences emerged on the primary outcome of interest, the NIH toolbox cognition battery (Table 7), nor were there any differences on visual acuity, central auditory processing (SCAN-3A), walking speed (4 m walk test), or fine motor speed/dexterity (Grooved Pegboard); see online Appendix for complete tabular results. Additionally, the mTBI groups had equivalent results on neuroendocrine labs (e.g. thyroid stimulation hormone, testosterone and insulin-like growth factor), and rates of both self-reported and medical record coded epilepsy (see online Appendix).

In contrast to the performance tests, both sensory and pain symptom reporting (Table 8) and self-reported psychological, functional and global status ratings (Table 9) were universally worse in the mTBI positive group. These self-report measures encompassed neuropsychiatric and multiple emotional domains, pain, headache, tinnitus, dizziness and hearing problems, life satisfaction, functional status, social role participation and overall health status.

Discussion

This study addresses an important research gap for scientific evidence of chronic residual effects from mTBI within the post-9/11 era military population, using a large sample size and wide-ranging assessments. A methodologic strength relative to existing literature are the methods used to establish our non-TBI comparators. Prior military and veterans studies employing non-TBI military combat-exposed comparators are uncommon, and those doing so typically consider only an index event(s). The few studies in this population that have considered the entire lifetime of PCEs (41–44), generally have used a less rigorous screening interview method than ours. Our non-TBI comparators are confirmed as definitively absent any lifetime TBI, after carefully assessing for all potential TBIs, not only during military deployment but also through the entire lifespan. The non-TBI comparators are from the same combat-exposed sample as the mTBI positive participants; they were recruited in the same manner, with the same eligibility criteria, thereby minimizing sampling bias. Additionally, the multicentre design further minimizes sampling bias of both the TBI and non-TBI participants, by representing a geographically and culturally broad population of post-9/11 combat veterans and SMs.

Table 3. Demographics by TBI exposure.

Characteristic	Study group: TBI (*N* = 414)	Study group: No TBI (*N* = 78)	Adjusted *p*-value[a]
Gender[C]			
Male	365 (88.2%)	62 (79.5%)	0.0996
Female	49 (11.8%)	16 (20.5%)	
Race[C]			
White	274 (66.2%)	54 (69.2%)	0.8433
African-American	97 (23.4%)	18 (23.1%)	
Other	43 (10.4%)	6 (7.7%)	
Ethnicity[C]			
Not Hispanic or Latino	315 (76.1%)	54 (69.2%)	0.3345
Hispanic or Latino	97 (23.4%)	24 (30.8%)	
Not sure	2 (0.5%)	0 (0.0%)	
Education[W]			
Some high school	1 (0.2%)	2 (2.6%)	0.6485
High school graduate	71 (17.1%)	9 (11.5%)	
Some college	192 (46.4%)	36 (46.2%)	
College Graduate	150 (36.2%)	31 (39.7%)	
Currently in the military?[C]			
Yes	25 (6.1%)	7 (9.1%)	0.5190
No	387 (93.9%)	70 (90.9%)	
Most recent service rank[C]			
Officer	49 (12.0%)	17 (22.1%)	0.0556
Enlisted	361 (88.0%)	60 (77.9%)	
Age at initial visit[KW]			
Median (IQR)	36.0 (31.0, 47.0)	40.5 (32.0, 50.0)	0.3036
Current marital status			
Married	244 (58.9%)	43 (55.1%)	0.6807
Not married	170 (41.1%)	35 (44.9%)	
Currently employed[C]			
Yes	192 (46.7%)	46 (59.7%)	0.0959
No	219 (53.3%)	31 (40.3%)	
Years since index date[T]			
Mean (StdDev)	9.0 (4.5)	8.9 (4.5)	0.8837
Years since first TBI			
Mean (StdDev)	18.0 (11.6)	–	
Years since last TBI			
Mean (StdDev)	10.0 (8.8)	–	

C = Chi-square test; T = *T*-Test; W = Wilcoxon–Mann–Whitney Test; KW = Kruskal–Wallis.
[a] False discovery rate (FDR) method used to adjust *p*-value.

Table 4. Military life environmental factors.

Characteristic	Study group: TBI (*N* = 414)	Study group: No TBI (*N* = 78)	Adjusted *p*-value[a]
Service branch[C]			
Air force	38 (9.3%)	11 (14.3%)	0.6721
Army	285 (69.5%)	51 (66.2%)	
Marines	60 (14.6%)	9 (11.7%)	
Navy	27 (6.6%)	6 (7.8%)	
Number of years in military[KW]			
Median (IQR)	12.0 (6.0, 21.0)	14.0 (6.0, 23.0)	0.6142
Combat exposure intensity[KW]			
Median (IQR)	38.0 (27.0, 52.0)	28.5 (20.0, 36.0)	0.0005
Number combat deployments[P]			
Median	2.0	1.0	0.1645
Q1, Q3	1, 3	1, 3	
Potential concussive event exposures[P,1]			
Median	3.0	1.0	0.0005
Q1, Q3	2, 5	0, 3	
Controlled detonations exposures[P]			
Median	7.0	3.5	0.0005
Q1, Q3	0, 45	0, 24	
Post-deployment social support[KW]			
Median (IQR)	38.0 (33.0, 44.0)	41.0 (36.0, 47.0)	0.0307
Reason leave military[C]			
Medical reason	123 (31.8%)	9 (12.9%)	0.0058
Other Reason	264 (68.2%)	61 (87.1%)	
Service connection disability[C,2]			
Yes	326 (84.2%)	52 (74.3%)	0.0632
No	56 (14.5%)	18 (25.7%)	

C = Chi-square test; KW = Kruskal–Wallis; P = Poisson regression.
p-value for Poisson regression is testing the null hypothesis that the regression coefficient is equal to zero.
[a] False discovery rate (FDR) method used to adjust *p*-value.
[1] Excludes controlled detonation exposures.
[2] Service connected disability self-reported in the Military Status and Mental Health (DVBIC) form.
Don't know responses not included so variable total counts may not add up to 100%.

The chief findings of this study are higher widespread symptom levels, poorer psychological health, and poorer perceived overall health and functional status among combat-exposed SMs and veterans with historical mTBI(s) versus those absent TBI. This generally agrees with past research in this population using no or less rigorous non-TBI comparators (45–47). Importantly though, past research is inconsistent on whether mTBI history remains related to outcomes when including other covariates, especially psychologic health (14,42,48), and the current study had differences in psychological and many other characteristics between TBI positive and negative groups. While this prevents firm conclusions about attribution, it does indicate that historical mTBI serves as a marker of symptom distress and perceived life functioning difficulties, and that further assessment for therapeutic opportunities is warranted in such individuals. From a research perspective, there clearly is need for further and more long-term study to better understand mTBI chronicity, once considered a benign and transient medical condition.

In contrast to the marked differences in self-report outcomes, performance test outcomes were more similar between the two groups analysed. This pattern is consistent with several prior investigations that showed subjective greater than objective abnormalities in the post-deployment population (46,49,50). The specific performance tests that did show mTBI group differences in unadjusted analysis were WAIS-IV coding, TMTB and computerized posturography. Importantly, the scores of each within the mTBI positive group were above the range generally considered impaired, raising doubt about clinical significance. Nevertheless, these findings offer insights for future research. WAIS-IV coding is typically interpreted as a measure of visual processing speed and is known to be sensitive to the effects of mTBI (51). Trail Making B, designed to test executive function but also a measure of visual-motor processing speed, is also known to be sensitive to the effects of mTBI. Postural instability is also a well described mTBI effect and has been shown to be abnormal chronically in another post-deployment sample (52). Like the self-report outcomes, these performance test differences were shown associated with historical mTBI, but cannot be concluded as mTBI effects due to the differences in other characteristics of the sample. This caveat is further emphasized by the use of univariate statistics in this analysis, as the primary objective was to guide future multivariate adjusted analyses.

The observed differences in demographic and other characteristics between our mTBI groups highlight the challenges of establishing comparable control participants in this population. Within our target post-9/11 era military population, we used the eligibility criteria to select only individuals with

Table 5. Health, lifestyle and trait factors.

Characteristic	Study group: TBI (*N* = 414)	Study group: No TBI (*N* = 78)	Adjusted *p*-value[a]
Current PTSD on MINI[W]			
Not experience traumatic event	50 (12.3%)	30 (39.5%)	0.0005
Full DSM-5 criteria not met	217 (53.4%)	36 (47.4%)	
Positive PTSD	130 (32.0%)	10 (13.2%)	
Ever treated for PTSD[C]			
Yes	228 (55.7%)	20 (26.3%)	0.0005
No	181 (44.3%)	56 (73.7%)	
Ever treated for depression[C]			
Yes	181 (44.3%)	26 (33.8%)	0.1941
No	228 (55.7%)	51 (66.2%)	
Other neurological disorder[C]			
Yes	25 (6.1%)	6 (7.7%)	0.6969
No	387 (93.9%)	71 (91.0%)	
High cholesterol[C]			
Yes	154 (37.4%)	30 (38.5%)	0.9509
No	247 (60.0%)	47 (60.3%)	
High blood pressure[W]			
Yes	158 (38.3%)	22 (28.2%)	0.2073
Borderline high	9 (2.2%)	2 (2.6%)	
No	245 (59.5%)	54 (69.2%)	
Arthritis[C]			
Yes	180 (43.7%)	23 (29.5%)	0.0611
No	228 (55.3%)	54 (69.2%)	
Asthma[C]			
Yes	81 (19.7%)	5 (6.4%)	0.0170
No	328 (79.6%)	73 (93.6%)	
Heart attack[C]			
Yes	13 (3.2%)	0 (0.0%)	0.2310
No	399 (96.8%)	78 (100.0%)	
COPD[C]			
Yes	27 (6.6%)	1 (1.3%)	0.1645
No	382 (92.7%)	76 (97.4%)	
Diabetes[W]			
Yes	17 (4.1%)	5 (6.4%)	0.9509
Pre-diabetes	11 (2.7%)	0 (0.0%)	
No	383 (93.0%)	73 (93.6%)	
Any physical activity last month[C]			
Yes	309 (75.0%)	62 (79.5%)	0.5858
No	103 (25.0%)	16 (20.5%)	
PSQI[W]			
Good sleep	61 (15.4%)	27 (35.1%)	0.0005
Poor sleep	334 (84.6%)	50 (64.9%)	
Modified STOP-BANG risk[W,1]			
Low	132 (33.5%)	34 (44.7%)	0.0684
Intermediate	61 (15.5%)	14 (18.4%)	
High	201 (51.0%)	28 (36.8%)	
General self-efficacy (GSE) scale[KW,2]			
Median (IQR)	31.0 (28.0, 35.0)	32.0 (30.0, 36.0)	0.0555
TBI-QoL: resilience[KW,3]			
Median (IQR)	33.0 (29.0, 39.0)	36.5 (32.0, 41.0)	0.0569
Current smoker[C]			
Yes	56 (13.6%)	11 (14.1%)	0.9476
No	356 (86.4%)	67 (85.9%)	
DAST-10 drug use problem[W]			
No problem	346 (84.8%)	69 (88.5%)	0.5850
Mild problem	52 (12.7%)	8 (10.3%)	
≥Moderate problem	9 (2.2%)	1 (1.3%)	
AUDIT-C; hazardous alcohol use[C]			
Yes	146 (35.6%)	24 (30.8%)	0.6007
No	264 (64.4%)	54 (69.2%)	
mBIAS validity[C]			
Pass	400 (98.3%)	78 (100.0%)	0.4285
Fail	7 (1.7%)	0 (0.0%)	
MSVT[C]			
Pass	356 (87.3%)	69 (90.8%)	0.5827
Fail	52 (12.7%)	7 (9.2%)	
Ever diagnosed with learning disability in school[C,4]			
Yes	44 (10.8%)	5 (6.5%)	0.4378
No	365 (89.2%)	72 (93.5%)	
TOPF score[T,5]			
Mean (StdDev)	99.1 (11.4)	99.6 (11.9)	0.8050
BMI category[C]			
Normal (18.5 < 25)	58 (14.2%)	12 (15.6%)	0.7693
Overweight (25 < 30)	158 (38.6%)	32 (41.6%)	
Obese class I (30 < 35)	123 (30.1%)	24 (31.2%)	
Obese class II (35 < 40)	40 (9.8%)	7 (9.1%)	
Obese class III (>40)	30 (7.3%)	2 (2.6%)	

C = Chi-square test; T = *T*-Test; W = Wilcoxon–Mann–Whitney test; KW = Kruskal–Wallis.

[a] False discovery rate (FDR) method used to adjust *p*-value.

[1] A modified STOP-BANG assessment was used. Results should not be compared against the published STOP-BANG assessment.

[2] GSE total score derived by summing all responses, where 'Not at all true' = 1 and 'Exactly true' = 4. Higher score indicative of greater self-efficacy.

[3] Score range is 10–50; higher scores indicate greater resilience.

[4] Includes ADHD, Dyslexia, Autism and Other.

[5] Mean is 100 and SD is 15 (score of 100 shows ability that is average compared to similar demographic group). Higher score indicates better performance.

Don't know responses not included so variable total counts may not add up to 100%.

Table 6. Performance measures with group differences.

Characteristic	Study group: TBI (*N* = 414)	Study group: No TBI (*N* = 78)	Adjusted *p*-value[a]
WAIS-IV coding[KW,1,2]			
N	355	68	
Median (IQR)	9.0 (8.0, 11.0)	10.0 (8.5, 12.0)	0.0170
Trail making test B[KW,2]			
N	356	69	
Median (IQR)	49.0 (43.0, 56.0)	51.0 (46.0, 59.0)	0.0468
CDP SOT condition 2[T,3,4,5,6]			
N	272	49	
Mean (StdDev)	87.1 (8.6)	89.8 (3.7)	0.0054
CDP SOT condition 3[T,3,4,5,6]			
N	272	49	
Mean (StdDev)	87.2 (8.9)	89.6 (3.7)	0.0214

T = *T*-Test; KW = Kruskal–Wallis.

[a] False discovery rate (FDR) method used to adjust *p*-value.

[1] Score ranges from 1 to 19. Mean is 10 and SD is 3 (score of 10 shows ability that is average compared to similar demographic group).

[2] Excludes MSVT failures (*n* = 59) and non-completers (*n* = 8).

[3] Score ranges from 0 to 100. Mean is 50 and SD is 10 (score of 50 shows ability that is average compared to similar demographic group).

[4] Score of 100 represents perfect stability, a score of 0 indicates a loss of balance.

[5] Test conducted at San Antonio, Tampa and Richmond sites only.

[6] Excludes 6 subjects with invalid effort (average score on condition 1, 2, or 3 higher than condition 5 or 6).

combat exposure without regard for mTBI status. To further avoid sampling bias, we focused recruitment efforts outside of TBI or post-deployment clinics. Despite this, multiple differences in military life, health comorbidities, lifestyle and trait factors between the historical mTBI positive and negative groups existed. Some of these may simply reflect differences in risk for sustaining trauma. For example, the mTBI positive group had a higher level of combat exposure and greater number of lifetime PCEs, and although not statistically significant, tended to have higher proportion of males and enlisted rank military service members (SMs). Enlisted personnel are more likely than officers to be on the front lines of combat. Males are not only more likely to serve in more combat intense roles than females but are well known to be greater risk takers in general (53). However, it is possible that these variables have additional influences on our outcomes

Table 7. NIH toolbox cognitive performance.[1]

Characteristic	Study group: TBI (*N* = 414)	Study group: No TBI (*N* = 78)	Adjusted *p*-value[a]
NIH TB: dimensional change card sort computed score[KW,1,2]			
N	321	66	
Median (IQR)	8.1 (7.4, 8.8)	8.1 (7.6, 8.9)	0.6925
NIH TB: flanker inhibitory control computed score[KW,1,2]			
N	324	65	
Median (IQR)	8.1 (7.4, 9.0)	8.3 (7.4, 9.1)	0.6691
NIH TB: list sort working memory raw score[KW,1,3]			
N	323	65	
Median (IQR)	18.0 (16.0, 20.0)	18.0 (16.0, 20.0)	0.4456
NIH TB: pattern comparison raw score[KW,1,4]			
N	321	66	.
Median (IQR)	54.0 (44.0, 66.0)	51.5 (41.0, 65.0)	0.6013
NIH TB: picture sequence memory raw score[KW,1,5]			
N	319	65	
Median (IQR)	507.7 (434.4, 573.9)	515.1 (406.2, 582.9)	0.9509
NIH TB: picture vocabulary computed score[KW,1,6]			
N	327	66	.
Median (IQR)	1724.0 (1607.0, 1831.0)	1727.5 (1588.0, 1864.0)	0.9509
NIH TB: fluid composite[KW,1,7,8]			
N	310	64	.
Median (IQR)	94.6 (80.6, 109.3)	93.1 (79.6, 112.1)	0.8808

KW = Kruskal–Wallis.
[a] False discovery rate (FDR) method used to adjust *p*-value.
[1] Excludes MSVT failures (*n* = 59) and non-completers (*n* = 8); also excludes 30 subjects not administered NIH Toolbox during study start-up phase.
[2] Score range is 0–10; higher scores indicate better performance.
[3] Score range is 0–26; higher scores indicate better performance.
[4] Score range is 0–130; higher scores indicate better performance.
[5] Score range is 0–34; higher scores indicate better performance.
[6] Score range is 200–2000; higher scores indicate better performance.
[7] Mean is 100 and SD is 15 (score of 100 shows ability that is average compared to similar demographic group). Higher score indicate better performance.
[8] Composite measure includes: Flanker Inhibitory Control and Attention, Dimensional Change Card Sort, Picture Sequence Memory, List Sorting Working Memory and Pattern Comparison Process Speed. Score near 100 indicate ability that is average compared with others in age group.

Table 8. Sensory and pain symptom scales.

Characteristic	Study group: TBI (*N* = 414)	Study group: No TBI (*N* = 78)	Adjusted *p*-value[a]
Hearing handicap index (HHI)[W]			
No hearing problems lately	194 (47.8%)	60 (76.9%)	0.0005
No handicap	50 (12.3%)	4 (5.1%)	.
Mild-moderate handicap	104 (25.6%)	12 (15.4%)	.
Severe handicap	58 (14.3%)	2 (2.6%)	.
Tinnitus functional index (TFI)[W].			
No Tinnitus over the past week	132 (32.5%)	36 (46.2%)	0.0303
Not a problem	49 (12.1%)	12 (15.4%)	.
Small problem	61 (15.0%)	9 (11.5%)	.
Moderate problem	76 (18.7%)	10 (12.8%)	.
Big problem	61 (15.0%)	8 (10.3%)	.
Very big problem	27 (6.7%)	3 (3.8%)	.
Dizziness handicap index (DHI)[W].			
No dizziness lately	210 (51.6%)	63 (80.8%)	0.0005
No handicap	84 (20.6%)	8 (10.3%)	
Mild handicap	105 (25.8%)	6 (7.7%)	
Moderate handicap	8 (2.0%)	1 (1.3%)	
Pain intensity[KW,1,2]			
N	211	50	
Median (IQR)	5.0 (3.0, 6.0)	3.0 (1.0, 5.0)	0.0005
TBI-QoL: pain interference[KW,3]			
N	369	72	
Median (IQR)	24.0 (15.0, 33.0)	16.0 (10.5, 20.0)	0.0005
Headache impact test (HIT-6)[W]			
No headaches lately	119 (29.2%)	43 (55.8%)	0.0005
Little to no impact	22 (5.4%)	10 (13.0%)	
Some impact	44 (10.8%)	5 (6.5%)	
Substantial impact	50 (12.3%)	5 (6.5%)	
Very severe impact	172 (42.3%)	14 (18.2%)	

W = Wilcoxon–Mann–Whitney test; KW = Kruskal–Wallis.
[a] False discovery rate (FDR) method used to adjust *p*-value.
[1] 0 = no pain; 10 = worst imaginable pain; pain intensity measure was added later in the study resulting in fewer completions.
[2] Pain intensity was added during year-2 of study enrolment, thus higher rate of missing values.
[3] Score range is 10–50; higher scores indicate worse pain interference.

beyond mTBI risk elevation, as either a confounder, covariate, mediator or moderator. Their differences will need to be carefully considered in future studies using multivariate statistical methods.

Three symptom outcomes analysed in this study are of special note; PTSD, depression and pain. The higher rate of PTSD and greater pain impairment among mTBI participants provides further evidence of the polytrauma clinical triad described in prior investigations (9,54,55). While these associations could stem from the same factors that elevate risk for traumatic events in general, these comorbid conditions may also influence the causal pathway connecting mTBI with later life difficulties. Seen in this context, they may be considered as both outcomes (dependent variable) and explanatory factors (independent or covariate or mediator). For example, PTSD and pain could both impact sleep quality and directly or indirectly be contributing to the poorer sleep measures in the TBI group, and vice-versa (56). Depression is also well known to be interrelated with mTBI and outcomes, but with an uncertain place in the causative pathway (57,58). Clearly the role that mTBI may play with these and other comorbidities remains uncertain and in need of further research including multivariate and longitudinal modelling in this growing CENC cohort.

An inherent limitation of this study is that the univariate statistics applied do not adjust the relationship between mTBI history and outcomes for other suspected influencers, most importantly psychological factors such as depression and PTSD. Thus, the present findings on the association of mTBI to symptom and performance outcomes should be considered preliminary, and future multivariate statistical modelling is planned for this growing cohort using information gained here as a guide. Another limitation is the retrospective identification of the main insult of interest, mTBI, which is unavoidable given the high incidence of mTBI during childhood, adolescence and young adulthood. Nonetheless, our careful, structured interview process represents a significant improvement over much of the existing literature. Although our non-TBI group represents a more valid comparator than prior research, differences in many other attributes confounded our outcome comparisons. Additionally, we limited these analyses to dichotomous mTBI group comparisons, rather than considering dose effect, such as number and severity of mTBIs and post-mTBI time duration.

Table 9. Psychological, functional and global status ratings.

Characteristic	Study group: TBI (*N* = 414)	Study group: No TBI (*N* = 78)	Adjusted *p*-value[a]
PTSD checklist DSM5 version (PCL-5)[KW,1]			
Median (IQR)	29.0 (16.0, 48.0)	15.0 (6.0, 35.0)	0.0005
PHQ-9: depression severity[W]			
None measured	25 (6.2%)	11 (14.5%)	0.0005
Minimal	76 (18.9%)	27 (35.5%)	
Mild	116 (28.8%)	18 (23.7%)	
Moderate	99 (24.6%)	13 (17.1%)	
Moderately severe	51 (12.7%)	4 (5.3%)	
Severe	36 (8.9%)	3 (3.9%)	
TBI-QoL: anger[KW,2]			
N	373	71	
Median (IQR)	21.0 (14.0, 29.0)	16.0 (12.0, 24.0)	0.0048
TBI-QoL: anxiety[KW,3]			
N	374	70	
Median (IQR)	23.0 (16.0, 30.0)	17.0 (12.0, 23.0)	0.0005
TBI-QoL: Emot/Behav dyscontrol[KW,4]			
N	372	68	
Median (IQR)	23.0 (18.0, 29.0)	20.0 (14.5, 24.0)	0.0052
Satisfaction with life scale (SWLS)[W]			
Extremely dissatisfied	45 (11.1%)	5 (6.5%)	0.0143
Dissatisfied	71 (17.5%)	11 (14.3%)	
Below average satisfaction	97 (23.9%)	9 (11.7%)	
Average satisfaction	78 (19.2%)	21 (27.3%)	
High satisfaction	71 (17.5%)	14 (18.2%)	
Very high satisfaction	44 (10.8%)	17 (22.1%)	
TBI-QoL: participate social roles[KW,5]			
N	365	70	
Median (IQR)	30.0 (24.0, 37.0)	36.0 (28.0, 42.0)	0.0307
EQ5D5L: functional status index[KW,6]			
Median (IQR)	0.8 (0.6, 0.8)	0.8 (0.8, 0.9)	0.0005
EQ5D5L: overall health VAS rating[KW,7]			
Median (IQR)	70.0 (60.0, 80.0)	80.0 (70.0, 86.0)	0.0025
BRFSS overall health status[W]			
Excellent	18 (4.4%)	7 (9.0%)	0.0073
Very good	86 (20.9%)	19 (24.4%)	
Good	158 (38.3%)	39 (50.0%)	
Fair	135 (32.8%)	13 (16.7%)	
Poor	15 (3.6%)	0 (0.0%)	
CRIS total score[KW,8]			
Median (IQR)	39.0 (32.0, 44.0)	44.0 (37.0, 48.0)	0.0005

W = Wilcoxon–Mann–Whitney test; KW = Kruskal–Wallis.

[a] False discovery rate (FDR) method used to adjust *p*-value.

[1] Score range is 0–80; higher scores indicate worse PTSD symptoms (score > 48 suggest PTSD diagnosis).

[2] Score range is 10–50; higher scores indicate worse anger functioning.

[3] Score range is 10–50; higher scores indicate worse anxiety functioning.

[4] Score range is 10–50; higher scores indicate worse emotional and behavioural functioning.

[5] Score range is 10–50; higher scores indicate greater ability to participate in social roles and activities.

[6] Score range is 0–1; lower index values suggest lower overall general health status.

[7] 0 = Worst health you can imagine; 100 = Best health you can imagine.

[8] Only a subset of 9 questions were asked from the published community reintegration of service members form. Score range is 1–63 and higher scores indicate better reintegration into community.

Importantly, because of ongoing data processing, several objective tests were not included in these analyses, including brain imaging, biomarkers and electrophysiology. Also, from the traditional neuropsychological test battery, only a few *a priori* scores from each test module were utilized, rather than exploring every subscore available. Nevertheless, these performance data findings may offer more mechanistic insights of potential mTBI late effects to be examined in future studies.

Conclusions

This interim, unadjusted cross-sectional analysis demonstrates persistent, chronic symptomatology and life functioning difficulties in the historical mTBI group. Performance measures were less revealing, but differences between those with and without historical mTBI did emerge in several domains known to be highly sensitive to effects of mTBI, namely processing speed, visual-motor integration and executive function and postural control. Given the exploratory nature of this interim analyses, more analyses adjusted for psychopathology and other characteristics of cross-sectional data from this cohort, as well as analyses of mTBI subgroups and longitudinal assessments, and inclusion of the specialized data (e.g. brain imaging, electrophysiology, biomarkers and eye tracking) are planned.

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Appendix 17

Obstructive Sleep Apnea Risk is Associated with Cognitive Impairment After Controlling for TBI: A Chronic Effects of Neurotrauma Consortium Study

Obstructive Sleep Apnea Risk is Associated with Cognitive Impairment After Controlling for TBI: A Chronic Effects of Neurotrauma Consortium Study

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Background: Persons with TBI demonstrate a greater prevalence of sleep disorders relative to the general population.[1] Meta-analysis of civilian post TBI sleep disturbances highlight sleep apnea is 12 times higher than in large community-based non-TBI studies.[1] Epidemiologic studies have shown that individuals with sleep apnea have impaired performance on tasks such as driving and work productivity,[2-4] and are at risk for unemployment and work disability.[3,5] Studies conducted on large non-TBI samples demonstrate that the ill-effects of sleep apnea were detectable several years prior to a clinical diagnosis.[6-7] The negative consequences of sleep apnea across health, functioning, disability, and economic outcomes are well documented and may influence TBI outcomes. Finally, O'Hara and colleagues propose that sleep apnea may contribute to early cognitive decline in chronic stages post-TBI.[8] Unfortunately, no study has prospectively examined the relationship of sleep apnea and the effect that it may have on outcomes critical for military readiness such as cognitive functioning. Although sleep apnea is a risk factor for traumatic brain injury, the effect of sleep apnea on cognition in the context of mild TBI is understudied. Obstructive sleep apnea is a modifiable comorbidity with the potential to improve cognition in persons with a history of TBI. Therefore, the purpose of this study is to explore obstructive sleep apnea risk group differences on cognitive outcome in the Chronic Effects of Neurotrauma Consortium (CENC) participants.

Methods: Data were collected as part of a multi-center longitudinal study of mild TBI. Baseline data collected during the initial enrollment evaluation were used for study analyses. Evaluations were part of an in-person assessment across multiple domains (demographics, service history, injury characterization, physical health, psychological health, and neuropsychological testing) conducted by trained research assistants. Inclusion criteria for study analyses included completion of both the STOPBANG to determine sleep apnea risk and formal neuropsychological testing. The subsequent sample (N=433) included participants with history of TBI (n=362) and non-TBI controls (n=71). The sample was primarily male (87%) with a median age of 37 (IQR; 31-47) with a median of 13-15 years of education. A majority were Veterans (93%) at the time of evaluation.

STOPBANG scores were divided into risk categories and the sample stratified (STOPBANG 0-2 = Mild Risk, N = 150; STOPBANG 3-4 = Moderate Risk, N = 184; STOPBANG 5-8 = High Risk, N = 99) with a majority of the sample showing moderate to high risk. To explore the association of obstructive sleep apnea risk, group differences in cognitive performance was evaluated with TBI Status (positive or negative history) and obstructive sleep apnea risk (mild, moderate, high) as independent predictors after controlling for residualized age as a covariate.

Results: A significant main effect was only found for TBI status on verbal memory (CVLT II LDFR: $F(2, 429) = 11.9$, $p < .05$); whereas, a significant main effect of OSA was found on measures of processing speed (TMT A: $F(2, 429) = 97.3$, $p < .05$; WAIS IV Coding: $F(2, 429) =$

19.7, $p < .05$), executive functioning (DKEFS Letter Fluency: $F(2, 429) = 4.2$, $p < .05$; Flanker Test: $F(2, 429) = 8.4$, $p < .05$; TMT B: $F(2, 429) = 11.5$, $p < .05$), and memory (BVMT Free Recall: $F(2, 429) = 12.1$, $p < .05$, CVLT II LDFR: $F(2, 429) = 19.5$, $p < .05$). Post hoc analyses generally demonstrated significantly worse performance for those with high risk as compare to those with mild/moderate risk. The only significant interaction between TBI and OSA risk was found for a measure of verbal memory (CVLT II LDFR: $F(2, 429) = 5.0$, $p < .05$). Specifically, participants without a history of TBI who were at high risk for OSA performed significantly worse than all other groups.

Conclusion: Obstructive sleep apnea risk is prevalent in the CENC cohort. In this analysis, obstructive sleep apnea risk appears to be uniquely associated with several domains of cognitive functioning. Findings suggest that cognitive sequelae attributed to the downstream effects of mild TBI may be even more strongly related to treatable comorbid conditions providing potential targets for future treatment in mild TBI.

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Appendix 18

Diagnosing Mild Traumatic Brain Injury: Description and findings of methods used in the Chronic Effects of Neurotrauma Consortium (CENC) multicenter observational study

MHSRS Walker Abstract #1

Title: Diagnosing Mild Traumatic Brain Injury: Description and findings of methods used in the Chronic Effects of Neurotrauma Consortium (CENC) multicenter observational study

Authors: William C. Walker (presenter), Shawn Hirsch, David X. Cifu, Sidney Hines, Rick Williams, Rodney Vanderploeg, Heather Belanger, Nancy Temkin, William Carne.

Background: Mild TBI (mTBI), also known as concussion, is by far the most prevalent form of TBI among both civilians and military personnel. The term “mild” suggests a favorable prognosis, and although this is true for most, there are many exceptions. Unresolved constellations of symptoms after mTBI are collectively termed postconcussion syndrome, which in itself can be disabling. There is also mounting evidence that repeated concussions heighten the risk of other long-term effects. Thus, the accurate diagnosis of lifetime concussions has importance. However, mTBI can be very challenging to diagnose. In one study, clinician emergency department assessments had a 56% false negative rate. Of equal concern are false positives, due to incomplete understanding of and/or imprecision of the diagnostic criteria, including the DoD/VA common definition. Because of these challenges, many interview tools have been developed for both clinical and research use; however, most are intended as screening rather than diagnostic instruments. This presentation will review TBI diagnostic criteria, discuss the challenges in making a valid mTBI diagnosis, and discuss the distinction in diagnosing post-concussion syndrome or other residual effects that may be related to mTBI. The Chronic Effects of Neurotrauma Consortium (CENC) standardized method of diagnosing mTBI will be described, along with tips on integrating facets of the assessment into a clinical or research practice.

Methods:

This large multicenter study is observational with ongoing prospective longitudinal data collection. The intended population is post-9/11 era servicemembers and Veterans who experienced combat situation(s) and have varying mTBI histories, from none to many. The exclusion criteria were 1) history of moderate or severe TBI, or 2) history of a) major neurologic disorder (e.g. stroke, spinal cord injury), b) major psychiatric disorder (e.g. schizophrenia). Notably, PTSD and mood disorders were not considered exclusionary. This report contains data from the first 1,100 individuals enrolledand completing initial assessments. The eight enrollment sites included one military installation (Intrepid Spirit Center at Fort Belvoir) and seven large regional Veterans Affairs Medical Centers (VAMCs) in Houston, TX, Richmond, VA, San Antonio, TX, Tampa, FL, Boston, MA, Minneapolis, MN, and Portland, OR.

In-depth structured interviews were used to identify all lifetime potential concussive events (PCEs) and determine a TBI diagnosis for each PCE. A modification of the Ohio State University TBI Identification (OSU TBI-ID) instrument was used to detect all PCEs during military deployments and outside of deployments including childhood. Each PCE was interrogated to determine whether or not it was a true clinical mTBI via a detailed structured interview, the Virginia Commonwealth University retrospective Concussion Diagnostic Interview (VCU rCDI). To minimize interview fatigue of individuals with numerous PCEs, specific criteria were utilized capping the number of VCU rCDIs in certain conditions, and the results of the OSU TBI ID screen were used for PCEs not undergoing full rCDI. Each VCU rCDI renders a preliminary TBI diagnosis of either mTBI with posttraumatic amnesia (PTA), mTBI without PTA, or not mTBI through an embedded algorithm using the structured interview data and based on the DoD/VA

common definition of mTBI. Every preliminary algorithm-based TBI diagnosis is reviewed and vetted against the unstructured free text portion of the interview, and against any medical documents recorded in proximity to the event (i.e. first responder, emergency department, or in-theatre documentation). Using this process, the site principal investigator confirms or overrides every preliminary mTBI diagnosis to yield the final diagnosis, conducting additional unstructured interviews for further information when needed. The event is also assessed for TBI severity to ensure eligibility (any severity greater than mild is excluded). If any doubt remains on TBI diagnosis, the event is adjudicated by a central diagnosis committee consisting of national experts in TBI. Additional rigorous central review and quality assurance systems were also in-place with oversight by the Study Chairman, with referral of questionable TBI ratings to the central TBI diagnosis committee.

Results:

Of the initial 1,100 participants, almost all (n=1,078, 98%) experienced at least one lifetime PCE. Overall, a total 6,320 PCEs were identified for a median (IQR) of 5 (3,8) PCEs per participant. A total of 3,575 PCEs (56.6%) underwent full VCU rCDI, with the remainder getting screening interview (OSU TBI-ID) only. The study's multilayered review process confirmed the automated algorithm diagnosis in 97.0 % of CDIs, overturning only 108 (3.0%). Of the 108 overturned algorithm diagnoses, 63 were false positives, 34 were false negatives, and 11 correctly diagnosed mTBI but had a classification change regarding presence/absence of posttraumatic amnesia. After finalizing all TBI diagnoses, 207 (18.8%) participants were completely negative for any lifetime TBIs, and the remainder had sustained a median (IQR) of 2 (1, 3) mTBIs. At enrollment, the mTBI positive participants were a median (IQR) of 16.1 (10.1, 26.7) years from their first mTBI and a median (IQR) of 8.7 (5.1, 12.4) years from their most recent.

Conclusion:

The fully structured algorithm diagnosis from the VCU rCDI performed exceedingly well, but the algorithm did yield a few false negatives and false positives. This rigorous and highly standardized process of lifetime mTBI determinations will facilitate studying the dose effect of mTBI and the high transparency of diagnostics will facilitate generalizability of study results. The process of vetting and confirming or overriding the algorithm TBI diagnosis will be described, and red flags that might render the VCU rCDI algorithm suspect will be discussed. The general strategy used during the interview will be described and discussed along with related clinical interview tips and the distinction between diagnosing mTBI and postconcussion syndrome.

Appendix 19

The relationship between repetitive mild traumatic brain injury and balance performance; a Chronic Effects of Neurotrauma Consortium (CENC) Multi-Center Observational Study interim analysis.

MHSRS Walker Abstract #2

TITLE

The relationship between repetitive mild traumatic brain injury and balance performance; a Chronic Effects of Neurotrauma Consortium (CENC) Multi-Center Observational Study interim analysis.

AUTHORS

William C. Walker MD (presenter), Kayla Nowak, Kimbra Kenney, Laura Manning Franke PhD, Blessen C. Eapen MD, Karen Skop, Harvey S. Levin, PhD, Amma A. Agyemang, PhD, David F. Tate PhD, Elisabeth A. Wilde PhD, Sidney Hinds MD, Shawn Hirsch, Tracy Nolen DrPh.

ABSTRACT

Background: Traumatic brain injury (TBI) is considered the 'signature wound' of post-9/11 combat deployments, with 19% of warfighters estimated to have sustained a TBI. Mild (mTBI), also known as concussion, accounts for well over 80% of TBIs in both civilian and military populations. One important sequela of TBI is postural instability or imbalance, which can have a major impact on functional status, capacity to return to work, and quality-of-life. Acutely after mTBI, subjective dizziness and unsteadies (imbalance) are near universally present, and studies of balance performance uniformly demonstrate objective decrements of postural control. Persistence of imbalance symptoms after mTBI is common, but there is a paucity of rigorous research in that quantifies balance and postural stability with objective measures when mTBI is more remote. The current study addresses this research gap using computerized dynamic posturography (CDP) testing and thorough mapping of all lifetime mTBI events in a large sample of previously combat deployed Service members (SMs) and Veterans. We hypothesized that mTBI history would be associated with lowered CDP performance even after considering the following variables for possible inclusion into a statistical model: study site, combat exposure level, combat deployment duration, time since index event, PTSD, depression, anxiety, pain, pain medications, arthritis, estimated premorbid intelligence, alcohol consumption, as well as age, and sex.

Methods: The CENC Multicenter Observational Study enrolls post-9/11 era SMs and Veterans with combat exposure and a spectrum of historical mTBI. These analyses from the interim sample (n=492) included all participants completing CDP testing at the 3 performance sites and excluded symptom magnifiers (elevated mild Brain Injury Atypical Symptom scale or Neurobehavioral Symptoms Inventory Validity-10 scale) and aphysiologic CDP profiles (poorer scores on easier versus harder conditions) for a final sample size on n=295. The study utilized an observational design with cross-sectional analyses using structural equation modeling (SEM) to test for causal inference. Comprehensive structured interviews were used to determine all lifetime mTBIs and when present categorize them by presence versus absence of posttraumatic amnesia (PTA), and by blast versus non-blast cause. For these analyses, we considered the overall presence versus absence of any lifetime mTBI as well as the subcategories of PTA blast causality, and repetitive mTBI (defined as $\geq$ 3 lifetime mTBIs) versus non-repetitive mTBI. Balance was measured on CDP dual-plate force platform using the Sensory Organization Test (SOT). The SOT assesses six different sensory conditions: 1. eyes open with fixed surface and visual surroundings; 2. eyes closed with fixed surface; 3. eyes open with fixed surface and sway referenced visual surroundings; 4. eyes open with sway referenced surface and fixed visual field; 5. eyes closed with sway referenced

surface; and 6. eyes open with sway referenced surface and visual surroundings. Assessments for candidate variables included structured interviews, record review, and questionnaires.

Results: When only adjusting for site, compared to the non-mTBI participants, mTBI participants had a significantly ($p < 0.05$) greater proportion of PTSD (32.0% vs. 10.6%), arthritis (51.0% vs. 34.8%), and non-analgesic pain medication use (35.2% vs. 13.0%), while also having significantly higher combat intensity exposure (36.0 vs. 26.0), anxiety (22.0 vs. 18.0), and pain interference (22.0 vs. 15.0). In the final SEM for the overall mTBI classification, history of any mTBI had a significant indirect effect of lowering the composite equilibrium score by 2.25 points (SD= 0.90; p=0.0125) that was primarily mediated through pain interference. The Test of Premorbid Functioning (TOPF), a neuropsychological test of estimated premorbid intellect, had a significant covariate effect of raising the composite equilibrium by 0.16 point per point increase in TOPF (SD=0.06; p=0.0013). Similar primary mediating effects of pain interference and covariate effects of TOPF were also observed for the Repetitive and Blast mTBI models. The Repetitive mTBI classification was the only model to show a significant total effect in addition to a significant indirect effect; those with 3 or more mTBIs showed a 4.98 (SD=1.76; p=0.0046) lower mean composite equilibrium score compared to those with 1-2 mTBIs. The direct portion of the Repetitive mTBI effect was not significant (p=0.1134). However, when examining the effect of Repetitive mTBI across the equilibrium sensory conditions, the direct effect was significant in conditions 2 and 3, and trended towards significance in conditions 4 (p=0.0795) and 5 (p=0.0614).

Conclusions: This study implicates a history of repetitive mTBI ($\geq$ 3) in reducing balance performance among previously combat-deployed Veterans and SMs, with pain acting as the primary mediator. These findings have important implications for the screening and identification of persons with mTBI histories who may benefit from interventions to improve or compensate for balance difficulties. They also highlight the importance of incorporating pain management strategies into such interventions. Further research in this area is warranted.

Appendix 20

Pain and chronic mild traumatic brain injury in the US military population: a Chronic Effects of Neurotrauma Consortium study

Pain and chronic mild traumatic brain injury in the US military population: a Chronic Effects of Neurotrauma Consortium study

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Background: Between the year 2000 and August 2017, more than 375 000 Service Members (SMs) were diagnosed with TBI, with 82.3% of those cases classified as mild TBI (mTBI). SMs with mTBI report ongoing pain at twice the rate as those with non-head injuries and co-morbid mTBI and pain is often associated with significant functional impairment. To date, no study has firmly established the relationship between mTBI and pain, as most studies have used models which only include a handful of covariates and mediators. This study examined the associations between mTBI exposure and pain interference, pain intensity, and a wide variety of demographic factors and common co-morbid conditions such as PTSD, depression and anxiety. The purpose of this analysis is to better understand the relationship between mTBI, pain intensity and pain interference, and other common mTBI comorbidities among Veterans and SMs.

Methods: Cross-sectional snapshot of baseline data from the prospective, longitudinal Chronic Effects of Neurotrauma (CENC) study. An interim sample of 492 participants was recruited between January 2015 and August 2016 at four VA Medical Centers (VAMC). The 454 with pain data reported were split into two groups; participants with at least one prior mTBI (n= 379) and participants without any mTBI (n= 75). Effects of mTBI on pain intensity and pain interference were compared between participants with or without mTBI exposure. Data were analyzed using covariate adjusted regression analyses as well as structural equation modeling (SEM) methods to assess the robustness of findings across different modeling assumptions. As results of the two approaches were consistent with respect to the overall association between mTBI exposure and pain, the results focus primarily on the SEM findings.

Results: The mTBI group reported more pain interference compared to the non-mTBI group and were more likely to report greater pain intensity. In the SEMs there was a significant total effect ($p<0.0001$) for both pain interference (parameter estimate = 5.29) and pain intensity (parameter estimate = 0.35). While neither model showed a significant direct mTBI effect on outcome (pain interference parameter estimate=1.58; pain intensity parameter estimate=0.19); the indirect effects on each outcome were statistically significant (pain interference parameter estimate=3.71; pain intensity parameter estimate=0.16). All mediators (PTSD, depression, anxiety, and sleep difficulty) were significant on the path of mTBI to mediator, with mTBI exposed participants being significantly more likely to have each mediating condition. PTSD (parameter estimate=1.63), depression (parameter estimate=1.62), anxiety (parameter estimate=0.41) and sleep difficulty (parameter estimate=0.39) each mediated the relationship between mTBI and pain interference. Sleep difficulty (parameter estimate=0.05) was the only mediator that was directly significant along the path to pain intensity, with greater sleep disturbance contributing to more severe pain.

Conclusions: Our SEMs demonstrate that mTBI has a significant, but indirect, effect on both pain intensity and pain interference. PTSD, depression, anxiety and sleep, the incidences of which were also significantly higher in the mTBI exposed group, each mediated the relationship between mTBI and pain interference. Sleep was the only mediator that was directly significant

along the path to pain intensity, with greater sleep disturbance contributing to more severe pain. Our findings underscore the clinical relevance of assessing co-morbid pain interference and pain intensity in Veterans and SMs who may have chronic effects of mTBI. Identifying these co-morbidities at early stages of post-deployment could facilitate referral for treatment and mitigate disability.

Appendix 21

Elevated exosomal total and phosphorylated tau among veterans with chronic repetitive mild TBI; A CENC study interim analysis

Elevated exosomal total and phosphorylated tau among veterans with chronic repetitive mild TBI; A CENC study interim analysis

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ABSTRACT

Background: Chronic symptoms and disabilities after traumatic brain injury (TBI) are common.[1-5] Evidence suggests that secondary injury processes (e.g. neuronal, inflammatory and vascular) contribute to TBI outcomes.[6-7] Blood-based brain-derived proteins, including exosomal, are increasingly recognized for their potential to improve diagnosis, prognosis, and treatment of acquired neurological and neurodegenerative disorders.[8-9] We used ultrasensitive immunoassays to profile plasma and peripherally-circulating exosomal biomarkers (tau, amyloid, neurofilament light chain, cytokines), and hypothesize that biomarker profiles correlate with TBI severity, number and outcomes.

Methods: We analyzed samples from 195 Chronic Effects of Neurotrauma Consortium (CENC) participants, including: 1) 98 subjects with mild TBI (mTBI) with at least one mTBI with loss of consciousness or post-traumatic amnesia; 2) 52 subjects with mTBI with alteration of consciousness only; and 3) 45 subjects without a history of TBI. Fifty-six of the 150 TBI subjects reported ≥3 mTBI (rTBI). Tau, phosphorylated tau (p-tau), amyloid beta 40 (Aβ40), amyloid beta 42 (Aβ42), neurofilament light chain (NFL), tumor necrotizing factor alpha (TNFa), Interleukin 6 (IL-6) and Interleukin 10 (IL-10) were each measured by ultrasensitive immunoassay in both plasma and exosomes by an investigator blinded to group assignment. Protein biomarkers were compared among the 4 groups and correlated with neurobehavioral symptom surveys [Neurobehavioral Symptom Inventory (NSI), Patient Health Questionnaire (PHQ-9) and post-traumatic stress symptoms (PCL-5)].

Results: Exosomal tau and p-tau were elevated in rTBI compared to those with ≤ 2 mTBIs ($p<0.05$). There was a trend towards elevated plasma tau among the rTBI group ($p=0.08$). Exosomal p-tau correlated weakly, but significantly, with PCL-5 ($r=0.326$, $p=0.026$) and NSI-somatic ($r=0.33$, $p=0.02$). Exosomal tau significantly correlated with PCL-5 ($r= 0.37$, $p=0.011$), NSI ($r=0.36$, $p=0.012$), NSI-somatic ($r=0.35$, $p=0.02$), NSI-affective ($r=0.33$, $p=0.015$), and NSI-cognitive ($r=0.33$, $p=0.032$). Plasma tau correlated with: PHQ-9 ($r=0.29$, $p=0.042$), PCL-5 ($r=0.40$, $p<0.01$), and NSI ($r=0.39$, $p<0.01$).

Conclusion: Exosomal proteins differ in Veterans with rTBI, in particular, levels of exosomal tau and p-tau are increased and correlate with some chronic neurobehavioral symptoms, though weakly. This has potential implications as elevated p-tau levels have been linked to a greater risk of dementia among elderly individuals.[2] Further analyses are underway.

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Appendix 22

Advances in the study of mild traumatic brain injury among Warfighters: Findings from The Chronic Effects of Neurotrauma Consortium (CENC)

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Tract Session Name: Advances in the study of mild traumatic brain injury among Warfighters: Findings from The Chronic Effects of Neurotrauma Consortium (CENC)

JPC alignment: 5 (Military Operational Medicine); 6 (Combat Casualty Care); 8 (Clinical and Rehabilitative Medicine)

Tract Session Description (4 sentences or less): The purpose of this Tract Session is to update the field about the latest advancements in the study of the nature and associated sequelae of mild traumatic brain injury (mTBI) and its long-term effects among Veterans and Service Members, including dementia risk. Abstracts should present findings from CENC, a coordinated, multicenter, research collaboration between the VA and DoD, jointly funded for $62.2 million in 2013, that links basic, translational, and clinical neuroscience researchers from the VA, military, academia, and the private sector. Themes to be covered will be: (1) Methodological considerations and strategies for success in implementing a multi-center consortium; (2) Important findings from CENC's longitudinal study of chronic mTBI and associated sequelae among Iraq and Afghanistan (OEF/OIF/OND) Veterans and Service Members; and (3) Findings from the complementary epidemiological studies, which harness existing data on TBI and dementia among 1.6 million Veterans, to further characterize chronic mTBI effects and associated healthcare utilization and costs.

Learning objectives:
(1) At the end of this session, the participant should be able to describe some of the challenges in implementing a multi-center consortium study and strategies for addressing these challenges.
(2) At the end of this session, the participant should be able to understand the complexities in the nature of mTBI among Veterans and Service Members and the resultant implications for assessment and management as well as dementia risk.
(3) At the end of this session, the participant should be able to discuss the role of existent databases in contributing to the study of mTBI among Warfighters and some of the important questions that these databases can help us answer.

Funding: The Chronic Effects of Neurotrauma Consortium is jointly funded by the Department of Defense (award # W81XWH-13-2-0095) and the Department of Veterans Affairs (award #'s I01 CX001135, I01 CX001246, I01 RX001774, I01 RX001135, I01 RX002076, I01 RX001880, I01 RX002172, I01 RX002173, I01 RX002171, I01 RX002174, and I01 RX002170).

Appendix 23

Otolith Dysfunction and Postural Stability

Learning Objectives: (1) Describe the impact of otolith dysfunction on postural stability; (2) Describe the impact of otolith dysfunction on quality of life.

Title: Otolith Dysfunction and Postural Stability

Background: Dizziness and imbalance are common symptoms following mild traumatic brain injury (mTBI) and blast exposure, and recent evidence suggests that mTBI and/or blast exposure may preferentially affect the otolith organs (gravitoinertial sensors in the inner ear). This is a novel finding because previous studies examining the effect of mTBI on the vestibular system were limited to tests of horizontal semicircular canal function (rotational sensors in the inner ear). Although otolith organ testing is becoming more widely used in vestibular clinics throughout the world, the clinical significance of otolith organ dysfunction is unclear.

The purpose of this study was to determine the functional consequences of otolith organ dysfunction and mTBI on postural stability and quality of life. We measured balance, gait, and quality of life in Veterans and persons in the Reserves or National Guard and compared outcomes in those with and without vestibular dysfunction and mTBI.

Methods: A prospective case-control study design was used. Comprehensive vestibular site-of-lesion testing was performed and participants were grouped according to patterns of vestibular test findings. Three vestibular groups (n = 52 combined) included individuals complaining of dizziness and/or imbalance with: (1) otolith organ dysfunction only (Otolith Only), (2) semicircular canal and otolith organ dysfunction (Canal+Otolith), and (3) semicircular dysfunction only (Canal Only). Two control groups (n = 78 combined) included (1) individuals complaining of dizziness and/or imbalance with normal canal and otolith organ function (Dizzy Control) and (2) individuals with no complaints of dizziness and/or imbalance and normal canal and otolith organ function (Healthy Control). To determine horizontal semicircular function, each participant underwent caloric testing, rotational chair testing using slow harmonic acceleration, and video head impulse testing. To determine otolith organ function, each participant underwent cervical and ocular vestibular evoked myogenic potential testing.

Balance, gait, and quality of life measures were used to determine the impact of otolith organ dysfunction on postural stability and were performed within four weeks of vestibular laboratory tests. Gait and balance outcome measures included the Sensory Organization Test, preferred gait speed, and the Functional Gait Assessment. Quality of life outcome measures included a visual analog scale to measure impact on activities, the Activities-specific Balance Confidence scale, the Dizziness Handicap Inventory, and the Vestibular Activities and Participation measure.

Multivariate analyses of variance (MANOVAs) were performed to determine significant group differences ($p < 0.05$) for balance and gait and quality of life outcome measures. As appropriate, post hoc analyses of covariance and pairwise comparisons were performed to identify specific group differences ($p < 0.05$).

Results: There were no significant group differences for age, race, ethnicity, gender or occupational status. Nearly a third of participants (n = 40) reported a history of mTBI, and 29 of these were related to blast exposure.

MANOVAs indicated significant group differences for both gait and balance and quality of life outcome measures. Post hoc comparisons of gait and balance measures revealed that the Otolith Only group performed significantly worse than the Healthy Control group on the Sensory Organization Test. The Otolith+Canal group performed significantly worse than both control groups and the Otolith Only and Canal Only groups on the Sensory Organization Test. The Otolith+Canal group also performed significantly worse than both control groups on the Functional Gait Assessment.

Post hoc comparisons of quality of life measures revealed that the Otolith Only group performed significantly worse than the Healthy Control group on the visual analog scale to measure impact on activities, the Activities-specific Balance Confidence scale, and the Dizziness Handicap Inventory. The Otolith+Canal group performed significantly worse than the Healthy Control on the visual analog scale to measure impact on activities, the Activities-specific Balance Confidence scale, Dizziness Handicap Inventory, and Vestibular Activities and Participation measure.

Conclusions: Otolith organ dysfunction negatively impacts balance, gait, and quality of life particularly in conjunction with semicircular dysfunction. The findings of this study have important implications for developing effective clinical protocols for the diagnosis and management of individuals with dizziness. Because the otolith organs are susceptible to damage from a blast or blow to the head, the inclusion of otolith organ testing is critical in the clinical management of Veterans with dizziness or imbalance following mTBI or blast. This research effort is part of a long-term goal to establish a unique treatment platform to diagnose, localize, and treat dizziness and imbalance related to mTBI.

Appendix 24

Clinical and Neuropathological Features in a Case Series of 15 Operation Enduring Freedom/Operation Iraqi Freedom Veterans exposed to Civilian and Military-Related Traumatic Brain Injury

Clinical and Neuropathological Features in a Case Series of 15 Operation Enduring Freedom/Operation Iraqi Freedom Veterans exposed to Civilian and Military-Related Traumatic Brain Injury

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BACKGROUND:
From 2000 to 2017 approximately 400,000 military service members sustained a traumatic brain injury (TBI). The clinical and neuropathological consequences of these "signature injuries" of the recent conflicts are not well understood. Presidential Executive Orders and Congressional mandates have led to expert panel meetings and recommendations but the literature describing the clinical and neuropathological outcome of military-related blast and impact TBI is limited. The few existing studies have reported varying diagnoses including chronic traumatic encephalopathy (CTE), honeycomb axonal pathology and interface astroglial scarring. This report presents the clinical and pathological features of a large cases series of Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) veterans (n=15) with a history of military-related TBI.

METHODS:
Brains of 15 OEF/OIF veterans were donated by their next-of-kin to the Chronic Effects of Neurotrauma Consortium (CENC) and Veterans Affairs-Boston University-Concussion Legacy Foundation (VA-BU-CLF) brain banks. A comprehensive neuropathological examination using published criteria for diagnosis was performed blinded to any clinical or demographic information. Retrospective clinical evaluations were performed using online surveys and structured and semi-structured post-mortem telephone interviews between researchers and informants. Researchers conducting these evaluations were completely blind to the neuropathological analysis and informants were interviewed before receiving the results of the neuropathological examination. A behavioral neurologist, neuroscientist, or neuropsychologist obtained a detailed history, including a timeline of cognitive, behavioral, mood and motor symptomology. Additionally, other neuropsychiatric symptoms, exposures and symptoms consistent with posttraumatic stress disorder (PTSD), features of a substance use disorder, neurodegenerative diagnoses made in life, headaches that impaired function, symptoms and diagnoses made in life of sleep disorders and causes of death were assessed. Clinician's also assessed for symptoms associated with mental health illness, such as depression and anxiety. Clinician's qualitatively summarized the subject's clinical presentation (e.g., presence and course of symptoms, functional independence) into a narrative, and presented the case to a multidisciplinary team of clinicians, during which it was determined whether the subject met criteria for dementia.

RESULTS:
Demographics: Participants were veterans of United States military representing three branches: Army, Marine Corps, and Navy. All 15 subjects were male and had an average of 2.75 years of combat exposure (6 pending duration of combat). Mean age at death was 35.6 years (range=22-55). Causes of death were suicide (n=7), aneurysm (n=2), overdose (n=2), accident (1) cardiovascular disease (1), cancer (1) and dementia (1).

TBI Exposure: All had at least one military-related TBI (mean=7.0; range=1-30, 4 pending). Eleven experienced blast TBIs, 2 experienced only impact TBIs, and 2 are pending. Two veterans played college football, 7 played youth or high football, 1 played rugby recreationally, another participated in mixed martial arts, 4 are pending. One veteran had no contact sport history.
Clinical: Nine of the 15 veterans had available clinical data (6 others are pending). Eight out of nine veterans experienced cognitive symptoms (mean age of onset=30.13; mean symptom duration=3.88 years). The most common cognitive symptoms were memory problems (n=6), behavioral/mood symptoms (n=9), including depression and anxiety in 8. Eight of the 9 veterans were diagnosed with post-traumatic stress disorder (PTSD) during life.
Neuropathological: Nine of the 11 veterans met diagnostic criteria for CTE; the CTE was typically mild (n=6 Stage II; n=3 Stage I, 4 cases pending) with no evidence of comorbid neurodegenerative disease. Diagnostic CTE lesions (perivascular collections of tau containing neurofibrillary tangles (NFTs)) were most often found in the dorsolateral frontal and temporal cortices. NFTs were frequently found in the hypothalamus, median raphe, and locus ceruleus. Evidence of axonal disruption and white matter pathology was found in the majority of cases.

CONCLUSIONS:
To date, this is the largest case series reporting the neuropathological and clinical features of OEF/OIF veterans with exposure to military-related TBI. There is a high rate of CTE in this series and the clinical presentations of veterans with neuropathological CTE in this sample match those reported in larger studies of contact sport athletes.

Most of the veterans in this sample had mixed exposure to TBI from blast and contact sports. Given their mixed exposure, the neuropathological outcomes resulting from the interaction between sport and military activities needs to be further elucidated.

PTSD was common in veterans with neuropathological CTE, and the correlation of specific CTE pathology in the cortex, hypothamus and brainstem to the symptoms of PTSD is the focus of ongoing studies.

This case series represents an important step in understanding the clinical and neuropathological features of OEF/OIF veterans with a history of sports and military-related TBI. Ascertainment bias and sample size limitations limit the generalizability of these findings.

Appendix 25

The relationship between mild traumatic brain injury and neurobehavioral symptoms among those who served in OEF/OIF/OND combat: A Chronic Effects of Neurotrauma Consortium study

The relationship between mild traumatic brain injury and neurobehavioral symptoms among those who served in OEF/OIF/OND combat: A Chronic Effects of Neurotrauma Consortium study

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Guidelines for creating an abstract

1. The abstract title is restricted to 255 characters (including spaces).
2. The abstract content is restricted to 8000 characters (including spaces).
3. Format the abstract to contain these sections: Background, Methods, Results and Conclusion.
4. Do not include pictures or tables in the abstract.

5. When filling out the Co-Author box on the abstract submission form, include presenter/first author name and affiliation. Follow the formatting guidelines for this section. If your abstract is submitted as a poster, the information for program book is downloaded directly from this box only.

Learning Objectives:

1. Describe neurobehavioral symptom severity among a sample of OEF/OIF/OND combat Service Member and Veteran participants.
2. Examine the direct and indirect relationship of traumatic brain injury (TBI) to neurobehavioral symptoms, while accounting for potential mental health confounders.
3. Describe the impact of mental health conditions, especially Depression and Post trauamtic Stress Disorder (PTSD), on neurobehavioral symptoms.

Background: Since 2000, more than 375,000 U.S. military Service Members have sustained a traumatic brain injury (TBI).[1] The majority of these injuries are classified as mild TBI (mTBI), also known as concussion.[2] Symptom resolution typically occurs within three months post injury, but there is a significant minority who report post-concussive symptoms months to years after the event. The Departments of Defense (DoD) and Veterans Affairs (VA) clinical programs commonly use the Neurobehavioral Symptom Inventory (NSI)[3] to assess four symptom domains of post-concussive symptoms: affective, cognitive, somatosensory, and vestibular.[4] Many who served in Operations Enduring Freedom, Iraqi Freedom, New Dawn, and their follow-along conflicts (hereafter referred to as OEF/OIF/OND) also have mental and physical health conditions that frequently co-occur with mTBI, thus making it difficult to attribute symptoms to specific conditions. TBI is the precipitating event for assessing postconcussive symptoms, but those characterized as post-concussive symptoms are not unique to mTBI, especially in the OEF/OIF/OND Veteran population.[5-11] To estimate the impact of mTBI on NSI outcomes among a sample of those who served in OEF/OIF/OND combat, we examined the relationship between mTBI and each of the four NSI domains, accounting for the potential mediating, covariate, and confounding effects of comorbid health conditions, combat-related exposures, and demographic/military factors.

Methods: This study included an interim sample of 492 OEF/OIF/OND combat Service Members or Veterans who voluntarily enrolled between January 2015 and August 2016 at four geographically--dispersed VA or DoD research sites. Study inclusion criteria included OEF/OIF/OND deployment and combat exposure. Exclusion criteria included moderate or severe TBI history or a history of major neurologic function or psychiatric disorder that resulted in a significant decrease in functional status.[12] Additionally, those who scored above recommended thresholds (n = 27) or had missing data (n = 10) for two symptom exaggeration measures (mild brain injury atypical symptoms scale (mBIAS) and embedded NSI Validity-10) were excluded. The final sample comprised 455 total participants, 380 with mTBI positive histories and 75 with mTBI negative histories.

Participants completed an exhaustive structured interview to determine all lifetime mTBIs along with an index event date consisting of the worst mTBI during deployment, or if absent the worst outside of deployment, and if also absent, then a comparable sham date. Blast- and non-blastrelated lifetime potential concussive events (PCEs), injuries that did not result in mTBI, were also recorded. Participants also completed the Deployment Risk and Resilience Inventory-2 to measure combat exposure, the Posttraumatic Stress Disorder (PTSD) Checklist for DSM-5 (PCL-5) to determine PTSD symptom severity, the Patient Health Questionnaire (PHQ-9) Depression Scale to assess depression, a TBI Quality--of--Life (TBI QoL) module to assess anxiety, and the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) to screen for hazardous alcohol use. Demographic (e.g., age, gender) and military history (e.g., branch) characteristics were also documented.

The outcome measures were mean subscale scores of the four NSI domains: affective, cognitive, somatosensory, and vestibular. Domains were derived from participants rating the extent to which 22 symptoms (e.g., irritability, poor concentration, headaches, feeling dizzy) disturbed them in the last 2 weeks, with anchors of 0 (None) to 4 (Very Severe). Mean domain scores were used for analyses, so that all outcomes ranged continuously from 0 to 4.

Characteristics of the sample stratified by mTBI exposure were summarized by median and range for non-normally distributed continuous variables and frequency and percentage for categorical variables. Separate structural equation models (SEMs) were used to examine the relationship of mTBI history on each of the four NSI domains. These models included confounders, mediators, and covariates hypothesized to have a role on the causal pathway. Confounders included study site, combat exposure, uncontrolled-blast-related and non-blastrelated PCEs, and military branch. Mediators were PTSD symptom severity, depression, and anxiety. Covariates were years since index date, age, hazardous alcohol use, and gender. All SEMs explored two variations of mTBI exposure: a binary measure of any lifetime mTBI exposure versus unexposed, and a continuous measure of the total number of lifetime mTBIs (ranging from 0 to 11).

Results: Site-adjusted univariate analyses demonstrated that those with mTBI exposure reported significantly higher symptom severity that those without mTBI exposure across all four NSI domains ($p<0.05$).

When accounting for confounders, mediators, and covariates, significant total and indirect effects ($p<0.05$) were observed for all four NSI outcomes in both the binary and continuous mTBI SEMs. Significant direct effects of mTBI were observed in the cognitive ($p = .0085$) and somatosensory domains ($p = .0018$) for both exposure classifications, as well as the vestibular domain for the continuous exposure only. No significant direct effects of mTBI were observed for the affective domain.

Overall, total effects showed an increase (worsening) of the NSI mean scores associated with greater levels of mTBI exposure. In the binary mTBI models, any lifetime mTBI exposure increased mean NSI subscales cores by 0.52 points ($SD=0.11$, $p <0.0001$) for the affective

domain, 0.59 points (SD=0.11, p <0.0001) for the cognitive domain, 0.41 points (SD=0.08, p <0.0001) for the somatosensory domain, and 0.33 points (SD=0.09, p=0.0004) for the vestibular domain. Similar results were observed for the continuous mTBI SEM models.

Significant indirect effects were largely driven by two key mediators: PTSD and depression. PTSD displayed a significant full mediating effect (a significant effect of the exposure and as a subsequent significant effect on the outcome, $p < 0.05$) for all NSI outcomes in both mTBI exposure models. Depression also had a full mediating effect in the binary mTBI models. Although anxiety also played a role in several models, it did not behave consistently across all models.

Of the confounders, combat exposure and non-blast PCEs had a significant effect on mTBI exposure (both binary and continuous) but largely did not have a significant effect on the NSI outcomes. Additionally, blast-related PCEs, military service branch, age, and gender had some significance signals, but did not perform consistently across the various outcomes and exposures.

Conclusion: Affective, cognitive, somatosensory, and vestibular complaints are typical postconcussive symptoms, but they are also associated with non-TBI related injuries and mental health conditions. Both binary and continuous repetitive mTBI exposure had significant total and indirect effects for all four NSI outcomes, while the direct effect was only significant for the cognitive, somatosensory, and vestibular (continuous mTBI exposure only) domains. These models also displayed a mediator effect, primarily driven through PTSD and depression. This demonstrates that mTBI and mental health symptoms overlap, thus making it difficult to attribute particular symptoms to specific conditions that commonly co-occur in those who served in OEF/OIF/OND combat. As the more than 2.7 million[13] Service Members that were deployed in support of OEF/OIF/OND separate from the military, the VA and other healthcare systems must identify and track their diagnostic and symptom profiles so that they can leverage the appropriate resources to meet current and anticipate future needs of Veterans.

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Appendix 26

Differences in Comorbidity Phenotypes in Afghanistan and Iraq War Veterans with mild and no TBI: A Chronic Effects of Neurotrauma Consortium Study

Differences in Comorbidity Phenotypes in Afghanistan and Iraq War Veterans with mild and no TBI: A Chronic Effects of Neurotrauma Consortium Study

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This work was funded by the Chronic Effects of Neurotrauma Consortium, (CENC) by joint U.S. Department of Defense or the U.S. Department of Veterans Affairs funds, W81XWH-13-2-0095-04 and I01 CX001246.

Background

There is an established association between traumatic brain injury (TBI), pain, and psychological conditions (i.e., Polytrauma Clinical Triad [PCT]) among both civilian and Veteran patients. This study compared longitudinal comorbidity phenotypes in Iraq and Afghanistan Veterans (IAV) by TBI status (no TBI, mild TBI [mTBI]) to examine its impact on health status.

Methods

Among IAV who received three or more years of Department of Veterans Affairs (VA) care between 2002 and 2011, we identified diagnoses of pain and psychological conditions commonly associated with TBI. We used latent class analysis stratified by TBI status to identify subgroups with similar probabilities of exhibiting distinct comorbidity phenotypes during the first five years of care.

Results

We found statistically significant differences in the five comorbidity phenotypes identified for mTBI and no TBI cohorts. Among those with no TBI, comorbidity phenotypes were stable over the first five years of care, with a substantial (38%) Healthy group, a ‘Sort-of Healthy’ group (i.e., emerging pain and tinnitus/hearing loss diagnoses), and groups comprised of pain,

psychological conditions, and pain+psychological conditions. Among those with mTBI, there were two 'Sort-of Healthy' groups: one that remained relatively stable and another that deteriorated to PCT by year five. We also found a psychological conditions group and two PCT groups: one that was relatively stable and another that improved (i.e., lower probabilities of pain and psychological conditions) by year five.

Conclusions

Our analysis revealed three comorbidity phenotypes unique to IAV with mTBI: an initially 'Sort-of Healthy' group that deteriorated to PCT, a group with stable probability of PCT conditions between years one and five, and a group that initially exhibited PCT but improved by year five. Future research particularly focused on deteriorating and improving groups may help identify risk factors or types of treatment associated with these changing outcomes.

Appendix 27

Symptom validity screening and mild traumatic brain injury in a non-treatment seeking veteran sample

Symptom validity screening and mild traumatic brain injury in a non-treatment seeking veteran sample

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Background. Assessment of symptom validity in veterans with a history of traumatic brain injury (TBI) is often completed in clinical neuropsychological evaluations, as an accurate assessment of TBI characteristics is critical for diagnosis and treatment. Outside of the clinical context, such as in a research study, it is still important to assess symptom validity, but studies have not approached this in a uniform manner and may be reluctant to add time to protocols to do so.
Methods. In this study, veterans with a reported history of mild TBI were compared with those that reported no TBI history (controls). Two measures that have been developed in the context of assessing validity of symptom reporting in veterans are the Mild Brain Injury Atypical Symptoms Scale (mBIAS) and the Validity-10 Scale of the Neurobehavioral Symptom Inventory. Mild TBI presence and severity was assessed via consensus review of responses to the Minnesota Blast Exposure Screening Tool (MN-BEST) semi-structured interview.
Results. Veterans with mTBI (n=79) had significantly elevated scores on both the mBIAS ($t=3.0$, $p=.003$) and Validity-10 ($t=4.8$, $p<.001$) compared to controls (n=83). Notably, scores on the mBIAS and Validity-10 were strongly correlated with traditional validity measures from the MMPI-2-RF, as well as with mTBI severity scores from the MN-BEST.
Conclusion. Veterans with a history of mTBI had a tendency to report a higher level of symptoms than did veterans without mTBI, and greater symptom reporting was associated with greater mTBI severity. Importantly, while mBIAS and Validity-10 scores were higher in the mTBI sample, scores were not in a range that would be considered clinically elevated. Results suggest that the mBIAS and Validity-10 are useful measures of symptom validity in non-treatment seeking veterans.

Appendix 28

Chronic Effects of Neurotrauma Consortium Study 34 FY18 Annual Report

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Increased Small-World Network Topology Following Deployment-Acquired Traumatic Brain Injury Associated with the Development of Post-Traumatic Stress Disorder

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Abstract

Cross-sectional and longitudinal studies in active duty and veteran cohorts have both demonstrated that deployment-acquired traumatic brain injury (TBI) is an independent risk factor for developing post-traumatic stress disorder (PTSD), beyond confounds such as combat exposure, physical injury, predeployment TBI, and pre-deployment psychiatric symptoms. This study investigated how resting-state brain networks differ between individuals who developed PTSD and those who did not following deployment-acquired TBI. Participants included postdeployment veterans with deployment-acquired TBI history both with and without current PTSD diagnosis. Graph metrics, including small-worldness, clustering coefficient, and modularity, were calculated from individually constructed whole-brain networks based on 5-min eyes-open resting-state magnetoencephalography (MEG) recordings. Analyses were adjusted for age and premorbid IQ. Results demonstrated that participants with current PTSD displayed higher levels of small-worldness, $F(1,12) = 5.364$, $p < 0.039$, partial eta squared = 0.309, and Cohen's d = 0.972, and clustering coefficient, $F(1, 12) = 12.204$, $p < 0.004$, partial eta squared = 0.504, and Cohen's d = 0.905, than participants without current PTSD. There were no between-group differences in modularity or the number of modules present. These findings are consistent with a hyperconnectivity hypothesis of the effect of TBI history on functional networks rather than a disconnection hypothesis, demonstrating increased levels of clustering coefficient rather than a decrease as might be expected; however, these results do not account for potential changes in brain structure. These results demonstrate the potential pathological sequelae of changes in functional brain networks following deployment-acquired TBI and represent potential neurobiological changes associated with deployment-acquired TBI that may increase the risk of subsequently developing PTSD.

Keywords: graph theory; magnetoencephalography; post-traumatic stress disorder; risk factor; traumatic brain injury

Introduction

Over the course of the wars in Iraq and Afghanistan, over 346,000 service members have been diagnosed with a traumatic brain injury (TBI), most mild in severity. Much like in the civilian population, the majority of mild TBIs are unlikely to require medical attention and therefore unlikely to be captured by medical records (Davenport, 2016). This raises the possibility that the number of TBIs, particularly mild TBIs, is much higher than those receiving a formal diagnosis. A growing literature suggests that TBI acquired during deployment represents an independent risk factor for developing post-traumatic stress disorder (PTSD). Both cross-sectional (Brenner et al., 2010; Hoge et al., 2008; Kontos et al., 2013; Lindquist et al., 2017; Morissette et al., 2011; Schneiderman et al., 2008) and longitudinal (Mac Donald et al., 2017; Stein et al., 2015; Yurgil et al., 2014) studies in active duty and veteran populations demonstrate that experiencing a TBI during deployment increases the risk for developing PTSD, even after adjusting for other important risk factors

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(e.g., combat exposure, bodily injury, and predeployment psychiatric symptoms). However, no work to date has addressed the specific neurobiological conditions or mechanisms through which deployment TBI increases the risk for subsequently developing PTSD.

Synthesis across several types of neuroimaging methods has suggested that chronic phase TBI may be a disorder of disconnection, representing a potential mechanism through which TBI may increase the risk of developing PTSD (Hayes et al., 2016). As reviewed by Hayes et al. (2016), disconnection is related to injury effects on axons and may result from a variety of mechanisms, including axonal shearing or effects secondary to inflammation, and can occur subsequent to any injury mechanism. Network analyses allow quantification of network topology and communication throughout the brain, providing an ideal approach to understand the effect of TBI and potential disconnections on brain function (Bullmore and Sporns, 2009).

Two studies to date have utilized magnetoencephalography (MEG) to conduct whole-brain network analyses of individuals with TBI history. Alhourani et al. (2016) found reduced local efficiency in brain regions associated with the default mode network in civilian participants with mild TBI, a median of 8 months postinjury. Reductions in local efficiency occurred across several frequency ranges, most notably in the alpha and delta ranges. Rowland et al. (2017) found increases in small-worldness of whole-brain networks associated with TBI history, an average of 6.2 years postinjury and decreased levels of small-worldness associated with a diagnosis of PTSD in postdeployment Iraq and Afghanistan war veterans. Small-worldness is a network configuration characterized by short path lengths from any point in the network, while simultaneously maintaining high levels of clustering among nodes. *Post-hoc* analyses indicated the networks of participants with PTSD displayed decreases in clustering coefficient, but no differences in path length, while the networks of individuals with mild TBI history displayed increased levels of clustering coefficient without differences in path length. The findings of these two studies are not consistent; however, there was a significant difference in the time since injury and sample population that may explain these discrepancies.

Three studies have utilized functional magnetic resonance imaging (fMRI) to conduct whole-brain network analyses of TBI with mixed results. Higher modularity and a significant reduction in between module connectivity were associated with TBI history in a sample of active duty military personnel examined within 90 days of blast exposure (Han et al., 2014). Conversely, a reduction in modularity was observed in a civilian sample with TBI history and current postconcussive symptoms at 6 months postinjury (Messe et al., 2013). Finally, Spielberg et al. (2015) examined postdeployment veterans from the conflicts in Iraq and Afghanistan, finding no effect of PTSD or TBI on whole-network metrics, instead TBI moderated the relationship between graph metrics of specific brain regions and reexperiencing symptoms.

Overall, findings of studies utilizing network analyses to study TBI have produced mixed results that vary by the sample examined (e.g., civilian, veteran, and mixed severities), the time since injury, and the technology employed (Alhourani et al., 2016; Han et al., 2014; Messe et al., 2013; Rowland et al., 2017; Spielberg et al., 2015). However, differences in connectivity and network structure have been consistently reported, observed as soon as 24 h and as late as a decade following the injury. Alterations in brain networks offer insights into potential mechanisms through which TBI may increase the likelihood of developing PTSD. However, the changes in brain networks related to mild TBI are not yet fully characterized, and the circumstances under which these changes occur are not yet fully understood.

This study will determine differences in whole-brain resting-state functional networks associated with the development of PTSD following deployment-acquired mild TBI. Based on previous findings, it is hypothesized that higher levels of small-worldness, clustering coefficient, and modularity will be associated with the development of PTSD following deployment-acquired mild TBI.

Materials and Methods

This project was reviewed and approved by the Institutional Review Board at the W.G. ''Bill'' Hefner VA Medical Center in Salisbury, North Carolina. The welfare and privacy of human subjects were protected. Each participant voluntarily provided verbal and written informed consent before any study activity.

Participants

Participants were identified from a larger ongoing study (Blast Study) funded by the Chronic Effects of Neurotrauma Consortium. Inclusion criterion for the larger study was combat exposure during an Iraq or Afghanistan war deployment. Exclusion criteria for the larger study were as follows: TBI history outside of deployment involving loss of consciousness (LOC), neurological disorder, severe mental illness (schizophrenia or bipolar disorder), current substance use disorder, current psychotic symptoms, or presence of any contraindication for neuroimaging. Sixteen participants were identified from the larger study with a history of deployment-acquired mild TBI and included in this analysis. Seven participants met criteria for current PTSD. No participant met diagnostic criteria for PTSD before experience of deployment-acquired mild TBI. There was no requirement that the participants be experiencing current postconcussive symptoms.

Characterization

The Structured Clinical Interview for DSM-IV Diagnosis (SCID; First et al., 1996) was used to determine the presence or absence of any Axis I psychiatric diagnosis with the exception of PTSD. The SCID is a structured clinician-administered interview considered the gold standard for psychiatric diagnosis. The Clinician-Administered PTSD Scale–5 (CAPS-5; Weathers et al., 2017) was used to determine the presence or absence of current and lifetime PTSD using the past month and worst month versions. The CAPS-5 represents the gold standard assessment of PTSD. Participants were considered to have a current diagnosis of PTSD if they met at least one Criterion B symptom, one Criterion C symptom, two Criterion D symptoms, two Criterion E symptoms, as well as Criterion F and G. A structured clinician-administered interview was used to determine the presence or absence of mild TBI history across the lifespan according to the American Congress of Rehabilitation Medicine criteria

(Menon et al., 2010). Specifically, participants were considered positive for TBI if they experienced a force acting on the central nervous system that resulted in LOC, alteration of consciousness (AOC), or post-traumatic amnesia (PTA) of any duration. Severity was based on VA/DoD consensus criteria, with mild TBI displaying LOC less than 30 min, AOC less than 24 h, and/or PTA less than 24 h (Management of Concussion/mTBI Working Group, 2009).

Demographically adjusted premorbid IQ was estimated using the Test of Premorbid Function (Wechsler, 2009). Self-report questionnaires were used for further characterization of participants. Postconcussive symptoms were measured using the neurobehavioral symptoms inventory (Cicerone and Kalmer, 1995), a 22-item self-report inventory asking about the severity of common postconcussive symptoms over the past 2 weeks. PTSD symptoms were measured using the PTSD Checklist–5 (PCL-5; Blevins et al., 2015), a 20-item self-report inventory asking about the severity of PTSD symptoms over the past month. Severity of combat exposure was measured using the Deployment Risk and Resilience Inventory–2 Combat Experiences questionnaire (Vogt et al., 2012), a 17-item self-report inventory asking about the frequency of combat experiences during deployment.

MEG recordings

Data were acquired using a whole-head CTF Systems Inc. MEG 2005 neuromagnetometer system equipped with 275 first-order axial gradiometer coils. Head localization was achieved using a conventional three-point fiducial system (nasion and preauricular points). Resting-state recording was conducted with the participant seated upright, sitting quietly, and with eyes open for 5 min. Data were sampled at 2400 Hz over a DC-150 Hz bandwidth. MEG data were preprocessed using synthetic third-order gradient balancing, whole trial DC offset, and band pass filtered from 0.5 to 80 Hz with a 60 Hz notch filter. Data were visually inspected for obvious muscle artifact, and such epochs were discarded from further analyses. Following MEG recording, a T1-weighted MRI scan was obtained for each participant for the purpose of coregistration and localization of MEG signals.

Network analysis

The network analysis applied as part of this study is identical to that used by Rowland et al. (2017). Rowland et al. (2017) analyzed networks within the alpha bandwidth as well as a wide-band network (1–70 Hz). Based on results from that study, this analysis examined wide-band connectivity only. Network analysis proceeds in a stereotypical manner, first identifying nodes of the network (node identification section) and then quantifying communication among those nodes (estimating functional connectivity between nodes section). The resulting matrices are conducive to the application of graph theory for calculating metrics describing the topology of the network (calculation of network metrics section).

Node identification. A well-validated beamformer (synthetic aperture magnetometry; SAM) (Hillebrand et al., 2005; Robinson and Vrba, 1998) was applied (voxel size of 5 mm^3, lead fields for equivalent current dipoles, maximizing noise-normalized power) using a three-spherical shell, multiple local spheres head model based on the participant's MRI (Huang et al., 1999) to construct noise-normalized statistical parametric maps, identifying areas of significant brain activity for each participant individually. SAM was applied in the following frequency ranges: delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), gamma (30–80 Hz), as well as 0.5–80 Hz. Source series representing the unique weighted sum of the output across all MEG sensors for a specific location in the brain were calculated for each identified peak across all frequency ranges (Hillebrand et al., 2005; Robinson and Vrba, 1998).

Estimating functional connectivity between nodes. The weighted phase lag index (wPLI; Vinck et al., 2011) was calculated between all pairs of source series to measure functional connectivity between nodes. Each source series was divided into 6-sec epochs for this calculation. Connectivity was operationalized at the frequency with the highest wPLI value.

Thresholding. Data were first thresholded using 10,000 unique pairs of phase randomized surrogate time series calculated for each participant individually (Prichard and Theiler, 1994). Connectivity between node pairs was retained if at least two standard deviations higher than the surrogate data at the identical frequency bin (i.e., 10.25 Hz or 8.75 Hz). The resulting networks were then thresholded by satisfying the equation $S = \log(N)/\log(K)$ where N represents the number of nodes in the network and K the average degree (Hayasaka and Laurienti, 2010). We selected $S = 2.5$ as prior research has demonstrated equivalence of S values between 2 and 4 (Hayasaka and Laurienti, 2010).

Calculation of network metrics. Network metrics calculated are listed in Table 2. *Clustering Coefficient* was calculated as defined in Stam and Reijneveld (2007). The clustering coefficient is a measure of grouping within the network, indicating how likely the neighbors of a node are to also be connected with one another. *Small World* was calculated as defined in Watts and Strogatz (1998). The average of the clustering coefficient and path length of 500 independently generated random networks with the same number of nodes and degree distribution as the original network were used for the calculation of Small World. Small-worldness is a network configuration with the benefits of both lattice-like and random networks, in that it simultaneously possesses high clustering coefficient and short path length. It is calculated by comparing the clustering coefficient and path length within a network, both normalized by the same coefficients in a random network. *Modularity* was calculated using the Louvain method of community detection as defined in Blondel et al. (2008). Following the recommendations of the Brain Connectivity Toolbox (Rubinov and Sporns, 2010), the analysis was run 500 times, using the average Q and average number of modules (*Number Modules*) as outcome variables. Modularity indicates how many subnetworks can be identified within the larger network by iteratively breaking the network into cohesive subnetworks.

The number of nodes within each participant's network varied, ranging from 69 to 128, but were not significantly different between groups ($p > 0.45$). To control for possible effects of network size, each network metric was normalized by the number of nodes in the network from which it was calculated.

Materials

Beamforming and source series construction were completed using software provided by CTF MEG International Services LP (Coquitlam, BC, Canada). Further analyses of source series data and network creation were conducted using Matlab 2016a. Network metrics were calculated using the Brain Connectivity Toolbox (Rubinov and Sporns, 2010), as well as functions created by members of the study team. Statistical analyses were conducted using IBM SPSS Statistics Version 21.

Analyses

Between-group differences in continuous demographic and self-report variables were examined using *t*-tests. Differences in categorical variables were examined with chi-square analyses. Between-group differences in normalized network metrics were examined using univariate ANCOVAs controlling for age and estimated premorbid IQ. Results are presented using an uncorrected alpha level of 0.05 along with effect sizes (partial eta squared and Cohen's d) to aid interpretation.

Results

Characterization

Table 1 for means and standard deviations of demographic variables. Seven participants met diagnostic criteria for current PTSD according to the CAPS-5 and 9 did not. Participants diagnosed with PTSD were significantly younger, $F(1,14) = 6.63$, $p = 0.022$, and scored significantly higher on the PCL-5, $F(1, 14) = 15.83$, $p < 0.001$. There were no other significant between-group differences. All participants were in the chronic stage of TBI (e.g., at least 1 year postinjury) at the time of participation. All participants met criteria for history of mild TBI (e.g., <30 min LOC, <24 h AOC, and <24 h PTA), none had history of TBI greater than mild. All TBIs occurred during deployment. Six of seven participants with PTSD developed the condition as a result of deployment-related traumatic events. For one, the traumatic event occurred after deployment. No participant diagnosed with PTSD had onset of the disorder before deployment.

Table 1. Participant Characterization Presented as Mean (*SD*), Unless Otherwise Indicated

	PTSD n = *7*	*No PTSD* n = *9*
Age*	34.9 (4.7)	43.4 (7.8)
Education	15.1 (1.6)	16.6 (2.2)
Number of deployments	2.4 (1.1)	2.1 (1.1)
Number of combat deployments	1.7 (1.1)	1.9 (1.2)
Time since TBI (days)	3312.0 (1377.6)	4781.0 (2802.1)
TOPF	102.4 (7.4)	100.0 (12.4)
DRRI combat experiences	52.1 (9.1)	41.4 (14.2)
% Male	100	100
% Minority	14.3	28.6
NSI	31.1 (17.2)	16.9 (15.6)
PCL-5*	46.1 (12.8)	21.1 (12.3)
Psychiatric medication (% positive)	57 ($n = 4$)	44 ($n = 4$)

Total sample size = 16.
*Significant group difference, $p < 0.05$.
TBI, traumatic brain injury; TOPF, test of premorbid function; DRRI, deployment risk and resiliency inventory; PTSD, post-traumatic stress disorder; NSI, neurobehavioral symptom inventory; PCL-5, PTSD checklist–5.

Table 2. Mean (*SD*) of Network Metrics

	PTSD $n = 7$	*No PTSD* $n = 9$
Clustering coefficient*	0.43 (0.12)	0.33 (0.10)
Small World*	2.01 (0.50)	1.57 (0.40)
Q	0.44 (0.16)	0.34 (0.12)
Number of modules	17.67 (9.60)	18.21 (10.38)

All variables have been normalized by the number of nodes in a network and are presented $\times 10^2$ for ease of reading. Total sample size = 16.
*Significant group difference, $p < 0.05$.

Network outcomes

Mean and standard deviation of network metrics can be seen in Table 2. Participants with deployment-acquired TBI who developed PTSD displayed higher levels of small-worldness, $F(1,12) = 5.364$, $p < 0.039$, partial eta squared = 0.309, Cohen's d = 0.972, and clustering coefficient, $F(1, 12) = 12.204$, $p < 0.004$, partial eta squared = 0.504, Cohen's d = 0.905, than participants who did not develop PTSD. This is visually displayed in Figure 1. Modularity (Q) and the number of modules present were not different between groups. All participants except one had Small World greater than 1. In other words, PTSD diagnosis was associated with increases in the small world nature of the networks, and relatedly clustering within the networks. The group separation is not perfect, but clearly present in Figure 1. The increased clustering did not alter the modularity of the networks or the number of modules present.

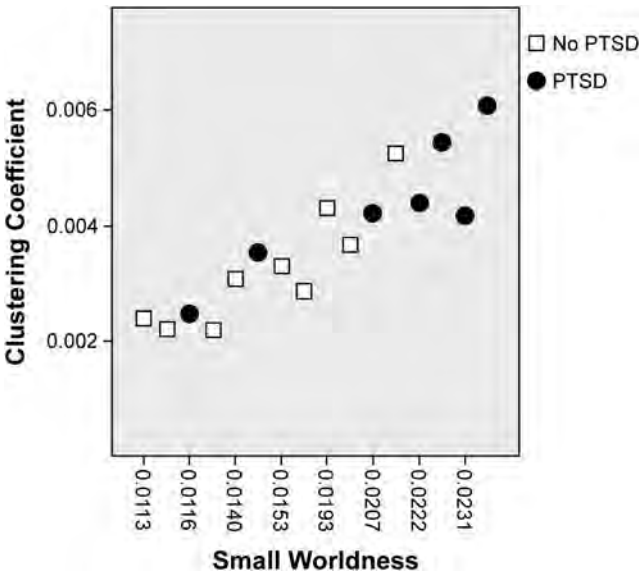

FIG. 1. Scatter plot comparing normalized clustering coefficient and small-worldness by PTSD. PTSD, post-traumatic stress disorder.

Discussion

This study adds to the small, but growing literature combining resting-state MEG and network analyses to better understand TBI and PTSD. Previous work has clearly demonstrated that deployment-acquired TBI is a risk factor for the development of PTSD, beyond confounds such as combat exposure, physical injury, predeployment TBI, and predeployment psychiatric symptoms. This study demonstrates significant differences in whole-brain resting-state network topology between individuals who did and did not develop PTSD following deployment-acquired TBI. These differences represent one possible neurobiological mechanism through which deployment-acquired TBI may increase the risk of subsequently developing PTSD.

Two previous studies have identified potential mechanisms through which TBI may increase the risk of developing PTSD. Morissette et al. (2011) reported a potentially mediating role of postconcussive symptoms in the development of PTSD following deployment-acquired TBI. However, postconcussive symptoms are nonspecific and can result from many conditions and experiences, including PTSD itself. Postconcussive symptoms were not significantly different between individuals with and without PTSD in this study. Glenn et al. (2017) examined fear learning and extinction processes as potential mediators between deployment-acquired TBI and the development of PTSD. The study demonstrated that fear processes were altered as a result of deployment-acquired TBI. However, altered fear processes mediated the relationship between deployment-acquired TBI and PTSD only in cases where the participant had sustained a nondeployment TBI within the 2 years before deployment. Neither of these prior studies included neurobiological outcomes. Comparisons between changes in resting-state network topology, postconcussive symptoms, and fear processes may help better characterize the circumstances under which TBI increases the risk of developing PTSD and identify potential relationships across these modalities of inquiry. Future studies are encouraged to gather data across various modalities, including imaging, behavioral, and symptom report.

Two studies have utilized MEG to conduct whole-brain network analyses of individuals with TBI history. Alhourani et al. (2016) found reduced local efficiency in brain regions associated with the default mode network in civilian participants with mild TBI, a median of 8-months postinjury. Reductions in local efficiency occurred across several frequency ranges, most notably in the alpha and delta ranges. Rowland et al. (2017) found increases in small-worldness of whole-brain networks associated with TBI an average of 6.2 years after the injury and decreased levels of small-worldness associated with a diagnosis of PTSD in postdeployment Iraq and Afghanistan war veterans.

These findings extend those of Rowland et al. (2017) demonstrating the potential pathological implications of differences in network topology. While this entire sample was diagnosed with deployment-acquired mild TBI, the subsample who developed PTSD displayed higher levels of small-worldness and clustering coefficient than individuals who did not develop PTSD. Changes in clustering coefficient did not result in alterations in modularity, suggesting that the increase in clustering is not occurring specifically within modules, but is balanced by increases in intramodule clustering as well.

These findings do not clearly support the view of TBI as a disorder of disconnection (Hayes et al., 2016). The observed changes demonstrate that an increasing number of nodes are connecting to neighbors of nodes with which they are already connected, suggesting an increased level of order in the network, similar to the findings of James et al. (2013). The nature of this analysis maintains a particular ratio between the number of nodes and the number of connections (Hayasaka and Laurienti, 2010) If network changes were seen as a result of disconnection, the additional connections being maintained would be expected to occur randomly, decreasing clustering coefficient and small-worldness of the networks. While not directly evaluated as part of this analysis, these findings are consistent with the hyperconnectivity hypothesis (Hillary et al., 2014), suggesting the brain responds to TBI with increased connectivity in particular pathways as a potential coping or repair mechanism. It is possible these alterations also create a neurological milieu conducive to the development of PTSD, potentially within specific subnetworks. Future studies could investigate the anatomic consistency of network changes across individuals and how those changes affect particular subnetworks.

Limitations of this study include a small sample size. These findings should be considered preliminary until replicated in a larger sample. However, calculations suggest that the observed differences represent a moderate effect size. The findings are also consistent with those of Rowland et al. (2017), a study applying identical methods to an independent sample, suggesting the findings are robust and replicable. Another limitation is the cross-sectional nature of the study. It is possible that the observed differences in resting-state networks were present before the TBI event rather than a consequence of it. Alternatively, the TBI event may have created transient neurobiological alterations that resolved before study participation.

An additional limitation relates to the continuous nature of psychopathology. This study divided participants by PTSD diagnosis; however, many participants who did not meet full criteria for PTSD diagnosis nevertheless displayed subthreshold levels of symptoms. Future studies using larger sample sizes should consider alternative analytic approaches that could incorporate and potentially explain this variance across symptom presentations and its relationship to alterations in network metrics. It is also possible the observed group differences are the result of a cascade of changes initiated by the TBI event, but not yet present when PTSD initially developed. Future studies applying longitudinal designs or nonhuman models may help clarify temporal relationship between TBI, PTSD, and functional network differences. Finally, the methods applied to create networks generate a partial network solution, identifying areas of the brain active at rest and quantifying communication among them. This approach by definition does not identify when expected regions are not part of the network, potentially as a sequelae of TBI. Future studies may consider combining this approach with a standardized region of interest or voxel-based approach to allow an understanding of differences in the brain regions present in the networks or their role in the network.

Conclusion

Deployment-acquired TBI has been demonstrated to be an independent risk factor for the subsequent development of

PTSD, beyond other known risk factors. This study demonstrates differences in small-worldness and clustering coefficient of resting-state brain networks between individuals who did and did not develop PTSD following a deployment-acquired TBI. These findings suggest the possibility that neurobiological mechanisms contribute to the increased risk for developing PTSD and highlight the need for further study in this area.

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Disclaimers

The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs, the Department of Defense, or the U.S. government.

Author Disclosure Statement

All authors declare that no competing financial interests exist.

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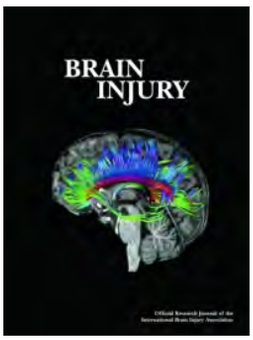

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Longitudinal changes in neuroimaging and neuropsychiatric status of post-deployment veterans: A CENC pilot study

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Longitudinal changes in neuroimaging and neuropsychiatric status of post-deployment veterans: A CENC pilot study

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ABSTRACT

Primary objective: The purpose of this study was to evaluate preliminary data on longitudinal changes in psychiatric, neurobehavioural, and neuroimaging findings in Iraq and Afghanistan combat veterans following blast exposure.
Research design: Longitudinal observational analysis.
Methods and procedures: Participants were invited to participate in two research projects approximately 7 years apart. For each project, veterans completed the Structured Clinical Interview for *DSM-IV* Disorders and/or the Clinician-Administered PTSD Scale, Neurobehavioral Symptom Inventory, and magnetic resonance imaging (MRI).
Main outcomes and results: Chi-squared tests indicated no significant changes in current psychiatric diagnoses, traumatic brain injury (TBI) history, or blast exposure history between assessment visits. Wilcoxon signed-rank tests indicated significant increases in median neurobehavioural symptoms, total number of white matter hyperintensities (WMH), and total WMH volume between assessment visits. Spearman rank correlations indicated no significant associations between change in psychiatric diagnoses, TBI history, blast exposure history, or neurobehavioural symptoms and change in WMH.
Conclusion: MRI WMH changes were not associated with changes in psychiatric diagnoses or symptom burden, but were associated with severity of blast exposure. Future, larger studies might further evaluate presence and aetiology of long-term neuropsychiatric symptoms and MRI findings in blast-exposed populations.

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Traumatic brain injury (TBI) was reported in 375 230 Iraq and Afghanistan-era service members from 2000 through November of 2017 (1), the vast majority of which (82.3%) were consistent with mild TBI (i.e. concussion). Due to the high usage of improvised explosive devices (IEDs), rockets, and mortars in the recent conflicts, a large number of deployment TBIs are blast related (2). A large VA study of over 55 000 Veterans found that 36% of deployment TBIs were related to blast and 44% were blast plus blunt force causes (3). More recent research has also evaluated the effects of subconcussive blast exposure (4–6), in other words, exposure in which criteria for concussion are not met. The long-term effects of primary blast exposure on veterans returning from the wars in Iraq and Afghanistan are currently unknown. Although the prognosis of mild TBI is a fast and full recovery for most individuals, including veterans (7–9), initial studies (reviewed below) vary on how blast exposure (with or without TBI) may reflect a different underlying pathology and a potentially different set of outcomes. Given the high number of veterans who have been exposed to significant blasts in recent conflicts (10), it is imperative to identify any persisting underlying neuropathology and subsequent neuropsychiatric disruption secondary to blast wave exposure to inform large-scale diagnostic and treatment efforts with returning veterans.

Service members may be exposed to a multitude of different blast forces during their military service both throughout training and deployment (11). These events may or may not be accompanied by symptoms congruent with TBI. Primary blast exposure in the absence of other blunt force mechanisms is relatively unique to veterans not only due to the mechanism (s) of action, but to a number of other variables surrounding the injury event when experienced in combat (12). A post-mortem study comparing military service members with blast exposures to civilians with blunt TBI reported that astroglial scarring at interfaces between tissue types (e.g. grey matter/white matter, fluid/brain parenchyma) was unique to blast exposure (13). Characterizing blast exposure is difficult due to variability in exposure including mechanism (e.g. rocket, mortar, IED), distance from the blast, magnitude of the blast, and environmental barriers, among other factors (6).

The long-term neuropsychiatric outcomes following primary blast exposure in veterans are unknown. Assessment is complicated by presence of common comorbidities, including TBI and posttraumatic stress disorder (PTSD). For example, a recent systematic review found no difference in clinical or functional outcomes across TBI studies that were blast or blunt force related (14). However, results were inconsistent for PTSD, hearing issues, headaches, and some cognitive variables. A study of

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neurocognitive impairments found no differences in cognition across blast versus blunt force-related TBI after accounting for psychiatric symptoms (15). More recently, a longitudinal study compared cognitive and neuropsychiatric outcomes of veterans with blast-related TBI compared to combat controls with and without exposure to non-concussive blast (16,17). Early in the chronic stage (6–12-month follow up) symptom burden was elevated in blast-exposed controls compared to controls without blast exposure, indicating possible subconcussive effects (17). Although there was no significant difference between groups for any of the cognitive variables after controlling for family-wise error, there was notable worsening in global disability ratings and neuropsychiatric symptoms in the blast-related TBI group, leading the authors to suggest that veterans 'with concussive blast TBI experience evolution rather than resolution of symptoms from the 1- to 5-year outcomes' (16). Of note, in the predictive model for global disability status at 5 years, variables from year 1 included neurobehavioural symptoms and premorbid ability. This echoes the findings of Lange and colleagues (15) in which psychiatric variables accounted for the differences seen in blunt compared to blast-related TBI. Another study evaluating comorbidities and differing trajectories across 3 years following TBI found comorbid conditions, including psychiatric conditions, pain, and other medical conditions the rule rather than the exception (18). A common theme across studies are the numerous neuropsychiatric comorbidities that complicate the ability to distinguish the chronic effects of TBI and blast exposure.

Neuroimaging findings following blast exposure have also been mixed. An increase in the number and/or volume of white matter hyperintensities (WMH) seen on fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) in military members or veterans with blast-related TBI compared to controls has been found by some but not by others (19–21). Some of the difference may be due to how each study adjusted for age as a gradual increase in the number of such areas is considered a normal aspect of brain aging (19). Several studies have reported elevated levels of spatially heterogenous abnormal findings on diffusion tensor imaging (DTI) in groups with blast-related mild TBI (22). Individuals with blast-related TBI have shown to have a higher incidence of spatially heterogeneous white matter abnormalities detected with DTI, with no effect of blunt force TBI (23). However, an expanded sample including participants with PTSD did not replicate this effect (24). Blast-related TBI involving loss of consciousness (LOC) has been associated with increased numbers of regions of interest with white matter abnormalities (25). This is consistent with other work showing an increased likelihood of spatially heterogeneous white matter abnormalities associated with blast-related TBI involving LOC compared to injuries not involving LOC or blast exposure without resulting TBI (20). MacDonald and colleagues (26) demonstrated abnormalities in three of four individuals with a history of TBI due only to blast exposure, without history of blunt force TBI (i.e. primary blast TBI). Taber and colleagues (27) found that primary blast exposure both with and without symptoms at the time consistent with TBI was associated with increased spatially heterogenous abnormal DTI findings compared to non-exposed veterans.

Though the literature on blast exposure suggests the possibility of direct effects on brain function and structure, there is a dearth of information about the long-term consequences of primary blast exposure in the absence of other blunt force mechanisms. MacDonald and colleagues (28) found that white matter injuries remained, and potentially evolved, over a 5-year period in service members with blast-related mild TBI; however, most injuries involved additional non-blast mechanisms. Thus, the aim of this longitudinal study was to evaluate long-term neuroimaging changes and neuropsychiatric symptoms following primary blast exposure in a small sample of post-deployment veterans. The present analysis utilized clinical interviews, symptom self-report, and neuroimaging data collected from veterans who participated in two studies investigating outcomes associated with blast exposure conducted approximately 7 years apart. Based on existing literature on mild TBI and typical symptom course, we expected that (1) psychiatric symptoms would improve over time, such that there would be little incidence of new-onset PTSD and major depressive disorder (MDD) and that most participants with diagnoses at Time 1 (T1) would no longer meet current criteria for that diagnosis at Time 2 (T2); (2) neuropsychiatric symptom burden would decrease between T1 and T2; and (3) incidents of WMH observed on neuroimaging would remain stable between T1 and T2.

Methods

Data for the present analyses were obtained from two separate IRB-approved studies at the Salisbury Veterans Affairs Health Care System in North Carolina, USA. Participants from T1 (N = 48), conducted from 2007 to 2010, were invited 6.08–9.33 years (M = 7.39, SD = 1.00) later to participate in T2, which began in 2015. The second study was not a planned longitudinal follow-up to the first; therefore, the current sample represents a fortuitous convenience sample. Each study involved two in-person visits. The first was an assessment visit that included structured clinical interviews and symptom questionnaires; the second was a neuroimaging visit.

Nineteen participants from T1 completed the assessment visit for T2. Eleven participants completed the neuroimaging visit for both T1 and T2. Two participants did not complete T1 neuroimaging (unable to schedule) and seven participants did not complete T2 neuroimaging (six ineligible, one declined). Of note, 30 participants from T1 who may have been eligible to participate in T2 declined to be assessed (*moved* = 9, *uninterested* = 11, *other* = 2) or were unable to be contacted (n = 8).

Eligibility

Inclusion criteria for both studies were deployment after 11 September 2001 in support of the wars in Iraq and Afghanistan, English speaking, 18 years of age or older, and able to provide informed consent. Participants were excluded if they reported a lifetime history of moderate or severe TBI; history of any penetrating head injury or a non-deployment TBI with LOC for any period of time; history of major neurological disorder such as stroke, seizure, or spinal cord

injury; history of serious mental illness such as bipolar disorder or schizophrenia; and current presence of dementia, substance use disorder, or psychosis. Eligibility was determined through screening and confirmed by information from structured interviews. Exposure to conditions or events during or following deployment likely to result in a TBI due to forces other than primary blast (e.g. motor vehicle accident, contact sports, assault) was an additional exclusion criterion for T1. Exclusion criteria specific to neuroimaging activities included pregnancy, inability to tolerate an enclosed space for MRI, presence of ferrous metal other than fillings, including orthodonture or implanted objects known to generate magnetic fields (e.g. prosthetic devices, pacemakers, neurostimulators, etc.) that may interfere with neuroimaging data acquisition and/or be an MRI safety concern.

Psychological measures

All measures were administered in a standardized manner by licensed psychologists, neuropsychologists, and/or trained and supervised research staff and postdoctoral fellows. The Mid-Atlantic Mental Illness Research, Education and Clinical Center (MA-MIRECC) TBI Interview is a clinician-administered, structured interview developed at the MA-MIRECC to evaluate history of TBI (29). The cause, duration of LOC, alteration of consciousness, and post-traumatic amnesia, as well as symptoms immediately following each occurrence are evaluated. TBI severity was based on Department of Veterans Affairs (VA) and Department of Defense (DoD) consensus criteria (30). TBI history was determined using the MA-MIRECC TBI Interview for T2, and TBI history was determined by a VA polytrauma provider for T1. The Salisbury Blast Exposure Interview is a clinician-administered, structured interview evaluating blast exposure across the lifespan. Participants are asked about any history of exposure to blasts or explosions regardless of the setting (i.e. civilian, military training, combat) across the lifetime. Circumstances (e.g. in a vehicle, wearing protective gear, behind cover), effects (e.g. thrown to the ground), characteristics (i.e. wind, ground shaking, pressure change, temperature change, debris, sound), distance, and other information about each blast exposure are collected. Subjective ratings on anchored Likert scales (0–5) are obtained for all six characteristics. For the present analyses, blast exposure was operationalized as any explosion for which the participant reported feeling a slight pressure gradient (rating of 1 = *slightly, noticeable but not uncomfortable*), or more. For the purposes of this article, 'blast exposure' refers to the experience of pressure following a blast, which may or may not have been accompanied by symptoms congruent with a TBI.

The Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID) (31) is a structured interview to evaluate criteria of *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (*DSM-IV*) Axis I psychiatric disorders. All modules were administered to all veterans who participated in T1. All modules except for PTSD were administered to T2 participants. Outcome variables included current and lifetime presence/absence of all Axis I psychiatric disorders. The Clinician-Administered PTSD Scale (CAPS-5) (32) was used to evaluate *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (*DSM-5*) criteria of PTSD for T2. The CAPS-5 is a 30-item clinical interview that provides current and lifetime diagnosis of PTSD. This was administered in lieu of the SCID PTSD module.

Neuropsychiatric symptom burden was evaluated using the Neurobehavioral Symptom Inventory (NSI) (33). The NSI is a 22-item self-report questionnaire that evaluates neuropsychiatric symptoms. Each item is measured on a 5-point Likert scale, indicating the extent to which each symptom bothered the individual over the prior two weeks (0 = *none*, 4 = *very severe*). Higher scores are reflective of greater symptom severity. The mild TBI Brain Injury Atypical Scale (34) was also administered. All participants scored a 0, indicating good validity.

Neuroimaging

MRI data for T1 was acquired on a General Electric Signa HDxt 1.5 T scanner with an eight-channel receive coil. Imaging included T1-weighted, T2-weighted, and FLAIR pulse sequences. MRI data for T2 acquired on a 3 T Siemens Skyra MRI scanner using a high-resolution 32-channel human head/neck coil (Siemens Medical, Malvern, PA, USA) in accordance with the National Institute of Neurological Disorders and Stroke Common Data Elements advanced protocol recommendations including structural T1-weighted, T2-weighted, and FLAIR pulse sequences. Scan parameters for T1 are as follows: T1 SPGR TR 7876 TE 2.24 TI 300 FOV 208 voxel 0.5 × 0.5 × 1.5 mm; T2w GRE TR 517 TE 30 FOV 180 voxel 0.5 × 0.5 × 1.5mm; T2 FLAIR TR 9000 TE 143 TI 2250 FOV 260 voxel 0.5 × 0.5 × 1.5 mm. Scan parameters for T2 are as follows: T1 MPRAGE TR 2300 TE 2.98 TI 900 FOV 256 voxel 1 × 1 × 1.2 mm; T2 TSE TR 3200 TE 222 FOV 256 voxel 1 × 1 × 1.2 mm; T2 FLAIR TR 6000 TE 263 TI 2100 FOV 256 voxel 0.5 × 0.5 × 1.2 mm. Outcome variables included the number of WMH identified on FLAIR as well as the total volume of those areas calculated at both time points (procedure described below). It was expected that visibility of WMHs would be improved at T2, resulting in some increases in both numbers and total volumes (35).

Procedures

Both studies included an assessment visit preceding the neuroimaging visit to fully evaluate eligibility for enrolment into imaging. The T1 assessment visit included completion of the SCID, NSI, and structured interviews to determine TBI and blast exposure history. TBI history was determined by a VA polytrauma TBI provider. If the participant report and medical record conflicted, the medical record TBI status was used. The T2 assessment visit included completion of the SCID, CAPS-5, NSI, TBI interview, and blast interview. Additionally, participants were excluded from the neuroimaging visit of T2 if they invalidated performance validity (Medical Symptom Validity Test and b Test) or symptom validity (Structured Inventory of Malingered Symptomatology) measures during the assessment visit.

Areas of abnormally increased signal intensity (WMH) were identified on FLAIR images using the lesion prediction algorithm (LPA) (36) as implemented in the Lesion Segmentation

Toolbox (www.statistical-modelling.de/lst.html) for statistical parametric mapping. LPA was chosen for speed and reproducibility because no user input of parameters is required. Lesion maps were then manually reviewed and edited to remove artefacts. These maps were analysed using custom Python code to extract the number and volume of WMHs.

Data analysis

Data was analyzed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Non-parametric statistics were used due to small sample size. Change in psychiatric diagnoses (SCID), TBI history (MA-MIRECC TBI Interview), and blast exposure history (Salisbury Blast Exposure Interview) were evaluated using chi-squared tests for the presence/absence (coded dichotomously, 0 = *absent*, 1 = *present*) of diagnosis of interest at T1 and T2. Due to the small sample size, *p*-values for Fisher's exact test are provided in addition to chi-squared results. Diagnoses selected for analysis included current PTSD and MDD. Changes in neurobehavioural symptoms (NSI), number of WMHs, and WMH volume were evaluated using Wilcoxon signed-rank tests. To evaluate associations between changes in psychiatric diagnoses, neurobehavioural symptoms, and imaging, change scores were calculated by subtracting T1 scores from T2 scores for each variable. Change scores were then analysed with Spearman rank correlations.

Table 1. Participant characteristics at Time 1 and 2 (N = 19).

	T1		T2	
Variable	*n*	%	*n*	%
Sex				
Male			16	84.21
Female			3	15.79
Race/ethnicity				
White			11	57.89
Black			7	36.84
Hispanic			1	5.26
Blast exposed*				
No	10	52.63	5	27.28
Yes	9	47.37	13	72.22
TBI history				
None	17	89.47	7	36.84
Mild	2	10.53	10	52.63
Moderate	0	0	2	10.53
MDD current				
No	16	81.25	18	94.74
Yes	3	18.75	1	5.26
PTSD current**				
No	13	68.42	13	72.22
Yes	6	31.58	5	27.78
Branch of service				
Air Force			1	5.26
Army			6	31.58
Army National Guard			6	31.58
Army Reserves			2	10.53
Navy			2	10.53
Navy Reserves			2	10.53

Note. *Blast Interview missing for 1 T2 participant.
**Clinician Administered PTSD Scale (CAPS-5) missing for one participant in T2. Percentages only include available data. Branch of Service refers to the most recent branch of service. TBI = traumatic brain injury; MDD = major depressive disorder; PTSD = posttraumatic stress disorder.

Results

Aggregate demographic information for the sample is presented in Table 1. Table 2 reports participant-level exposure and outcome data. Participants were 19 veterans (15.79% female) between the ages of 24 and 60 at T1 (M = 39.05, SD = 9.42) and 30 and 68 at T2 (M = 46.32, SD = 9.63). The time between T1 and T2 participation was 6.08–9.33 years (M = 7.39, SD = 1.00). Participants reported between 12–19 years of education at T2 (M = 15.74, SD = 2.31). At T2, participants had 1–4 (M = 1.89, SD = .99) combat deployments, and 5 participants redeployed between T1 and T2. Service connected disability at T2 ranged from 0% to 100% (M = 44.47, SD = 35.94). At T2, three participants had no blast exposure or history of TBI (control group; Table 2 IDs 1–3). Three participants had no blast exposure but did have TBI (blunt TBI group; IDs 4–6). Of the 13 participants reporting primary blast exposure, 4 had only primary blast exposure (blast only group; IDs 7–10), and 9 also reported a history of TBI (blast and TBI group; IDs 11–19).

Chi-squared analysis indicated no significant differences in current PTSD diagnosis, χ^2 = 0.14, p = .710, Fisher's exact test p = .385, current MDD diagnosis, χ^2 = .20, p = .656, Fisher's exact test p = .842, TBI status, χ^2 = 0.17, p = .683, Fisher's exact test p = .491, or blast exposure history, χ^2 = 2.49, p = .114, Fisher's exact test p = .132, between T1 and T2. Results for Wilcoxon signed-rank tests are reported in Table 3. Analysis indicated that the median NSI scores at T2 were significantly higher than median NSI scores at T1. NSI scores were not significantly correlated between time points, $r_s(16)$ = .44, p = .088. Although most participants were in the normal range at both T1 and T2, the median total number of WMHs and total WMH volume were significantly higher at T2. As shown in Figure 1, this was primarily due to four participants (IDs 7, 8, 14, 19). All four participants had blast exposure at T1, two had TBI at T1, one of which had another TBI by T2. Visual comparisons of sectional images from T1 and T2 indicated that the higher quality of imaging at T2 was an influence, as several of the 'new' hyperintense areas were faintly present on the T1 images (see Figure 2 for an example).

Spearman rank correlations between difference scores on imaging metrics and psychiatric variables of interest are reported in Table 4. Notably, zero-order Pearson correlations between total number of WMHs, WMH volume, and psychiatric outcome variables at T1 were not significant (p = .808–.114). Correlations between current PTSD diagnosis and number of WMH (r = .61, p = .047) and total WMH volume (r = .66, p = .025) at T2 were significant. No other correlation between WMH number or volume and psychiatric outcome was significant at T2 (p = .845–.324). Overall, these outcomes indicate that changes in imaging metrics were unrelated to changes in PTSD and MDD diagnosis, TBI history, blast exposure, and NSI scores.

No participant in either the control group or the blunt TBI group had current PTSD or MDD at either time point. NSI scores increased from T1 to T2 for four participants in those groups (IDs 1, 3, 4, 5). Three had redeployed, one of whom also experienced a new TBI event between T1 and T2. One participant (25%) in the blast only group (ID 9) had PTSD at T1, which had not resolved at T2 (0% recovery). Another (ID 8) had new-onset MDD at T2. NSI increased from T1 to T2 for both participants. Five participants in the blast and TBI group (IDs 11, 12, 17, 18, 19) did not report another TBI between T1 and T2. Three (60%) of these participants (IDs 12, 18, 19) had PTSD at T1, all of which had resolved by T2 (100% recovery). Four participants in the blast and TBI group experienced another TBI between T1 and T2 (IDs 13–16). Two (50%) of these

Table 2. Individual participant data.

					T1				T2			
Subject	Blast Exposed	TBI History	Redeployed	New TBI	PTSD	MDD	NSI	WMH	PTSD	MDD	NSI	WMH
1	N	N	2	N	–	N	0	–	–	N	17	–
2	N	N	1	N	N	N	7	0	N	N	7	2
3	N	N	0	N	N	N	2	–	N	N	12	–
4	N	Y	1	N	N	L	11	2	N	L	16	3
5	N	Y	1	Mild	N	N	19	–	L	N	78	–
6	N	Y	0	N	N	N	–	2	N	N	3	4
7	Y	N	0	N	N	N	1	2	L	N	9	26
8	Y	N	0	N	N	N	7	11	L	C	22	51
9	Y	N	0	N	C	N	39	0	C	L	48	0
10	Y	N	0	N	N	N	4	0	N	N	2	2
11	Y	Y	0	N	N	N	1	–	C	N	58	–
12	Y	Y	0	N	C	C	53	–	L	L	22	–
13	Y	Y	1	Mild	N	N	10	–	C	N	42	–
14	Y	Y	0	Mild	N	N	7	49	C	L	33	208
15	Y	Y	0	Mod	C	C	27	–	C	N	31	–
16	Y	Y	0	Mild	C	C	–	–	L	N	20	–
17	Y	Y	0	N	N	N	4	2	N	N	3	3
18	Y	Y	0	N	C	N	17	0	L	N	35	1
19	Y	Y	0	N	C	N	–	1	N	N	18	13

Note. For blast-exposed and TBI history, Y = yes, N = no. No participants reported new blast exposure between T1 and T2.
TBI = traumatic brain injury, PTSD = posttraumatic stress disorder, MDD = major depressive disorder, NSI = Neurobehavioral Symptom Inventory. Redeployed = number of times redeployed between T1 and T2. New TBI = TBI acquired between T1 and T2, N = no new TBI, Mild = mild TBI, Mod = moderate TBI. T1 = baseline assessment. T2 = follow-up assessment. For PTSD and MDD, N = no history, L = lifetime history, C = current. WMH = number of white matter hyperintensities.
'–' indicates data not available.

Table 3. Wilcoxon signed-rank tests outcomes (N = 19).

	T1						T2							
	n	*M*	*SD*	Mdn	Min	Max	*n*	*M*	*SD*	Mdn	Min	Max	Z	*p*
NSI	16	13.06	15.02	7	0	53	19	25.05	20.27	20	2	78	45	.008
Number of WMH	11	6.27	14.51	2	0	49	11	28.45	61.52	3	0	208	27.5	.002
Total WMH volume	11	370.45	1178.50	12	0	3923	11	1369.27	4187.77	54	0	13987	27.5	.002

Note. T1 = study 1; T2 = study 2; *M* = mean; *SD* = standard deviation; Mdn = median; Min = minimum; Max = maximum; Z = *z*-value for Wilcoxon signed-rank test; *p* = significance; NSI = Neurobehavioral Symptom Inventory; WMH = white matter hyperintensity.

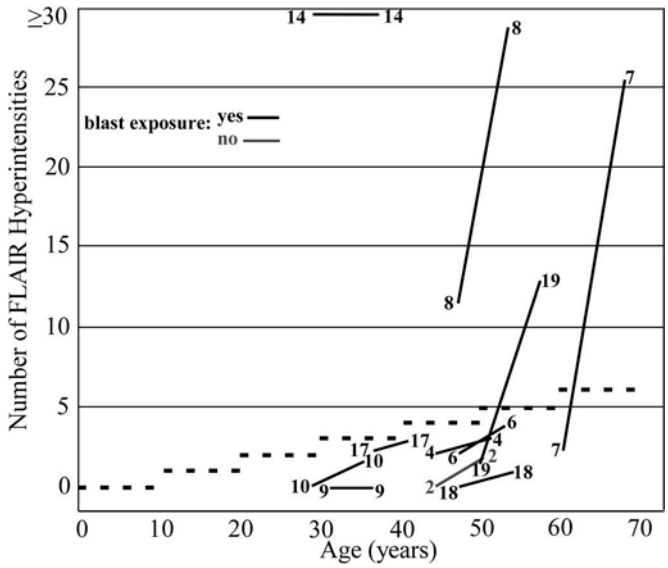

Figure 1. Number of FLAIR white matter hyperintensities (WMH) at T1 and T2. This figure illustrates the findings of number of WMH for each participant who was imaged at T1 and T2. The dashed lined indicates number of expected WMHs, based on one additional per decade of life as normal (19). Participant numbers correspond with subject number in Table 2. Of note, all but two participants are in the normal range at T1. Two additional participants have elevated number of WMHs at T2. Visual comparison of the sectional images indicated the higher quality of imaging at T2 was a major influence as most of the additional hyperintense areas were faintly present on T1 images.

participants (IDs 15, 16) had PTSD at T1, with one resolving by T2 (ID 16; 50% recovery). There were two cases (IDs 13, 14) of new-onset PTSD, both in the blast and TBI group, one with a new TBI event occurring between T1 and T2. Both cases were associated with increases in NSI scores at T2.

Exploratory analyses were conducted to determine if certain blast characteristics (frequency; severity, based on most severe overall) were correlated with WMH number and volume at both T1 and T2. Additional Pearson correlations were conducted to determine if blast characteristics and occurrence of new TBI (coded by severity) were correlated with changes in WMH number and volume between T1 and T2. At T1, the severity of blast exposure was significantly correlated with WMH number (r = .72, p = .011) and there was a trend towards WMH volume (r = .73, p = .061). Number of blasts was not correlated with either WMH number (r = –.06, p = .851) or volume (r = –.16, p = .735) at T1. Similarly, at T2 severity of blast exposure was significantly correlated with both number of WMHs (r = .76, p = .007) and WMH volume (r = .69, p = .019). Number of blasts was not correlated with either number of WMHs (r = –.06, p = .86) or WMH volume (r = –.14, p = .678) at T2. Regarding change between T1 and T2, there were significant associations between severity of blast exposure on changes in WMH number (r = .54, p = .018) and volume (r = .50, p = .031). There was no association between number of blasts on change in WMH number (r = –.07, p = .769) or volume (r = –.09, p = .720). There was also no association between new

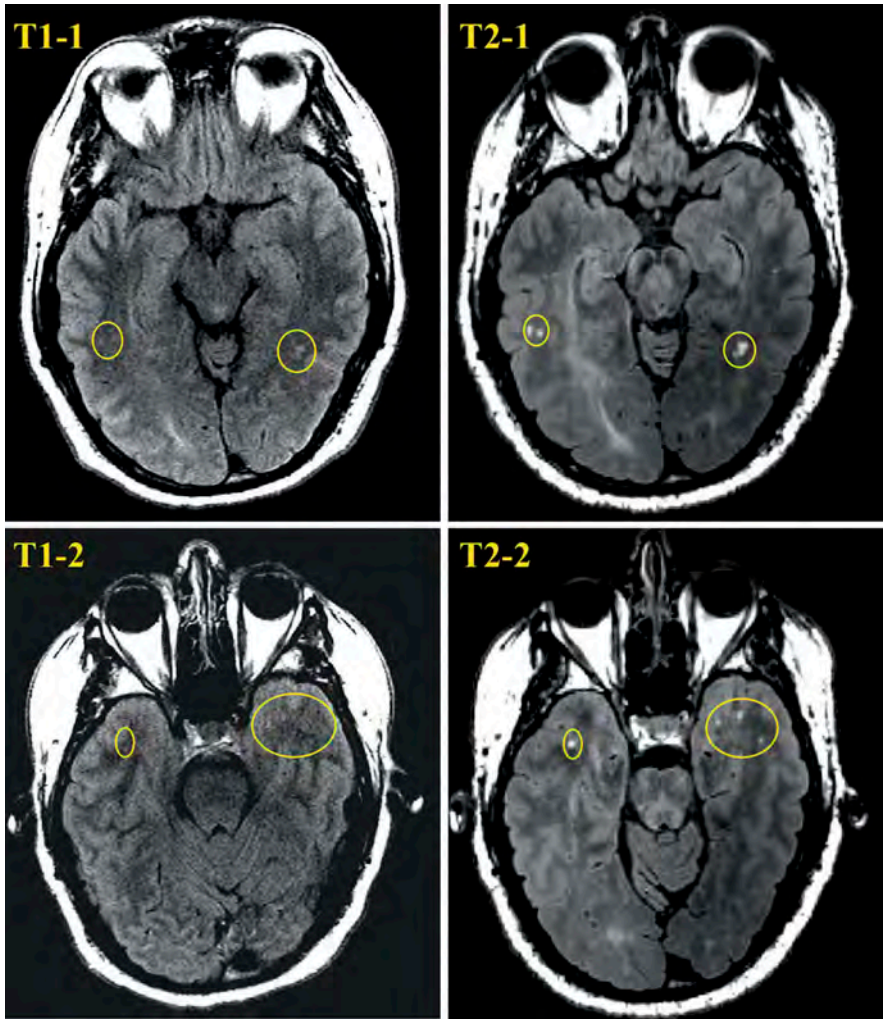

Figure 2. Visual comparisons of sectional images at T1 and T2. This figure illustrates differences in two sections (indicated by −1 or −2) at T1 and T2 of the same participant (Table 2 ID 14). Several 'new' white matter hyperintensities (WMH) detected at T2 (T2-1, T2-2) were faintly visible on images obtained at T1 (T1-1, T1-2).

Table 4. Correlation matrix of difference scores between imaging metrics and psychiatric variables.

	PTSD (n = 11)		MDD (n = 11)		TBI (n = 11)		Blast (n = 11)		NSI (n = 9)	
	ρ	p	ρ	p	ρ	p	ρ	p	ρ	p
Total number of WMHs	.325	.329	.408	.214	.026	.940	.041	.905	.289	.450
Total WMH volume	.377	.377	.400	.223	.280	.404	−.131	.702	.267	.488

Note. All variables represent difference scores (T2–T1).
PTSD = current diagnosis of posttraumatic stress disorder; MDD = current diagnosis of major depressive disorder; TBI = history of blunt traumatic brain injury; Blast = history of blast exposure; NSI = Neurobehavioral Symptom Inventory; ρ = Spearman rank correlation coefficient; WMH = white matter hyperintensity.

TBI and change in WMH number (r = .21, p = .384) or volume (r = .27, p = .257).

Discussion

The aim of this pilot study was to describe long-term neuropathological changes and neuropsychiatric symptoms following blast exposure with and without TBI during deployment. As would be expected, a history of both types of exposures (TBI, blast) was associated with worse outcomes at T1 than either exposure alone. In the absence of additional events (TBI, redeployment), a trend towards improved outcomes at T2 was observed.

Overall, our results indicated no significant changes in psychiatric diagnoses, TBI history, or blast exposure history over the course of 7 years. Though the overall trend was towards fewer psychiatric diagnoses, there were three new-onset PTSD diagnoses (one redeployed with new-onset TBI, all with blast exposure) and one new-onset MDD diagnosis (with blast exposure) in the sample. Five veterans in this sample redeployed following T1, though new blast exposure following T1 participation was not reported by any participant. Therefore, additional blast exposure was unlikely to affect our results.

Incongruent with our hypothesis, self-report of neurobehavioural symptoms increased between T1 and T2. Due to the non-specific nature of the symptoms evaluated by this measure, there are several possible reasons for this

including changing life circumstances, new-onset medical conditions, new-onset non-deployment-related injuries, or new-onset psychiatric conditions. Iverson and Lange (37) found post-concussive symptoms present in 36–76% of healthy adults, and symptoms were highly correlated to depression, suggesting the presence of neurobehavioural symptoms is not pathognomonic to TBI, and the increase seen in this sample not necessarily indicative of TBI or blast symptom evolution. Additionally, our results suggest the increase is unrelated to any changes in neuroimaging results, inconsistent with previous findings (20).

Possibly incongruent with our expectations, we detected significant increases in WMH number and volume, such that a greater number and volume of WMHs were seen at T2 compared to T1. This was primarily due to changes in four of the 11 participants who completed imaging, all with blast exposure at T1. However, five other participants also had blast exposure at T1 without significant increase in WMHs at T2. It is possible this increase is related to characteristics of blast exposure that were unable to be included as part of the current analysis. Interpretation of this finding is complicated by several issues, and we discuss the significant caveats associated with this below; however, if this finding were to generalize to the larger population of blast exposed service members and veterans, it would merit further study to clarify the mechanisms resulting in WMH progression as well as the relationship of such progression to clinical outcomes.

Because of differences in MRI scanner technology between the two studies, it is possible the observed changes in WMH are due to the improved image quality at T2. For example, a study of 15 healthy participants (M_{age} = 44 years) found a significant increase in WMH detectability on FLAIR at 3 T compared to 1.5 T (35). Two other studies using healthy participants and subjects with multiple sclerosis also found a similar increase (38,39). The general trend in our cohort of increased WMH number and volume at T2 might be attributed to increased sensitivity as opposed to WMH evolution. This is supported qualitatively through visual comparisons of sectional images from T1 and T2, with several 'new' hyperintense areas faintly visible at T1 (see Figure 2). The pattern of relationship between imaging data and characterization data could be said to support this interpretation as well. Imaging data from T2 demonstrated stronger relationship with PTSD diagnosis and blast exposure severity than either T1 imaging data or change scores. Thus, it is possible that the higher resolution of T2 imaging data allowed observations of relationships between brain structure, PTSD, and blast exposure severity that were not observable at previously obtained lower resolutions. These results are congruent with our previously published manuscript using the full T1 data set (N = 45) that demonstrated an association between PTSD, blast exposure, and altered values of DTI metrics (27). Given the small sample size in the current analysis, the higher resolution imaging at T2 may have been necessary to observe the effect. This could indicate a need for higher resolution structural imaging to observe the subtle and diffuse effects of blast exposure on the brain; however, further work is necessary to fully support this conclusion.

Further work is needed to clarify these relationships and address confounding factors. However, if our findings are the result of increased resolution due to improved imaging technology, they provide additional evidence for a relationship between blast exposure, PTSD, and WMH. If our findings represent progression of neuropathology following blast exposure and TBI, they would provide new evidence of a worrying relationship between events that occur frequently during deployment (blast exposure, mild TBI) and progression of WMH typically interpreted as pathological in clinical examinations. Unfortunately, due to changes in imaging technology, the question of progression remains unanswered and the conservative interpretation should be one of improved resolution.

There are several limitations to note for the present analysis. The small sample size limited quantitative methods. Different measures were used to evaluate TBI and blast exposure history across studies, which may have further influenced results. Five participants reported sustaining a new-onset TBI (*mild* = 4, *moderate* = 1) following participation in T1 though there were 10 new reported TBIs. In addition, one participant no longer met criteria for a TBI diagnosis at T2. These incidents indicate a potential difference in report of TBI symptoms between T1 and T2. A potential contributor to this was the difference in context between T1 and T2. At T1, the VA polytrauma evaluation results in the medical record were used to capture TBI diagnosis; at T2 an interview was conducted by research staff and the results were unavailable for clinical purposes. As mentioned above, imaging was acquired at 1.5 T for T1, whereas this data was acquired at 3.0 T at T2. This potentially biased the results towards finding increased numbers of lesions at T2 due to the higher resolution and tissue contrast, providing the ability to resolve smaller lesions that may have been present at T1 (40,41). There was a low rate of diagnoses in the overall sample at T1, limiting the ability of the analysis to observe remission of disorders. However, this did provide opportunity to observe new onset of disorders, which was not supported statistically. It should be noted that interviewers at T2 were blind to the diagnoses established at T1. In addition, 30 participants from T1 who may have been eligible to participate in T2 declined to be assessed (*moved* = 9, *uninterested* = 11, *other* = 2) or were unable to be contacted (n = 8), potentially biasing the sample. PTSD diagnosis was evaluated under *DSM-IV* criteria using the SCID at T1, but *DSM-5* criteria using the CAPS-5 at T2, and differences in interview tools and diagnostic classification might have affected results and general comparability for PTSD diagnosis.

Conclusions

In conclusion, this pilot study describes temporal increases in WMHs in a small cohort of veterans with history of blast exposure. These changes in WMHs were unrelated to neurobehavioural factors, though were associated with severity of blast exposure. Number of WMHs at T2 was additionally associated with a current diagnosis of PTSD at T2. Major limitations included differences in measurement at T1 and

T2, change in MRI sensitivity, and small sample size. Because the contribution of improved resolution is unclear, our results suggest one of two things: (1) if increases in WMH are solely due to improved imaging resolution, our results suggest that there is a relationship between blast exposure and WMH. or; (2) if increases in WMH are not due to improved imaging resolution, this would provide support for a relationship between blast exposure and progression of neuropathology. Considerable further research is needed to clarify these relationships and address confounding factors.

Declaration of interest

The authors report no conflicts of interest. The views, opinions and/or findings contained in this article are those of the authors and should not be construed as an official Veterans Affairs or Department of Defense position, policy or decision, unless so designated by other official documentation.

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Comparability of iPad and Web-Based NIH Toolbox Cognitive Battery Administration in Veterans

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Abstract

Objective: The purpose of this study was to evaluate the comparability of National Institutes of Health Toolbox Cognitive Battery test scores across iPad application and web-based personal computer administration platforms. Original test norms were developed using a personal computer-based administration and no previous studies assessing platform comparability have been published.

Method: Participants ($N = 62$; final analyzed sample $n = 49$) were combat-exposed post-deployment veterans without neurologic disorder, severe mental illness, current substance use disorder, or a history of moderate or severe traumatic brain injury. All participants completed both iPad and web-based versions of tests on the same day in an experimental within-subjects crossover design. Standalone validity measures were incorporated to exclude invalid performance. Outcome measures included the Dimensional Change Card Sort Test, Flanker Inhibitory Control and Attention Test, List Sorting Working Memory Test, and Pattern Comparison Processing Speed Test.

Results: Score differences between platforms were found on the Flanker Inhibitory Control and Attention Test. Scores were moderately correlated across tests, with the exception of low correlations for the Pattern Comparison Processing Speed Test. Most participants preferred iPad to web administration, regardless of administration order.

Conclusions: Results suggest caution when interpreting iPad-acquired scores, particularly for the Flanker Inhibitory Control and Attention Test. iPad-based testing offers valuable improvements; however, the development of iPad-specific norms may be necessary to ensure valid interpretation of acquired data.

Keywords: Cognition; Assessment; Toolbox; mHealth; Telehealth; Tablet

The National Institutes of Health Toolbox (NIHTB) is a compilation of computerized measures developed to provide an efficient assessment of neurological, cognitive, and behavioral function that promotes translation of research findings across diverse settings (Gershon et al., 2013). The NIHTB cognitive test battery (NIHTB-CB) measures key domains of brain function: language, processing speed, attention, episodic memory, and executive function. Four NIHTB-CB tests were normed for ages three through eighty-five: Picture Vocabulary Test, Flanker Inhibitory Control and Attention Test (Flanker), Dimensional Change Card Sort Test (Card Sort), and Picture Sequence Memory Test. Three additional tests were normed for ages seven through eighty-five: List Sorting Working Memory Test (List Sorting), Pattern Comparison Processing Speed Test (Pattern

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Comparison), and Oral Reading Recognition Test. Weintraub and colleagues (2014) confirmed the test–retest reliability of each individual NIHTB-CB measure (r = .73–.90), and data reported by Heaton and colleagues (2014) indicated high reliability for battery composite scores (r = .86–.92). Moderate convergent validity with existing neuropsychological tests has also been suggested (Weintraub et al., 2013).

The normative sample for the NIHTB-CB was acquired through a local personal computer (PC) administration. The battery was then deployed with minimal changes to PCs in a web-based form (Gershon et al., 2013). Recently, the NIHTB-CB measures were translated to an iPad app-administered format which has made their use more convenient for both clinical and research settings (Clay, 2016; Northwestern University, 2017). Although iPad administration has clear advantages (e.g., portability, simplicity, offline access, immediate scoring), many factors may affect test comparability across administration modalities including hardware characteristics (e.g., display size, device speed/memory, speaker quality), administration differences (e.g., instructions, timing), and participant/administrator comfort and familiarity with the administration modality used (Brearly et al., 2017; Cernich, Brennana, Barker, & Bleiberg, 2007; Grosch, Gottlieb, & Cullum, 2011; Luxton, Pruitt, & Osenbach, 2014).

There are several key differences between the PC web-based and iPad versions of the NIHTB-CB including: logistical requirements, user interface, number of test trials, and test prompts/instructions. First, the web-based version requires a relatively complex hardware configuration including a dual-screen computer, speakers, keyboard, and an external mouse. One screen is used to manage administration by the examiner and one screen is used to present stimuli to the examinee. Compared to the iPad version, where the participant and examiner share one screen, portability is limited and there are multiple avenues for computer peripheral variation or failure. Second, tactile differences in user interfaces require separate sets of training instructions for iPad and web-based versions of the Flanker, Pattern Comparison, and Card Sort. During web-based administration, participants are instructed to use keyboard directional keys when responding to test items, whereas iPad administration requires participants to return their finger to a standardized reference point (*home base*) on the table in front of them between each touchscreen response (National Institutes of Health and Northwestern University, 2017a). Further, differences in screen size and type may affect the viewing of test stimuli. Although the iPad screen is higher resolution than many computer monitors, it is also much smaller. There are fewer Pattern Comparison trials on the iPad than on the web version, rendering the raw scores between the two tests incompatible. Finally, iPad administration relies on displayed test instructions accompanied by audio of the instructions, whereas web-based administration requires the examiner to verbally repeat all test instructions that are displayed on-screen (National Institutes of Health and Northwestern University, 2017a; Northwestern University, 2017).

The importance of accounting for administration nuances specific to electronic administration of tests has been formalized in a joint consensus statement released by the American Academy of Clinical Neuropsychology and the National Academy of Neuropsychology. The consensus statement calls for developers of electronically administered tests to "provide users with sufficient technical information to ensure that [the test] will provide data that can be accurately compared to that which exists in the test's normative database" (Bauer et al., 2012, p. 183). The NIHTB-CB was developed with the goal of allowing modification and updates in the future without losing the comparability of previously collected data (Gershon et al., 2013). However, in accord with consensus statement precautions, an internal investigation described by e-mail to test users in 2016 reported incongruence between most norm-referenced scores produced by the web and iPad-based tests (Gershon & Diaz, personal communication, October 7, 2016). Specifically, iPad norm-referenced scores were reported as inappropriate for use with the Card Sort, Flanker, Pattern Comparison, and Picture Sequence Memory Test. The norm-referenced scores for the remaining cognitive tests (List Sorting, Picture Vocabulary, and Oral Reading Recognition) administered by iPad were reported to be accurate and comparable to web administration. Test developers have attempted to address this issue in two ways. First, a new scoring process was developed for the iPad data and previously collected data stored on iPads were rescored by application update in December 2016, to foster iPad compatibility with existing norms for all tests. Second, a Python-based program was released by test developers in March 2017 to allow for calculation of web-based norm-referenced scores that would be comparable across platforms (Casaletto et al., 2015; National Institutes of Health and Northwestern University, 2017b).

Most research on the NIHTB-CB has not utilized the iPad-administered form (Carlozzi, Goodnight, et al., 2017; Carlozzi, Tulsky, et al., 2017; Holdnack et al., 2017; Tulsky, Carlozzi, et al., 2017; Tulsky, Holdnack, et al., 2017). Therefore, it is important that independent validations of test rescoring be conducted to facilitate confident integration of iPad-collected data into existing protocols and clinical work. There are currently no published studies validating the iPad administration and the scores it produces, or comparing scores acquired by iPad to those acquired by web-based administration. The aim of the current study was to address this need by comparing iPad and web-based test scores using an experimental crossover design.

Methods

Participants

Study participants were Iraq and Afghanistan combat veterans ($N = 62$) recruited to participate in a larger Chronic Effects of Neurotrauma Consortium (CENC) study at the Salisbury Veterans Affairs Medical Center investigating the structural neurobiological and functional sequelae of primary blast forces. This study was approved as an addition to the parent study by the local Institutional Review Board. All participants provided informed consent prior to participation. Eligibility criteria included at least one Iraq or Afghanistan deployment with combat exposure, English speaking, 18 years of age or older, able to comply with instructions to complete study tasks, and able to provide informed consent. Exclusion criteria included a history of moderate or severe traumatic brain injury (TBI); penetrating head injury; non-deployment-related TBI with loss of consciousness; presence of neurologic disorder, severe mental illness, dementia, current substance abuse, psychotic symptoms, or any contraindication for neuroimaging. Participants were initially screened by phone call and then completed an in-person assessment visit confirming full eligibility before being enrolled in an imaging visit. Data for the current study were obtained during the in-person assessment visit.

Nine participants included in the current analyses disclosed a history of non-deployment TBI with loss of consciousness during the in-person assessment visit. Nine participants were excluded from current analyses due to performance below established cutoffs on standalone performance validity measures; seven failed the Medical Symptom Validity Test and two failed the b Test (Boone et al., 2000; Green, 2005). Two additional participants were excluded from analyses, one due to reported and observed fatigue during the second condition and one due to interruption of the study protocol. Two final participants were removed from analyses due to missing data. The final sample size for analysis was $n = 49$ participants.

Measures

Full descriptions and video illustrations of administered tests as well as references for reliability and validity data can be found in NIHTB-CB online manuals (National Institutes of Health and Northwestern University, 2017a; Northwestern University, 2017, 2018). List Sorting, a measure of immediate recall and sequencing, presents a series of stimuli (visually and verbally) that participants are required to immediately verbally re-order according to a particular characteristic. The Card Sort is described as a measure of cognitive flexibility and requires examinees to match a stimulus picture with one of two response options after being presented with a matching rule. For this test, examinees are also required to return their finger to a standardized position in front of the iPad (*home base*) between each response on that platform. Scores for List Sorting and Card Sort are generated based on the total items correctly completed. The Flanker is a timed measure of attention and inhibitory control requiring participants to indicate the direction of an arrow while inhibiting responding to "flanking" distractor arrows across a series of trials. This task, like the Card Sort, requires examinees to return their finger to *home base* between each trial to standardize measurement of response time. Finally, the Pattern Comparison measures speed of processing by requiring participants to quickly evaluate a series of picture pairs by providing a response indicating whether each pair of pictures are the same or different. The difficulty of items on both the Pattern Comparison and Flanker is limited and speed of responding is emphasized given the cognitive abilities these tasks are purported to measure. For this reason, computed scores that account for both accuracy and speed of responding are provided as an alternate measure to the raw correct response score.

Procedures

Participants completed NIHTB-CB tests in both web and iPad formats on the same day. NIHTB-CB tests were selected based on their inclusion in the primary study protocol. A randomized crossover design was employed. Condition order was counter-balanced by participant sequence to account for practice and order effects. Participants completed either the web-based or iPad version first, at the onset of the assessment visit, and the second administration was completed approximately 6 h later at the visit's conclusion. A battery of neurocognitive tests (including standalone performance validity measures), interviews, and self-report measures was completed between administrations per the primary study protocol. Standardized procedures outlined in NIHTB-CB test manuals were followed. To better understand participant perspectives regarding NIHCB-TB administration types, qualitative responses regarding administration preference were collected after the second condition for 35 participants ("Which administration format did you prefer?"). Testing was conducted by trained masters- or doctoral-level research staff.

Data Analysis

Chi-squared analyses were conducted to ensure demographic comparability between condition order groups. ANOVA/correlational analyses were run for each demographic characteristic (i.e., age, education, race/ethnicity) and each associated norm-referenced score to ensure that demographic effects were adequately addressed across platforms. Analyzed test data included raw, computed, and norm-referenced scores. Standardized scores adjust for age ($M = 100$, $SD = 15$) and T scores adjust for age, sex, education, and race/ethnicity ($M = 50$, $SD = 10$). Analyzed web data included raw or computed scores (for tests with both a speed and accuracy component), standardized scores (*Age-Corrected Standard Scores*), and T scores (*Fully Corrected T Scores*). The norm-referenced scores were produced from NIHTB-CB web data by the Python program recommended by test developers in March 2017 (National Institutes of Health and Northwestern University, 2017b; Casaletto et al., 2015). Analyzed iPad data included raw or computed scores, standardized scores (*Age-Corrected Standard Scores*), and T scores (*Fully Corrected T Scores*) produced by iPad after the December 2016 scoring update. Web-based scores were calculated using the recommended Python program. For the Pattern Comparison, raw web scores were compared to computed iPad scores per developer recommendations (National Institutes of Health and Northwestern University, 2017b).

RStudio was used to conduct statistical analyses (RStudio Team, 2018). Shapiro–Wilk normality tests indicated that scores on each of the included tests did not meet the normality assumptions for *t*-tests. Performance across modalities was compared using Wilcoxon signed-rank tests. Control of false discovery rate was used to account for multiple comparisons with a family-wise error rate of $\alpha = 0.05$ (Benjamini & Hochberg, 1995). Concordance correlation coefficients (CCC) were calculated to evaluate the reliability of scores acquired across modalities (Lin, 1989). The CCC accounts not only for precision, indicated by the distance data points fall from the line of best fit (i.e., Pearson's correlation coefficient), but also the accuracy of measurement reflected by how far that line falls from the 45-degree line of perfect agreement between scores (Watson & Petrie, 2010). Post-hoc Mann–Whitney *U* tests were used to compare combined raw/computed scores and score differences for carryover and period (practice or fatigue) effects by applying the procedure described by Tudor and Koch (1994).

Results

There were no demographic differences between condition order groups (Table 1). Demographically-corrected scores accounted for population specific relationships observed in raw/computed scores suggesting that norm-referenced scores adequately address demographically associated variability for both iPad and web platforms. Significant differences between conditions were found across scores on the Flanker that remained following correction for multiple comparisons (Table 2). List Sorting scores were not significantly different after correction for multiple comparisons. There was no statistical difference between median iPad and web scores for the Card Sort or Pattern Comparison. Raw/computed, standardized, and T scores were moderately correlated for the Card Sort, Flanker, and List Sorting across modalities. Pattern Comparison scores were poorly correlated, with relatively low precision across modalities (Table 2). There were no differential carryover or period effects for the Flanker, further supporting the presence of a true difference in test platforms with web scores being higher than iPad scores ($U = 122$, $p < .001$, $r = .51$). A period (practice) effect was found for List Sorting ($U = 107$, $p < .001$, $r = .56$) and Pattern Comparison ($U = 7$, $p < .001$, $r = .84$) with test scores improving significantly during the second administration. A carryover effect on Pattern Comparison ($U = 180$, $p < .05$, $r = .34$) indicated that scores during the second period improved more when this condition was web-based.

Thirty-five participants were queried regarding their administration preference: 19 completed web-administration first and 16 completed iPad administration first. Condition preference did not significantly differ by administration order, $\chi^2 = 5.03$, $p = .08$, $\varphi = .38$. Of those completing the web-based administration first, 47.4% (9/19) preferred web administration, 42.1%

Table 1. Demographic characteristics by condition order (Web first/iPad first)

Characteristic	Web First ($n = 24$) *M* (*SD*) or *n* (%)	iPad First ($n = 25$) *M* (*SD*) or *n* (%)	t/χ^2	*p*
Age	41.63 (9.02)	39.04 (9.24)	0.99	.327
Education (years)	14.63 (1.91)	14.16 (1.60)	0.92	.359
Race/Ethnicity			0.64	.571
Black	8	11		
Hispanic	1	2		
White/Asian	15	12		

Note: Race/ethnicity follows NIH Toolbox normative categorization.

Table 2. Wilcoxon Signed-Rank Comparisons and Correlation Coefficients of Administration Modality Scores

Score	PC/Web			iPad						*z*		
	Mean (*SD*)	Median	Range	Mean (*SD*)	Median	Range	*W*	*p*	*r*	*CCC*	ρ	χ_a
DCCS Computed	8.24 (0.74)	8.22	6.50–9.74	8.33 (1.07)	8.21	4.88–10.00	529	.409	0.08	.59	.63	.93
DCCS Standardized	100 (14)	98	72–136	103 (21)	104	67–146	495	.247	0.12	.51	.56	.91
DCCS T	50 (9)	50	30–70	52 (14)	52	27–79	472	.165	0.14	.46	.51	.90
FICAT Computed	8.58 (1.14)	8.86	3.75–9.91	8.16 (0.99)	8.37	4.75–9.67	974	<.001	0.36	.46	.50	.92
FICAT Standardized	100 (19)	103	41–134	90 (16)	89	57–121	996	<.001	0.39	.47	.56	.85
FICAT T	51 (11)	52	21–69	44 (10)	45	22–62	990	<.001	0.38	.46	.55	.83
LSWM Raw	19 (3)	19	12–26	18 (3)	18	12–26	642	.041*	0.21	.42	.45	.94
LSWM Standardized	107 (15)	108	73–138	101 (16)	98	73–138	824	.036*	0.21	.41	.44	.94
LSWM T	55 (9)	55	33–73	52 (10)	49	33–74	832	.028*	0.22	.40	.43	.93
PCPS Raw/Computed**	58 (14)	57	32–85	60 (13)	61	21–87	503	.386	0.09	.23	.24	.99
PCPS Standardized	100 (23)	97	62–158	103 (21)	106	40–143	520	.360	0.09	.23	.23	.99
PCPS T	50 (14)	51	24–80	53 (12)	54	20–72	506	.295	0.11	.21	.21	.97

Note: CCC = Concordance Correlation Coefficient, DCCS = Dimensional Change Card Sort Test, FICAT = Flanker Inhibitory Control and Attention Test, LSWM = List Sorting Working Memory Test, PCPS = Pattern Comparison Processing Speed Test, ρ = Pearson's correlation coefficient (precision), χ_a accuracy coefficient. Casaletto and colleagues (2015) adjustment is recommended only for web scores, thus standardized iPad scores were consistent across most comparisons. All non-computed scores are rounded to the nearest whole number post-analysis as per interpretive guidelines.

*Not significant after controlling false discovery rate.

**Current developer guidance indicates that for PCPS the web raw score should be compared to the iPad computed score, in contrast to other tests.

(8/19) preferred iPad administration, and 10.5% (2/19) reported no administration preference. Among those who completed the iPad condition first, 12.5% (2/16) preferred web administration, 75.0% (12/16) preferred iPad administration, and 12.5% (2/16) reported no administration preference. Across orders, 31.4% (11/35) of participants preferred web administration, 57.1% (20/35) preferred iPad administration, and 11.4% (4/35) denied any preference.

Discussion

The present study examined the comparability of iPad-administered NIHTB-CB test scores with the PC web-administered version of the tests in a sample of Iraq and Afghanistan combat veterans. Utilized scores were updated and calculated according to final developer recommendations released in March 2017, meant to ensure comparability between test modalities. The current study did not support the adequacy of these adjustments for any Flanker scores, where mean norm-referenced iPad scores fell nearly one standard deviation below those acquired using the web-administered version. Differences between web and iPad scores were not found across the Card Sort, List Sorting, or Pattern Comparison (although differences on List Sorting were significant prior to correction for multiple comparisons). Concordance correlations between modalities were low to moderate. Low correlation was found for Pattern Comparison, along with a moderate carryover effect for this test in our sample. Observed large practice effects on List Sorting and Pattern Comparison suggested a need for caution when re-administering either of these tests after a short delay. An unpublished investigation by test developers did not indicate discrepancies between the iPad and web versions of the Flanker, as observed in the current study. This may be due to differences between within-subjects and cross-sectional comparisons. The present analysis utilized a within-subjects crossover approach, whereas the test developers compared between-subjects using demographically similar groups (personal communication, April 7, 2016).

Patterns in findings hinted that specific test characteristics may be explanatory. In addition to the significant web-score advantage on the Flanker, the identification of a crossover effect on Pattern Comparison suggested a similar web-advantage when this test was administered after the iPad version (although overall median scores on Pattern Comparison were comparable). This is notable because both the Flanker and Pattern Comparison rely on accurate perception of small visual details to a greater extent than the other two included tests. It could be that stimuli are less clearly perceived on the smaller iPad screen compared to a PC. This hypothesis is consistent with the lack of identified differences on the Card Sort, given that it is arguably the non-verbal test least likely to be affected by display differences because the test relies on differentiating between only two distinct colors and shapes. The relative comparability of scores on the Card Sort also suggests that differences in outcomes cannot be fully attributed to use of the *home base* unique to the iPad administration which is also required for the Flanker. Finally, it seems reasonable that practice effects would be found for List Sorting and Pattern Comparison, both of which present a series of colorful and visually distinct stimuli that arguably would be most vulnerable to recognition benefit

during the second administration of the test, where the presented stimuli remain consistent. Of course, these hypotheses would need to be verified by future work.

Limitations of this study include sample size, the use of data collected within the context of a larger study (limiting the number of NIHTB-CB tests administered), and lack of control over demographic characteristics. All participants were combat veterans indicating a need for caution when generalizing study results to other populations. It is possible that intervening study activities may have differentially affected participants across conditions; although, it should be noted that the NIH Toolbox normative sample completed a 47-instrument battery (Gershon et al., 2013). Strengths of this study include a crossed and randomized design to account for practice and order effects, and the use of standalone performance validity measures to account for invalid responding. This is the first research study to examine the comparability between web-based and iPad administrations of NIHTB-CB tests. Results indicate a clear need for replication, particularly in non-veteran and non-adult samples. Future studies should also investigate additional NIHTB-CB tests not included here.

The continued incorporation of modern, efficient, and accessible measures into the collection of neurocognitive data is important for the evolution of neuropsychology, and the development of an iPad version of the NIHTB-CB was an important step towards this end (Miller & Barr, 2017). Although unique challenges such as frequent technology and software updates create inherent difficulties, the advantages of reduced administrative burden and apparent participant preference indicate the importance of continued development and implementation of the iPad version of the test. However, the NIHTB-CB should not be exempt from the iterative development and validation required of well-established measures. Further work is indicated, and current normative issues suggest a need for caution when interpreting the results of the iPad NIHTB-CB Flanker test, particularly when combining with previously collected web data. These results suggest the potential value of developing iPad-specific normative data for the NIHTB-CB, just as it was gathered for the PC.

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Conflict of Interest

None declared.

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Title: Challenges Associated with TBI Research and Clinical Practice in the DoD and VA: Diagnostics, Pathology, & Ethics.

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Abstract:

This workshop will cover various topics related to clinical care and empirical investigation with active duty service members (SM) and veterans who have experienced mild traumatic brain injuries (mTBI). The presentation will be broken down into three sections, with each section including discussion of recent research, applied clinical guidance, and ethical considerations. The first section will cover *screening and initial assessment of mTBI* and will include discussions on the potential iatrogenic effects of system-wide screenings, use of computerized neurocognitive assessment tools (NCAT) such as the ANAM, and the consistency of self-reported injuries across the active duty and veteran cycle of care. The second section will highlight aspects of the pathophysiology of concussion due to blast injury, an injury mechanism relatively unique to SMs and veterans, by presenting preliminary data from a Chronic Effects of Neurotrauma Consortium (CENC)-funded study on primary blast injury. The final section of this workshop will cover topics relating to *clinical guidelines for the treatment of mTBI*, with recent research on return to duty protocols discussed, as well as the potential consequences of misdiagnosed postconcussive symptoms in VA disability evaluations. The audience will obtain an understanding of the unique challenges and ethical considerations that exist in research and clinical practice with service members with mTBI.

Learning Objectives:

1. Understand the potential iatrogenic effects of mass screening for mTBI in the DoD and VA systems of care.
2. Raise awareness as to the limitations and potential uses of NCATs in screening for mTBI.
3. Understand the research related to consistency of self-reported concussions within service members and veterans
4. Review existing research on the neuropathology of blast injury and present initial data on outcomes following blast mTBI with post-deployed veterans.
5. Become aware of the DoD's clinical guidance on treatment of postconcussive symptoms and related issues.
6. Understand the emerging research on return to duty protocols and the associated ethical principles within the military environment.

Distress Tolerance and Symptom Severity Mediate Failure on a Symptom Validity Test in Iraq and Afghanistan Veterans with PTSD

Miskey, H. M., Martindale, S. L., Shura, R. D., & Taber, K. H.

Objective: Evaluate the relationship between PTSD and outcome on performance and symptom validity tests (PVT and SVT). Hypothesis: the association between PTSD diagnosis and performance on SVTs and PVTs will be serially mediated by distress tolerance and symptom severity.

Method: Iraq and Afghanistan veterans (n = 120, M_{age} = 41, 91% male) completed testing. Dichotomous variables were created for PTSD diagnosis (using CAPS-5) and failure on the Medical Symptom Validity Test (MSVT), b-Test, and Structured Inventory of Malingered Symptomatology (SIMS). Continuous variables were created for SIMS subscales, distress tolerance (DTS), and symptom distress (PCL-5). Hypothesis testing applied serial mediation analysis, with DTS and PCL-5 as mediators, respectively.

Results: Models predicting b-Test and MSVT failure were not significant. The specified model predicted failure on the SIMS, $p < .001$, B = 0.52, CI [0.20, 1.17], and SIMS subscale scores on Neurologic Impairment, $p < .001$, B = 0.55, CI [0.25, 1.10], Amnestic Disorders, $p < .001$, B = 0.64, CI [0.18, 0.92], Affective Disorders, $p < .001$, B = 0.61, CI [0.30, 1.15], and Low Intelligence, $p = .03$, B = 0.17, CI [0.00, 0.44], but not Psychosis. PTSD diagnosis only demonstrated a main effect for MSVT failure; PCL-5 demonstrated main effects for SIMS failure, and all subscales except Low Intelligence.

Conclusion: Difficulty tolerating negative affect may contribute to elevated symptom distress and result in over-reporting symptoms in Veterans with PTSD. Distress tolerance and symptom burden were not associated with PVT failure, supporting the independence of PVTs and SVTs. PTSD diagnosis and symptom self-report were differentially related to PVT/SVT performance.

Objective: A growing literature suggests traumatic brain injury (TBI) acquired during deployment represents an independent risk factor for developing posttraumatic stress disorder (PTSD). The current study will determine changes in whole-brain functional networks between individuals who do and do not develop PTSD following deployment acquired TBI. It was hypothesized that participants who developed PTSD would demonstrate higher levels of clustering coefficient, small worldness, and modularity.

Participants and Methods: Participants were post-deployment Iraq and Afghanistan war Veterans with a history of deployment acquired TBI determined by clinician administered interview. Seven participants were diagnosed with PTSD using the Clinician Administered PTSD Scale–5 (CAPS-5). Magnetoencephalography (MEG) was acquired in the resting state for 5 minutes. Active brain regions were identified using synthetic aperture magnetometry. Connectivity among all regions was calculated using the weighted phase lag index. Network metrics were calculated using the Brain Connectivity Toolbox. Univariate ANCOVA adjusting for age and estimated premorbid IQ were used to determine differences in network metrics between participants who did and did not develop PTSD following deployment acquired TBI.

Results: Participants who developed PTSD displayed higher levels of small-worldness, $F(1,12)=5.364$, $p<.039$, partial eta squared=0.309, and clustering coefficient, $F(1, 12)=12.204$, $p<.004$, partial eta squared=0.504 , than participants who did not develop PTSD. Modularity (Q) and the number of modules present were not different between groups.

Conclusions: Results demonstrate significant differences in whole-brain resting-state networks between individuals who do and do not develop PTSD following deployment acquired TBI. This is the first study to identify neurobiological differences through which deployment acquired TBI may increase the risk of subsequently developing PTSD.

Symptom Burden and Cognitive Outcomes in Iraq and Afghanistan Veterans: The Role of Validity

Sarah L. Martindale, Robert D. Shura, Timothy W. Brearly, Jared A. Rowland, and Holly M. Miskey

Determine what aspects of symptom burden drive failure on performance and symptom validity measures, and if these associations account for cognitive test performance.

Participants were 226 Iraq and Afghanistan veterans. Participants completed the Personality Assessment Inventory (PAI), stand-alone performance/symptom validity measures, the Frontal Systems Behavior Scale (FrSBe), and a comprehensive cognitive battery. Participants with psychotic symptoms, current substance use disorder, combat exposure before 1985, moderate/severe traumatic brain injury, posttraumatic stress disorder unrelated to combat, and/or with an uninterpretable PAI profile (INF, ICN) were considered ineligible.

All PAI clinical scales were directly associated with cognitive outcomes. Validity mediators of WMT failure and PIM were not associated with cognitive outcomes, though MFAST failure (verbal fluency) and NIM (visual learning, complex attention, verbal fluency, working memory) were. SCZ was the only PAI clinical scale indirectly associated with cognitive outcomes (verbal recall, verbal fluency, and working memory), through validity measures (MFAST, NIM). MFAST failure, $R^2_{adj} = .22$, NIM, $R^2_{adj} = .69$, PIM, $R^2_{adj} = .66$, visual processing speed (WAIS-III subtests), $R^2_{adj} = .26$, visual learning (BVMT-R), $R^2_{adj} = .16$, and subjective frontal dysfunction (FrSBe), $R^2_{adj} = .73$, were constructs best explained by the model.

Psychiatric symptom burden was independently associated with lower-order objective cognitive function (processing speed and learning) and subjective frontal dysfunction beyond validity measure performance.

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Preliminary Results from a Novel Method for Evaluating Blast Exposure

Shura, Rowland, Martindale, Spengler, & Taber

Blast exposure has received increased attention due to the use of explosives in the wars in Iraq and Afghanistan. We developed a structured interview of blast exposure that is unique in that it: evaluates all exposures across the lifespan, connects a blast event to PTSD and TBI events, bases the definition of "exposed" on the individual's physical experiences, and includes a method of rating multiple exposures. A sample of 396 single-blast events were drawn from an ongoing study on long-term effects of blast. Most (70.5%) occurred during combat, 13.1% co-occurred with PTSD criterion A, and 18.9% resulted in a TBI. Using a Likert scale for experienced wind, debris, ground shaking, pressure, heat, and noise, all items were rated significantly higher ($p <$ .001) if the event led to a TBI; distance was not a significant factor. Using a subsample ($n = 93$), there were no significant differences in cognitive test performance across 10 different scores when comparing blast-exposed versus not. In contrast, blast-exposed individuals reported significantly higher ($p < .001$) combat exposure, PTSD, depression, and neurobehavioral symptoms. Thus, this blast interview shows promise in evaluating blast events, which appear related to higher symptom report, though not remote cognitive deficits.

Background: Functional networks are a powerful means of characterizing communication among brain regions. Resting-state functional brain networks have become increasingly popular, both for the ease of acquisition and of calculation. However, little is known about the stability or reliability of these networks, particularly when calculated using magnetoencephalography (MEG). The current study will examine how resting-state network metrics change over time, and how varying time intervals in the calculation of resting-state networks affect those same network metrics.

Methods: Participants included 28 post-deployment veterans. Average age was 39 (9.5) years and education was 13.7 (1.2) years. MEG was acquired in the resting-state for 4 minutes. Active brain regions were identified using synthetic aperture magnetometry across all 4 minutes. Connectivity among identified regions was calculated using the weighted phase lag index for the entire 4 minutes, as well as each 1-minute segment. Network metrics were calculated using the Brain Connectivity Toolbox (clustering coefficient, path length, small worldness, modularity (Q), and the number of modules present). Repeated-measures ANOVA and Intraclass correlations were used to examine change in 1-minute network metrics over time. Paired t-tests were used to compare metrics of 1 and 4-minute networks.

Results: Results demonstrated that network metrics were highly reliable and consistent over time. Network metrics were not significantly different across the 1-minute networks. Intraclass correlations were considered high (>0.9) for all metrics except the number of modules present, which was considered good (>0.8). However, network metrics varied significantly when the time interval used to calculate them changed. The metrics of each 1-minute network were significantly different from the same metrics of the 4-minute network. The actual connections present in each of the 1-minute networks was highly variable. Each 1-minute network shared approximately 9% of connections with each other 1-minute network. Similarly, each 1-minute network shared approximately 10% of connections with the 4-minute network.

Discussion: This study investigated the consistency of network metrics across time and how the time interval used to calculate the network affected the subsequent metrics. Results suggest that the metrics of resting-state networks are stable across time and reflect reliable and robust constructs. However, the actual connections present across time varied significantly (>90%). While the actual content of the network changed almost completely over time, the resulting topology remained consistent, pointing to a common biologically bound solution to the complexity of brain communication.

Results also demonstrated that changes in the time interval used to calculate networks can significantly alter the resulting metrics. Clustering coefficient, small world, and modularity (Q) were lower on average in the 1-minute networks compared to the 4-minute network, while the path length was longer and the number of modules higher. This suggests that network metrics calculated across varying time intervals cannot be reasonably compared, even when calculated using the same data. This finding suggests that the study of resting-state networks using MEG would significantly benefit from the standardization of methods for network creation, particularly in regards to the time intervals used.

Taber – Society for Neuroscience 2018 annual meeting abstract

Citation:

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Influence of Primary Blast Exposure on Development of PTSD Following Deployment.

Theme and Topic:

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Disclosures: None

Body:

Service members are frequently exposed to blasts or explosions during deployment. These events may or may not be accompanied by acute symptoms of mild traumatic brain injury (mTBI). The long-term effects of primary blast exposure on veterans of the wars in Iraq and Afghanistan are currently unknown. As part of this study, we developed a structured interview

that evaluates lifetime blast exposures and connects blast events to mTBI events. Posttraumatic stress disorder (PTSD) diagnosis was determined using the Clinician Administered PTSD Scale – 5 (CAPS-5). The Salisbury VAHCS IRB approved this study to ensure that the privacy of research subjects was maintained and their welfare protected. Participants included 165 combat-exposed post-deployment veterans who passed performance and symptom validity measures. Chi-Square analyses were conducted to analyze differences in categorical variables. ANOVA were used to analyze differences in continuous variables. Logistic regression was used to evaluate the contributions of variables to PTSD diagnosis or recovery. Most blast exposure events (71%) occurred during combat and relatively few (19%) were associated with acute symptoms indicative of mTBI. Primary blast exposure was associated with higher rates of both current ($p < .026$, Cramer's V=0.173) and lifetime ($p < .001$, Cramer's V=.296) PTSD. Deployment mTBI was associated with higher rates of lifetime PTSD ($p < .001$, Cramer's V=.276). When participants with deployment mTBI were removed from the analysis, blast exposure remained associated with increased rates of lifetime PTSD ($p < .001$, Cramer's V=0.378). In addition, higher severity of blast exposure remained associated with higher rates of both lifetime ($p < .032$, Cramer's V=.227) and current ($p < .017$, Cramer's V=.252) PTSD. Logistic regression was used to predict lifetime and current PTSD diagnosis from deployment mTBI and blast exposure. The model did not significantly predict current PTSD diagnosis, but significantly predicted lifetime PTSD diagnosis. An interaction was observed between blast exposure and deployment TBI ($p < .053$) such that experience of either or both increased the likelihood of a lifetime PTSD diagnosis. For the model including higher severity blast exposure, only blast exposure significantly predicted either current or lifetime PTSD. These results indicate that primary blast exposure increases risk for developing PTSD even when the blast exposure was not associated with acute TBI symptoms.

SESSION TITLE

Blast Exposure: Cognitive, Biological, and Behavioral Effects Beyond TBI

PARTICIPANTS

Name	Affiliation	Role
Amy J. Jak, PhD	University of California San Diego	Discussant
Robert D. Shura, PsyD, ABPP	Salisbury VA Health Care System	Presenter
Jared A. Rowland, PhD	Salisbury VA Health Care System	Presenter
Sarah L. Martindale, PhD	Salisbury VA Health Care System	Presenter/Chair
Holly M. Miskey, PhD	Salisbury VA Health Care System	Presenter
Erica L. Epstein, PsyD	Salisbury VA Health Care System	Presenter

SYMPOSIUM PROPOSAL

Military service often results in exposure to a multitude of different blast forces throughout training, deployment, and combat. Many Servicemembers deployed to combat zones in support of Operations Enduring Freedom (OEF), Iraqi Freedom (OIF), and New Dawn (OND) are exposed to blasts or explosions, often without symptoms of traumatic brain injury (TBI) at the time of exposure. In the instance of TBI, exposure to blasts accounts for roughly 78% of wounded-in-action cases in OEF/OIF/OND servicemembers and veterans (Walker et al., 2014). Given the high prevalence of exposure to blasts and explosions, it is important to understand the potential sequelae of such exposures, and the circumstances that most likely lead to negative outcomes beyond a history of TBI. Available evidence suggests that exposure to blast during military service affects brain functioning independently of TBI (Robinson et al., 2015, 2017; Taber et al., 2016). Longitudinal evidence has also suggested that blast exposure could be associated with progression of neuropathology (Martindale et al., 2018).

This symposium will present new results from the Chronic Effects of Neurotrauma Consortium (CENC) Study 34 conducted at the Salisbury VA Health Care System (SVAHCS). This study uniquely focuses on the effects of blast in several domains. Results presented during this symposium will demonstrate the effects of blast exposure on brain function, cognitive function, development of psychopathology, and recovery from psychopathology. Additionally, a new method of comprehensively characterizing blast exposure will be presented. Dr. Jak, Principal Investigator for CENC Study 20, will serve as a discussant for the findings presented in this symposium.

Dr. Shura will first present a novel measure of blast exposure that identifies and characterizes exposure to blasts across the lifetime, independent from TBI. The Salisbury Blast Exposure Interview (SBEI) was developed for CENC Study 34 and provides a mechanism to improve our understanding of blast exposure and its sequelae. This measure is unique in its evaluation of all exposures across the lifespan and mechanism for rating multiple exposures, significantly improving the efficacy of the interview. In addition, the interview obtains behaviorally anchored Likert scale ratings of an individual's experience of the wind, debris, ground shaking, pressure, heat, and noise resulting from the blast. Higher levels of these ratings are related to negative outcomes such as TBI. The ratings also fluctuate in expected directions in response to protective factors. This blast interview shows promise for comprehensively evaluating blast exposure and is applicable to both clinical and research settings.

The second presentation by Dr. Rowland investigates the relationship between blast exposure and functional brain networks. Participants in this study completed both magnetoencephalography (MEG) and functional magnetic resonance imaging (fMRI). Available neuroimaging data (n = 115 fMRI, n = 40 MEG) was used to develop whole-brain resting-state functional brain networks and subsequently calculate whole network metrics. Results found no relationship between the full spectrum of blast exposure severity and network metrics. However, when higher severity blast exposure was examined, significant relationships to network metrics were observed for both MEG and fMRI networks. These findings were beyond the effects of traumatic brain injury (fMRI and MEG) and posttraumatic stress disorder (fMRI only). These results demonstrate that the severity of blast exposure is significantly related to potential outcomes, with increasing severity related to significant alterations in functional brain networks.

During the third presentation, Dr. Martindale will discuss effects of blast exposure on cognitive outcomes in OEF/OIF/OND combat veterans. As part of CENC Study 34, veterans completed a full Wechsler Adult Intelligence Scale – fourth edition, Trail Making Test, Controlled Oral Word Association Test, and several standalone performance validity tests. Analyses demonstrate that blast exposure does not have an independent effect on cognitive outcomes in this cohort of veterans with valid performance; however, blast exposure was found to exacerbate the effects of current PTSD and TBI history on cognitive outcomes, especially in the domain of attention. These results suggest that when veterans have a diagnosis of PTSD or history of TBI, the additional exposure to blast affects fundamental cognitive skills.

Dr. Miskey will discuss the association between blast exposure and the development of PTSD. Accumulating evidence has demonstrated that deployment-acquired TBI is related to the subsequent development of PTSD beyond pre-deployment factors as well as combat exposure. Results of the current study demonstrate that blast exposure is associated with higher rates of both current and lifetime PTSD diagnosis, with higher severity blast exposure demonstrating a stronger relationship. These relationships remained even when participants with deployment TBI were removed from the sample. Further, logistic regression demonstrated that higher-severity blast exposure was a stronger predictor of PTSD diagnosis than deployment TBI, with no interaction between the two. Given the high prevalence of blasts associated with events resulting in TBI during deployment, these results suggest blast exposure may be a more important indicator of prognosis than the experience of TBI.

In the final presentation, Dr. Epstein will present on behavioral health outcomes associated with PTSD recovery among combat veterans, how blast exposure affects PTSD recovery, and blast exposure interactions with behavioral health outcomes in PTSD recovery. As part of CENC Study 34, veterans also completed a number of behavioral health outcome questionnaires and interviews. Analyses indicate many behavioral health effects, such as pain, sleep, depression, physical symptoms, and quality of life are associated with PTSD recovery. Additionally, blast exposure and blasts that resulted in TBI were not significantly associated with PTSD recovery; however, exposure to higher blast pressure waves are significantly associated with recovery from PTSD. This study builds an understanding of how blast affects recovery from PTSD. Findings in this study have clinical implications that may affect treatment goals to facilitate PTSD recovery.

SUMMARY SYMPOSIUM ABSTRACT (2,000 CHARACTERS INCLUDING SPACES)
Military service often results in exposure to a multitude of different blast forces throughout training, deployment, and combat. Effects of blast on the brain have been only recently studied, and exposure may occur with or without acute symptoms indicative of a TBI. It is important to understand the potential sequelae of such exposures and the circumstances that lead to negative outcomes beyond TBI history. This symposium will first present a new interview method for evaluating lifetime blast exposure. Using the interview to identify presence and severity of blast exposure, results will be presented describing the effect of exposure on functional brain networks, neuropsychological outcomes, development of PTSD, and recovery from PTSD. A strength of these presentations is the comprehensive nature of evaluations from a cross-sectional study investigating biological and behavioral effects of blast exposure. Participants (N = 280) completed diagnostic interviews, questionnaires, and cognitive testing. Eligible participants (n = 164) completed neuroimaging, including magnetoencephalography and magnetic resonance imaging. The predominant theme of results across presentations is that, as severity of blast exposure increases, the likelihood of negative outcomes also increases. These presentations demonstrate that blast exposure can affect individuals across a variety of outcomes, from altering brain function to confounding patterns of recovery from PTSD, with associations often emerging only at higher severity of exposure. Blast exposure remained related to outcomes beyond the effects of these other variables. This demonstrates the robustness of the relationship and the importance of considering blast exposure history, beyond the effects of TBI history, in evaluations of physical and mental health of post-deployment veterans. Discussant will synthesize data presented and confer similarities and differences as blast relates to TBI literature.

Appendix 29

Impact of Otolith Dysfunction on Postural Stability and Quality of Life: A Chronic Effects of Neurotrauma Consortium Study

Title: Impact of Otolith Dysfunction on Postural Stability and Quality of Life: A Chronic Effects of Neurotrauma Consortium Study

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Background: Until recently, clinical vestibular function assessment was limited to measurement of horizontal semicircular canal pathways. Vestibular evoked myogenic potentials are becoming more widely used to supplement the vestibular test battery by providing information about the otolith organs and their pathways; yet, the clinical significance of otolith organ dysfunction is unclear. The purpose of this study was to determine the functional consequences of otolith organ dysfunction on postural stability and quality of life.

Methods: A prospective case-control study of Veterans (n=130) was completed. Comprehensive vestibular site-of-lesion testing was performed and participants were grouped according to patterns of vestibular test findings. Three vestibular groups included individuals complaining of dizziness/imbalance with: (1) otolith organ dysfunction only (Otolith Only, n=21), (2) semicircular canal and otolith organ dysfunction (Canal+Otolith, n=19), and (3) semicircular dysfunction only (Canal Only, n=12). Two control groups included individuals with normal vestibular function and (1) complaining of dizziness/imbalance (Dizzy Control, n=52) or (2) with no complaints of dizziness/imbalance (Healthy Control, n=26). Self-report questionnaires and physical performance measures of balance and gait assessed postural stability and quality of life. MANOVAs were performed to determine significant group differences ($p < 0.05$) for balance and gait and quality of life outcome measures. As appropriate, post hoc analyses of covariance and pairwise comparisons were performed to identify specific group differences ($p < 0.05$).

Results: There were no significant group differences for age, race, ethnicity, gender or occupational status. MANOVAs indicated significant group differences for both gait and balance and quality of life measures. The Otolith+Canal group performed significantly worse than both control groups and the Otolith Only and Canal Only groups on the Sensory Organization Test. The Otolith+Canal group also performed significantly worse than both control groups on the Functional Gait Assessment.

The Otolith Only group performed significantly worse than the Healthy Control group on a measure of the impact on activities, the Activities-specific Balance Confidence scale (ABC), and the Dizziness Handicap Inventory (DHI). The Otolith+Canal group performed significantly worse than the Healthy Control on a measure of the impact on activities, the ABC, DHI, and Vestibular Activities and Participation measure.

Conclusions: Otolith organ dysfunction negatively impacts quality of life, and in conjunction with semicircular canal dysfunction negatively impacts balance and gait. The findings of this study have important implications for developing effective clinical protocols for the diagnosis and management of individuals with dizziness related to otolith organ dysfunction.

Appendix 30

Structural Neuroimaging in Mild Traumatic Brain Injury: A Chronic Effects of Neurotrauma Consortium Study

Structural Neuroimaging in Mild Traumatic Brain Injury: A Chronic Effects of Neurotrauma Consortium Study (7.2.18)

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Abstract

The Chronic Effects of Neurotrauma Consortium (CENC) observational study is a multi-site investigation designed to examine the long-term longitudinal effects of mild traumatic brain injury (mTBI). All participants had a history of deployment in Operation Enduring Freedom (OEF, Afghanistan), Operation Iraqi Freedom (OIF, Iraq) and/or their follow-on conflicts [Operation Freedom's Sentinel (OFS)]. All participants undergo an extensive array of medical, neuropsychological and neuroimaging studies and either do or do not meet criteria for any lifetime mTBI. These assessments are integrated into six CENC cores-- *Biorepository, Biostatistics, Data and Study Management, Neuroimaging and Neuropathology*. The current study outlines the quantitative neuroimaging methods as managed by the *Neuroimaging Core,* which uses the FreeSurfer automated software for image quantification. At the time of this writing, 317 participants from the CENC observational study have had have completed all baseline assessments including the imaging protocol and tertiary data quality assurance procedures. Herein we report on the preliminary findings of this initial cohort to describe how the Neuroimaging Core manages neuroimaging quantification for CENC studies.

Traumatic brain injury (TBI) at any level of severity has been characterized as the most complex disease in the most complex organ (Wheble & Menon, 2016). Given the uniqueness of each brain at the time of injury combined with the varied mechanisms of how injuries occur, as well as the wide-ranging genetic, medical and psychosocial variables present, at the individual level no two injuries are identical (Kenzie et al., 2017; Maas et al., 2017). Furthermore, with lifetime prevalence estimates that one in five adults have experienced a TBI sufficient to cause loss of consciousness (LOC), underscores the commonness of brain injury (Corrigan, Yang, Singichetti, Manchester, & Bogner, 2017). This is particularly evident in modern warfare. Reportedly, from Operation Enduring Freedom (OEF, Afghanistan), Operation Iraqi Freedom (OIF, Iraq) and their follow-on conflicts, like Operation New Dawn (collectively OEF/OIF), estimates indicate that approximately ~378,000 military personnel who have served in the above mentioned conflicts meet criteria for a TBI diagnosis (http://www.dvbic.org/dod-worldwide-numbers-tbi), with the vast majority falling in the mild range of severity [Glasgow Coma Scale ≥13; LOC ≤30 minutes; (Walker et al., 2016)]. Those diagnosed with TBI often report heterogeneous mechanisms of injury ranging from combat blast and blunt-force trauma to injuries sustained in training such as falls, being struck by an object, assault, as well as the more traditional forms of motor vehicle accidents. Age at injury varies as well as potential sex differences in this cohort of injured servicemen and servicewomen (Lippa et al., 2017). For those in the military, the situation becomes even more complicated when one considers that brain injuries also can occur pre- or post-deployment, not just during combat deployment.

Recently, the Chronic Effects of Neurotrauma Consortium (CENC; https://cenc.rti.org/) was established to examine these very complex issues surrounding TBI in military and Veteran populations (Walker et al., 2016). As stated by Cifu and Dixon (2016) "…CENC is a coordinated, multi-center collaboration, linking experienced basic science, translational and clinical neuroscience researchers from the VA, military and academia to address the long-term effects of mTBI and its diagnosis and treatment (p. 1397)." Having a focus on late-life outcomes and neurodegeneration means that these military personnel with a history of mTBI will be tracked overtime, with the first wave of participant recruitment and brain imaging now underway. Ultimately, the CENC observational study will recruit over 1,200 current and former

military members, the majority of whom deployed in OEF, OIF or related follow-on operations, have varying histories of deployment and non-deployment mTBI. All will eventually be examined longitudinally and the majority will complete structural magnetic resonance imaging (MRI; see Walker et al., 2016). While the extracted demographic information obtained on each CENC participant is extensive, at a coarse level, approximately 80% of the sample will meet criteria for having sustained at least one mTBI, with the remaining 20% not meeting criteria for any prior mTBI, and thereby constituting a control military participant group. The majority of military TBIs occur in men, but CENC includes a substantial female cohort with injury as well. In those meeting criteria for mTBI, the number of mTBIs sustained is ascertained, along with the type of injury mechanism (blast, fall, blunt force trauma or combination; penetrating injuries excluded) and all other typical demographic factors. In addition to deployment related injuries, CENC also examines non-combat TBI, including brain injury that would have occurred both pre-combat as well as post. This design feature will ultimately permit ascertainment of the comparability of brain injuries not only related to the mechanism and timing of injury but the role of deployment related injuries. Importantly, whether presence of post-traumatic stress disorder (PTSD) is identified in a CENC participant is also part of the study.

CENC is comprised of 31member institutions, including 17 Department of Defense (DoD) or VA Hospitals where various aspects of participant recruitment and neuroimaging studies occur (see webpage: https://cenc.rti.org). As a multi-site study, CENC has six study cores that process all data for the consortium including the following: *Biorepository*, *Biostatistics*, *Data and Study Management*, *Neuroimaging* and *Neuropathology*. Given the central and foundational role that neuroimaging plays in brain injury research, data from the *Neuroimaging Core* will be used by all of the other cores, as well as the individualized research programs within CENC. Consequently, it is important to publish the basic methods used along with the emerging demographics and neuroimaging quantification findings of the CENC investigation for structural image analysis, which is the purpose of the current report. For quantitative neuroimaging, the automated image analysis software from FreeSurfer [https://surfer.nmr.mgh.harvard.edu/ (see Fischl, 2012) represents the structural neuroimaging platform used by CENC. Accordingly, the

current report provides a description of the emerging neuroimaging data from the mTBI cohort of CENC participants.

Often study designs, especially those with limited sample sizes, require restricted age ranges as a means of controlling for age effects. However, while it is true that the majority of those who sustain military related TBI are under 35 years of age at the time of injury (Mortera, Kinirons, Simantov, & Klingbeil, 2018), TBIs occur at all age ranges in military personnel, especially if non-deployment injuries are taken into account (DePalma, 2015). In a longitudinal study, age at the time of injury becomes an important factor, as older age carries with it potentially worse outcome assumed to be related to a variety of age as well as health-mediated effects associated with aging, including cognitive and brain reserve issues (see Bigler & Stern, 2015; Mathias & Wheaton, 2015). To address life-span issues of when an injury occurs, in the longitudinal within-subject design of CENC, sample size will be adequate to address these age-mediated effects. As such, the only age restriction in CENC participant requirements for study inclusion was the minimum military inductee age of 18, without an upper age limit; although to date the oldest participant was 68 at the time of enrollment.

Magnetic resonance (MR) scanning is performed across multiple CENC sites with all data transferred to the *Neuroimaging Core* for analyses. Herein we report on the *Neuroimaging Core* quantitative findings from the first 317 MR scans performed on CENC participants. For bilateral regions of interest (ROI), FreeSurfer quantification involves metrics for both left and right hemispheric findings as well as singular volumetric measures for structures like the corpus callosum, potentially yielding hundreds of volumetric measures from which to select ROIs. For this initial study, the selected ROIs included the following: Total intracranial volume (TIV), total brain volume (TBV), ventricular volume (lateral, III and IV), total cerebral cortical volume, and corpus callosum volume, along with bilateral (right+left) volumes for the hippocampus, amygdala, caudate nucleus, putamen, globus pallidus, thalamus and ventral diencephalon. Using the Query, Design, Estimate, Contrast (QDEC) function in FreeSurfer also permits a contrast comparison between those with TBI and controls (mTBI/no) in terms of cortical thickness, which

was also undertaken. Additionally, in the Supplementary File section of this report, the entire FreeSurfer dataset for all 317 subjects is included.

Another objective of CENC has been to examine a broad range of potential medical and historical issues, some of which are descriptively and demographically described in this report. Since at this stage, the study design is descriptive, no specific hypotheses were examined. For the purposes of this study, TBI classification was treated as a categorical variable with the simple distinction of either being present or not. Future studies, when the overall CENC sample size is in much larger, will permit a more in-depth analysis to include type of injury, number of TBIs, deployment related injury or not, etc. Since the CENC investigation is longitudinal with this initial report constituting the baseline, the current report provides only a broad overview of the initial findings. In the current report presented herein, body size demographics, including body mass index (BMI) are explicated in some detail because of the issues associated with aging, brain injury and body mass are critical baseline metrics for longitudinal investigations (Albanese et al., 2017; Arvanitakis, Capuano, Bennett, & Barnes, 2018; Fedor & Gunstad, 2013) as well as cognitive and brain reserve issues associated with TBI (Wood, 2017). Increased BMI represents a documented risk factor for greater adverse outcome from TBI (Chabok et al., 2014; Czorlich et al., 2017), but has actually received minimal research attention.

Methods

Participants

Participant details for CENC have been published previously (Walker et al., 2016), including the criteria for TBI inclusion. Being an in-progress longitudinal investigation as of this writing, we report herein the quantitative neuroimaging findings on the first 319 MR scans processed by the Neuroimaging Core at the baseline study entry time point. Table 1 provides demographic information for those included in the current quantitative neuroimaging analyses. Supplementary Table 1 overviews all of the CENC participating institutions where neuroimaging studies are obtained, including information about the MR scanner.

Inclusion criteria required prior combat exposure and deployment(s) in Operation Enduring Freedom, Operation Iraqi Freedom or one of their follow-on conflicts (collectively OEF/OIF).

All participants had to be 18 years of age or older. Exclusion criteria included a history of moderate or severe TBI as defined by initial Glasgow Coma Scale < 13, coma duration > ½ hour, post-traumatic amnesia duration > 24 hours or traumatic intracranial lesion on head CT. Participants were also excluded if they had a history of major neurologic or psychiatric disorder such as stroke, spinal cord injury, bipolar disorder or schizophrenia (major disorder defined as resulting in a significant decrement in functional status or loss of independent living capacity). CENC Participants have been enrolled across the entire spectrum of mTBI, from entirely negative (mTBI/no) to many mTBIs. Neuroimaging, both standard clinical as well as those involving advanced methods, has been performed on all participants (for additional CENC details see also Seal et al., 2017; Walker et al., 2016).

Table 1: Demographics

	Study Group		
Characteristic	**TBI (N=269)**	**No TBI (N=50)**	**P-Value**
Years Since Index Date[1,T]			
N	269	50	
Mean (std)	8.8 (4.6)	8.7 (5.0)	0.8526
Median	8.8	8.2	
Min, Max	1, 47	1, 29	
Age at Baseline (years)[T]			
N	269	50	
Mean (std)	39.1 (10.4)	40.3 (11.8)	0.4620
Median	36.0	37.5	
Min, Max	22, 69	23, 68	
Height at Baseline (cm)[T]			
N	268	49	
Mean (std)	175.9 (8.7)	175.3 (9.3)	0.6669
Median	175.8	175.3	
Min, Max	152, 196	152, 196	
Weight at Baseline (kg)[T]			
N	268	49	
Mean (std)	92.9 (18.7)	92.0 (19.7)	0.7696
Median	90.9	91.4	

Characteristic	Study Group		P-Value
	TBI (N=269)	No TBI (N=50)	
Min, Max	52, 149	57, 154	
BMI at Baseline[T]			
N	268	49	
Mean (std)	29.9 (5.0)	29.8 (5.0)	0.8578
Median	29.3	29.1	
Min, Max	19, 45	20, 44	
eTIV at Baseline (cm^3)[T]			
N	269	50	
Mean (std)	1524088 (138434.2)	1547939 (172432.7)	0.3590
Median	1527825	1532783	
Min, Max	1157187, 1891580	1206081, 1916601	
eTIV Adj. Total Brain Volume at Baseline (cm^3)[T]			
N	269	50	
Mean (std)	471896.5 (32,330.2)	468051.2 (39,544.5)	0.5191
Median	473554.2	462355.3	
Min, Max	377,824, 547,821	397,940, 549,390	
Total Social Support (DRRI-2)[2,T]			
N	268	50	
Mean (std)	37.9 (8.0)	40.1 (7.8)	0.0756
Median	39.0	41.5	
Min, Max	13, 50	16, 50	
Ever Arrested[C]			
Yes	93 (34.7%)	16 (32.0%)	0.7118
No	175 (65.3%)	34 (68.0%)	
Current Smoker[C]			
Yes	62 (23.0%)	13 (26.0%)	0.6513
No	207 (77.0%)	37 (74.0%)	
Education[C]			
Any High School/High School Grad	38 (14.1%)	7 (14.0%)	0.9812
Any College/College Grad	231 (85.9%)	43 (86.0%)	
Learning Disability[C]			
Yes	28 (10.4%)	4 (8.0%)	0.5974

Characteristic	Study Group		P-Value
	TBI (N=269)	No TBI (N=50)	
No	240 (89.6%)	46 (92.0%)	
Illicit Drug Use[C]			
Yes	46 (17.2%)	8 (16.0%)	0.8321
No	221 (82.8%)	42 (84.0%)	
Hazardous Alcohol Consumption[C]			
Yes	100 (37.2%)	16 (32.0%)	0.4849
No	169 (62.8%)	34 (68.0%)	
Heart Disease[C]			
Yes	4 (1.5%)	2 (4.0%)	0.2297
No	265 (98.5%)	48 (96.0%)	
High Cholesterol[C]			
Yes	97 (37.2%)	16 (32.7%)	0.5471
No	164 (62.8%)	33 (67.3%)	
Obesity[C]			
Normal	37 (13.8%)	7 (14.3%)	0.9635
Overweight	115 (42.9%)	20 (40.8%)	
Obese	116 (43.3%)	22 (44.9%)	
Diabetes[C]			
Yes	9 (3.4%)	1 (2.0%)	0.6134
No	259 (96.6%)	49 (98.0%)	
Hypertension[C]			
Yes	97 (36.1%)	11 (22.0%)	0.0537
No	172 (63.9%)	39 (78.0%)	
Employed[C]			
Yes	196 (72.9%)	37 (75.5%)	0.7001
No	73 (27.1%)	12 (24.5%)	
Gender[C]			
Female	35 (13.0%)	10 (20.0%)	0.1923
Male	234 (87.0%)	40 (80.0%)	
Race/Ethnicity[C]			
Non-Hispanic White	139 (52.3%)	25 (50.0%)	0.7696
Other	127 (47.7%)	25 (50.0%)	
Self-Efficacy (GSE)[3,T]			
N	268	50	
Mean (std)	31.5 (4.8)	33.7 (3.9)	0.0025

Characteristic	Study Group		P-Value
	TBI (N=269)	No TBI (N=50)	
Median	31.0	34.0	
Min, Max	17, 40	20, 40	
Total Combat Duration (months)[4,T]			
N	267	49	
Mean (std)	19.6 (13.5)	17.0 (10.7)	0.1982
Median	15.0	12.0	
Min, Max	0, 102	5, 51	
Total Combat Exposure (DRRI-2)[2,T]			
N	268	50	
Mean (std)	40.0 (15.8)	31.0 (12.5)	0.0002
Median	37.0	29.0	
Min, Max	17, 89	16, 71	
Total # Controlled Detonations[4,N]			
N	268	50	
Mean (std)	26.7 (36.1)	25.4 (37.7)	0.8682
Median	7.5	5.5	
Min, Max	0, 100	0, 100	
Total # PCEs[4,5,P]			
N	269	50	
Mean (std)	4.1 (2.4)	1.9 (1.5)	<.0001
Median	4.0	2.0	
Min, Max	1, 15	0, 5	
Service Rank[C]			
Enlisted	234 (87.6%)	40 (80.0%)	0.1476
Officer	33 (12.4%)	10 (20.0%)	

C=Chi-square test; T=T-Test; N=Negative Binomial Regression; P=Poisson

[1]Index date is based on the worst mTBI during combat or similar predefined reference event.

[2]DRRI-2: Deployment Risk and Resilience Inventory; higher social support scores indicate more social support.

[3]GSE: General Self-Efficacy; higher scores reflect greater self-efficacy.

	Study Group		
Characteristic	TBI (N=269)	No TBI (N=50)	P-Value

[4]Obtained from a potential post-concussive event structured interview. Number of controlled detonations truncated at 100.

[5]PCE: Post-Concussive Event.

FreeSurfer Analysis

All MRI acquisition sites transfer DICOM data to the Brain Imaging and Behavior Laboratory at Brigham Young University (BYU). The T1-weighted volume DICOM files were imported and conformed using the FreeSurfer mri_convert program. Next, data were fed into the BYU Fulton Supercomputing Lab for concurrent processing of all data. Specific to the FreeSurfer comparisons, all scans were analyzed following customary and established methods using the standard recon-all script on FreeSurfer version 6.0 (see http://freesurfer.net/fswiki/FreeSurferWiki). FreeSurfer output involves several hundred potential volumes, but for the purposes of this investigation, the analyses only examined the aforementioned volumes.

Several methods have been employed for quality assurance, including visual inspection as we have outlined in previous publications (see Bigler et al., 2010; Wilde et al., 2016). Once cleared for final analysis, data were collected in a CSV file, from the individual subjects using the asegstats2table or the aparcstats2table and then statistically analyzed as described below.

As already mentioned, ROIs included the following : TIV (total brain and CSF volume summed together), TBV (total brain parenchymal volume only), ventricular volume (lateral, III and IV), total cerebral cortical volume, and corpus callosum volume, along with bilateral (right+left) volumes for the hippocampus, amygdala, caudate nucleus, putamen, globus pallidus, thalamus and ventral diencephalon. Cortical thickness was assessed using the QDEC function in FreeSurfer. Since head size varies, to a certain extent related to body size and with sex-mediated differences in brain size also being present, for group comparisons it is important to adjust for

head size differences using an estimate of TIV or eTIV, which will be further discussed in the statistical section.

Statistical Analysis. General Linear Models adjusting for eTIV and age were used to compare brain volumes across mTBI and no mTBI groups. For each brain volume, expected group means and groups differences along with 95% confidence intervals of the difference were calculated. Reported *p*-values concerning group differences were unadjusted for multiple comparisons. Brain Volume comparisons were completed in SAS version 9.2.

General Linear Models were also used to study relationships between eTIV and total brain volume as a function of age, height, weight, BMI, and site. These models were fit and graphed using R (ttps://www.r-project.org/). For studying these relationships between eTIV or Total Brain Volume and age, height, weight, etc, two forms of General Linear Models were used. The "full" model included one of the age, height, weight, BMI, or eTIV covariates plus the site and site by covariate interaction. The "ANCOVA" or "analysis of covariance" model excluded the interaction, while the "simple" model included only the covariate. If the interaction term between the covariate and site in the "full" model was not statistically significant at the 0.05 level, then the second "analysis of covariance" model was fit. Since only one interaction term was significant at the 0.05 level, all but one plot of eTIV/Total Brain Volume by covariate illustrate the "analysis of covariance" model.

Results

The first analysis compared volumes of the 13 selected ROIs between the no mTBI (mTBI/no) and mTBI groups. As shown in Table 2 below there were no group differences, except for III Ventricle volume.

Table 2

	eTIV/Age Adjusted Group Means (mm^3)				
Variable	**No mTBI (mTBI/no) mean (std err)**	**mTBI mean (std err)**	**Estimated Difference**	**95% CI of Group Difference**	**P-Value**
Cortical Volume	468451.0 (3575.19)	471523.0 (1555.12)	3072.05	(-4597.87,10741.96)	0.43
III Ventricle	1054.19 (30.71)	985.15 (13.36)	-69.04	(-134.91, -3.16)	0.04
IV Ventricle	1957.81 (63.88)	1855.63 (27.78)	-102.19	(-239.22,34.85)	0.14
Corpus Callosum	3527.29 (66.80)	3607.79 (29.06)	80.50	(-62.81,223.82)	0.27
Hippocampus	8374.61 (79.89)	8329.35 (34.75)	-45.26	(-216.65,126.13)	0.60
Amygdala	3541.67 (46.47)	3609.33 (20.22)	67.66	(-32.04,167.36)	0.18
Caudate	7057.46 (108.86)	7010.05 (47.35)	-47.42	(-280.95,186.12)	0.69
Putamen	9953.43 (131.50)	10092.43 (57.20)	139.00	(-143.12,421.11)	0.33
Pallidum	4223.33 (57.48)	4253.37 (25.00)	30.04	(-93.26,153.34)	0.63
Thalamus	15360.52 (144.74)	15323.94 (62.96)	-36.58	(-347.09,273.93)	0.82

eTIV/Age Adjusted Group Means (mm^3)

Variable	No mTBI (mTBI/no) mean (std err)	mTBI mean (std err)	Estimated Difference	95% CI of Group Difference	P-Value
Temporal Horn	670.86 (36.02)	675.96 (15.67)	5.10	(-72.17,82.37)	0.90
Lateral Ventricle	17119.90 (1092.95)	16451.26 (475.41)	-668.64	(-3013.37,1676.09)	0.58
Hypothalamus (ventral diencephalon)	8405.85 (76.88)	8392.28 (33.44)	-13.57	(-178.51,151.36)	0.87

In addition to comparing select ROIs across the mTBI/no and mTBI groups, relationships between eTIV as well as TBV and age, height, weight, BMI, and site; also TBV as a function of eTIV were examined, regardless of group identification. Some of these relations are graphically presented in Figures 1 and 2. Table 3 below contains a summary of both "Full" and "ANCOVA" models studied, where "Full" models included a term for the interaction between site and the single covariate used in the model, while "ANCOVA" models only included site and the single covariate in the model. Table 3 shows that statistically significant negative relationships with age were found for eTIV and TBV; whereas statistically significant positive relationships with Height, Weight, and BMI were observed for eTIV, with some statistically significant positive relationships with Height and Weight found for TBV.

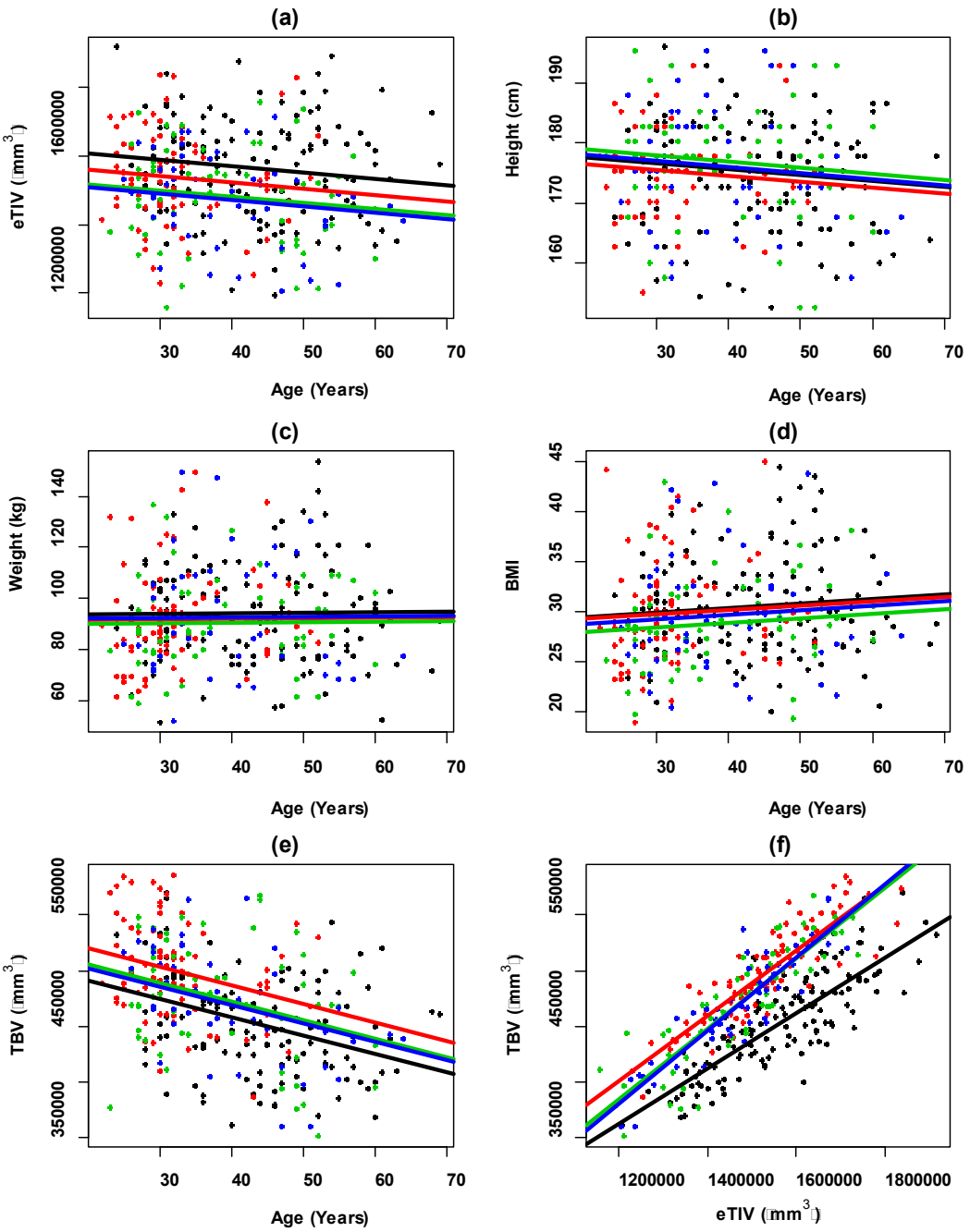

Figure 1. TIV and TBV relations with one another, age, height and BMI. Color codes reflect site differences: Black line = Richmond (Site 1), Red line = Houston (Site 2), Green line = Tampa (Site 3), Blue line (Site 4) = San Antonio.

A statistically significant positive relationship between TBV and eTIV was found, and this relationship had statistically significant differences across sites (see Figure 1f). The eTIV effect for Site 1 (Richmond) was 0.245 mm^3 per 1 mm^3 change in eTIV, 95% CI of eTIV effect (0.221, 0.269). The eTIV effect for Site 2 (Houston) was 0.289 mm^3 per 1 mm^3 change in eTIV, 95% CI of eTIV effect (0.252, 0.325). The eTIV effect for Site 3 (Tampa) was 0.317 mm^3 per 1 mm^3 change in eTIV, 95% CI of eTIV effect (0.275, 0.359). Finally, the eTIV effect for Site 4 (San Antonio) was 0.321 mm^3 per 1 mm^3 change in eTIV, 95% CI of eTIV effect (0.272, 0.370). Computation of these values permits the use of a correction factor to adjust for site differences.

With respect to age, the relationship with Height, Weight, and BMI were not found to be statistically significant while accounting for site, p-values = 0.10, 0.50 and 0.07 respectively (Table 3, Figures 1b, 1c and 1d). For each yearly increase in age, Height decreased on average, 0.081 cm, 95% CI of (-0.176, 0.014). For each yearly increase in age, Weight increased on average, 0.0272 kg, 95% CI of (-0.138, 0.282). For each yearly increase in age, BMI increased on average 0.051, 95% CI of (-0.004, 0.106).

In addition to studying the age relationship, Figure 2 and Table 3 show the relationships between eTIV/TBV and Height/Weight/BMI. For all cases, the relationships were statistically significant except for TBV and BMI. The p-value for the relationship between TBV and BMI was 0.56 (Figure 2f). For each unit increase in BMI, TBV changed on average by 436.8 mm^3, 95% CI of (-489.5, 1363.0).

Table 3: eTIV and Total Brain Volume Relationships with Age, Height, Weight, BMI, and eTIV

		Full Model	**ANCOVA Model***			
Outcome	**Covariate**	**Interaction p-value****	**Site p-value**	**Covariate p-value**	**Covariate Effect**	**95% CI of Covariate Effect**
eTIV (cm^3)	Age (yrs)	0.76	<0.001	0.02	-1858.1	(-3386.1, -330.0)
Height (cm)	Age (yrs)	0.52	0.26	0.10	-0.081	(-0.176, 0.014)
Weight (kg)	Age (yrs)	0.42	0.32	0.50	0.072	(-0.138, 0.282)
BMI	Age (yrs)	0.43	0.20	0.07	0.051	(-0.004, 0.106)
TBV (mm^3)***	Age (yrs)	0.45	<0.001	<0.001	-1617.6	(-2084.1, -1151.1)

eTIV (mm^3)	Height (cm)	0.70	<0.001	<0.001	6323.8	(4778.0, 7869.5)
TBV (mm^3)***	Height (cm)	0.47	<0.001	<0.001	1618.8	(1107.2, 2130.4)
eTIV (mm^3)	Weight (kg)	0.18	<0.001	<0.001	2387.1	(1666.8, 3107.3)
TBV (mm^3)***	Weight (kg)	0.09	<0.001	<0.001	447.2	(207.4, 687.0)
eTIV (mm^3)	BMI	0.62	<0.001	0.002	4647.1	(1795.1, 7599.0)
TBV (mm^3)***	BMI	0.56	<0.001	0.35	436.8	(-489.5, 1363.0)
TBV (mm^3)***	eTIV (mm^3)	0.004	NA†	NA†		NA†

* P-values for ANalysis of COVAriance model (ANCOVA) are based on Type III sum of squares.

** Full Model includes site, covariate, and site by covariate interaction.

*** Total Brain Volume (mm^3), Unadjusted for eTIV

† Since interaction term between TBV and eTIV was statistically significant at 0.05 level, the ANCOVA model results are not applicable. Potentially, each site has a unique relationship between TBV and eTIV.

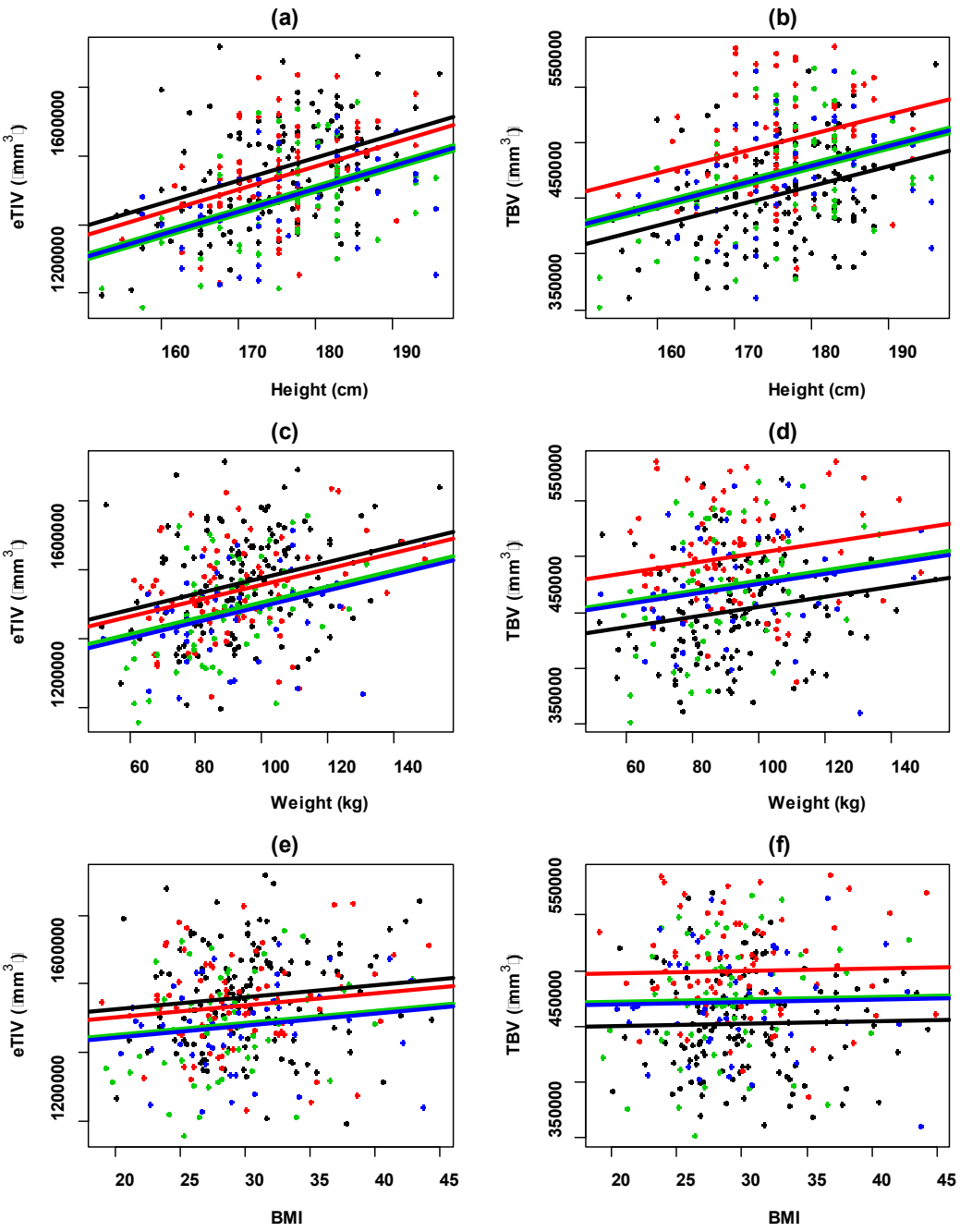

Figure 2: eTIV and TBV relations with height, weight, and BMI. Color codes reflect site differences: Black line = Richmond (Site 1), Red line = Houston (Site 2), Green line = Tampa (Site 3), Blue line (Site 4) = San Antonio.

Cortical Thickness

Figure 14 displays QDEC findings related to cortical thickness, depicting where clusters remained significant after false discovery rate (FDR) correction. The most prominent were in the left banks of superior temporal sulcus and gyrus, insular cortex and mid left frontal lobe. A significant cluster was also observed in the region of the left precuneus (not shown in this figure). No significant clusters were observed in the right hemisphere

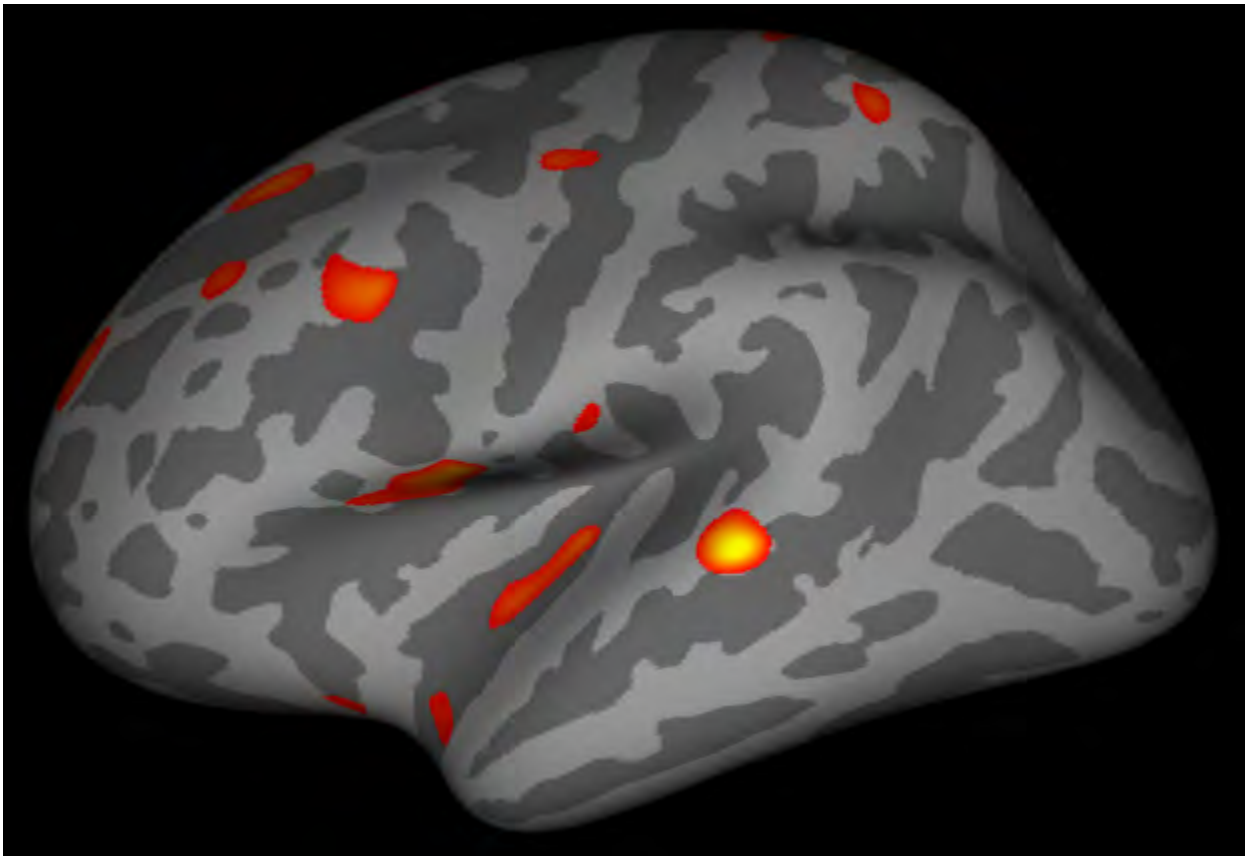

Figure 4. QDEC findings contrasting the mTBI participants to those with no brain injury (mTBI/no), where the mTBI group exhibited reduced cortical thickness in the regions colorized.

Discussion

This descriptive study outlines the FreeSurfer-based volumetric approach used by the CENC *Neuroimaging Core* and provides some preliminary analyses from the emerging CENC cohort comparing those participants with a history of mTBI to those not meeting criteria for TBI. As a longitudinal study, this initial acquisition of quantitative neuroimaging establishes a baseline to track CENC participants over time, a prelude for more fine-grained analyses in the future, once the full dataset is populated. At this stage, based on a simple binary group classification of control (mTBI/no group) versus mTBI, except for III Ventricle size, there were no significant differences in the FreeSurfer derived brain ROI volumes examined. However, there were some differences noted in cortical thickness. In the mTBI group, less cortical thickness was observed in several regions of the left hemisphere, most prominent in the left mid frontal lobe, insular cortex and the more posterior superior temporal sulcus and gyrus. Since the purpose of this descriptive study has been to outline the methods used in the CENC *Neuroimaging Core*, it is not designed to tease out the potential clinical significance of the observed cortical thickness findings or whether subsets of volumetric associations relate to certain aspect of mTBI demographics. Nonetheless, the regions of reduced cortical thickness in this CENC investigation have been implicated in other cortical thickness studies of mTBI, PTSD and symptoms associated with these disorders (Bajaj, Dailey, Rosso, Rauch, & Killgore, 2018; Govindarajan et al., 2016; Savjani, Taylor, Acion, Wilde, & Jorge, 2017). Future CENC studies will more closely examine these relationships as well as the role of other mediators and confounders.

There were, however, a variety of findings related to intracranial and brain volumetrics, including BMI, height and weight that have potential relevance for examining long-term sequela associated with mTBI. Understanding relations between brain and head size with body size metrics, injury and aging represent important issues for outcome studies following injury or disease and as variables, may act as surrogate markers of development, health status and/or brain reserve. For example, Pereira et al. (2016; see also Singh-Manoux et al., 2011; West et al., 2015) found height as "… an independent predictor of cognitive function in late-life." Similarly, there are interactive effects of aging, educational background and BMI that relate to cognition and cognitive functioning (Albanese et al., 2017; Garcia-Ptacek, Faxen-Irving, Cermakova, Eriksdotter, & Religa, 2014; Gavriilidou, Pihlsgard, & Elmstahl, 2015; Kirton & Dotson, 2016;

Ward, Carlsson, Trivedi, Sager, & Johnson, 2005). As shown in Figures 1 and 2, and as expected in this CENC sample, height and weight positively related to TIV and TBV. TIV is a well-established proxy for so-called "brain reserve" and an index of pre-injury brain volume, which is also a factor in TBI outcome (Bigler & Stern, 2015). Thus, an argument can be made for height as a general proxy index reflective of health status during developmental years, where studies have shown positive relationships of height to cognitive ability and educational attainment (Hagenaars, Gale, Deary, & Harris, 2017).

What is particularly interesting about this emerging CENC sample is the positive relationships between TIV and age, where younger participants had larger TIV. The relationships between height and TIV, as well as nutritional factors associated with their development (Leonard & Robertson, 1994) along with healthcare changes over the last 75 years, suggest that younger CENC participants have benefited from these conditions reflected in larger TIV and taller than older CENC participants. Likewise, epidemiological studies have shown that current generations are taller than their counterpart born during the mid-20th Century (Collaboration, 2016; Hruby & Hu, 2015). While clearly important to control for head size variation (see Mills et al., 2016), there has been no systematic examination of head size differences in TBI. Given the larger age span of the CENC cohort and this observation about head size and age, how these factors may relate to mTBI outcome in the military remain to be seen.

Weight also positively related to both TIV and TBV, but unlike the more static height metric once adulthood is reached, weight likely has a much more complex relation with brain volume and health. As shown in the analyses involving BMI, where weight is the denominator in calculating BMI, note the difference between the positive correlation concerning TIV and BMI, but the absence of correlation between TBV and BMI. As is being explored in sports-related concussion and retired National Football League (NFL) players, who are generally large in size, the issues of BMI may not be just a factor at the time of injury, but post-injury as well (Kelly et al., 2014; Lee et al., 2016; Trexler et al., 2017). This may include how brain injury influences pituitary function, vascular flow and weight (Klose & Feldt-Rasmussen, 2015; Silva et al., 2015), in association with injury. TBI studies to date have done little to examine these potential body-size contributions to brain injury outcome. From a reserve standpoint, older age has been repeatedly shown to be a vulnerability factor for mTBI (Mac Donald et al., 2017; Yue et al.,

2017). Potentially, this may be related to protective effects of preinjury brain volume associated with younger age and larger TIV. When the full CENC sample is constituted, and longitudinally examined, sample size and statistical power will be sufficient to address these issues.

Given the heterogeneity of TBI just in terms of mechanism of injury, let alone the host of life-history and medical variables that may play a role in mTBI, it is not surprising that coarse group differences at a ROI volumetric level did not distinguish the groups. This is especially the case given the CENC mTBI cohort is based on a non- or uncomplicated mTBI sample, meaning that day-of-injury CT imaging if even performed was negative. Non-complicated or uncomplicated mTBI samples may be less likely to exhibit volumetric findings in quantitative neuroimaging (Bigler et al., 2015; Hasan et al., 2014). Other studies that have examined global volumetric measures without performing more refined analyses that explore such factors as duration of loss of consciousness, symptom burden, time post-injury etc. have not found differences as well (Tate et al., 2016). Part of the reason for this was addressed in the earlier study by Bigler et al. (2015) that examined just pediatric mTBI cases but in whom all had had a complicated mild TBI. For those with definable lesions regardless of whether focal encephalomalacia, white matter hyperintensities and/or hemosiderin deposition, *none* of the lesions overlapped. If definable lesions were not overlapping in mTBI participants at the group level, then it would be unlikely that mTBI would result in a uniform volume reduction just within one ROI using the structural neuroimaging approach in this study that examines only group differences. This is not to say that once the full CENC cohort is amassed and detailed analytics undertaken to examine subgroup factors, that some may exhibit a uniform volumetric change within certain ROIs associated with pre-injury, injury and/or post-injury variables. Additionally, volume is but a singular metric that alone may not be that sensitive to the effects of mTBI. Recent studies that take a multimodality approach, for example combining lesion analysis methods, with shape, diffusion and metabolic analyses in addition to volumetrics and functional neuroimaging findings have proven to be much more sensitive in detecting subtle pathologies associated with mTBI (Astafiev, Zinn, Shulman, & Corbetta, 2016; Dall'Acqua et al., 2016; Tate et al., 2016).

Indeed, once more elaborate comparisons are undertaken with additional participant recruitment, we will better determine what may be present in the mTBI group analysis as

depicted in Figure 3. Lateral ventricular volume was selected because in TBI, ventricular expansion is an established marker of loss of brain parenchymal volume in TBI (Green et al., 2014), including mTBI (Wilde, Bigler, Pedroza, & Ryser, 2006). As shown in Table 2, the eTIV and age adjusted effect of mTBI group on Lateral Ventricle was -668.6 mm^3, 95% CI of (-3013.4, 1676.1) with a *p*-value of 0.58, and therefore non-significant. However, Figure 3 shows a side-by-side boxplot of eTIV and Age adjusted Lateral Ventricle by mTBI group and this shows an interesting characteristic of the data. Within the boxplots, we do see more variation and outliers in the mTBI group relative to the mTBI/no group. At this stage of CENC participant recruitment, there are differences in the sample sizes between the mTBI/no and mTBI groups, where more variation may be expected in the mTBI group since it is larger, but what is not known at this time is whether the increased variability associated with ventricular volume of the lateral ventricle in the mTBI participants represent something systematic, such as type of mTBI. As such it may be that when group analyses are performed, no differences occur. However, embedded within the non-significant group differences are individual cases where volumetric changes do result from the brain injury. This has implications that once established with the full complement of CENC participants, more detailed analyses of potential subgroups may yield interesting and important associations between ROI volumetrics and various demographic, historical factors and outcome variables.

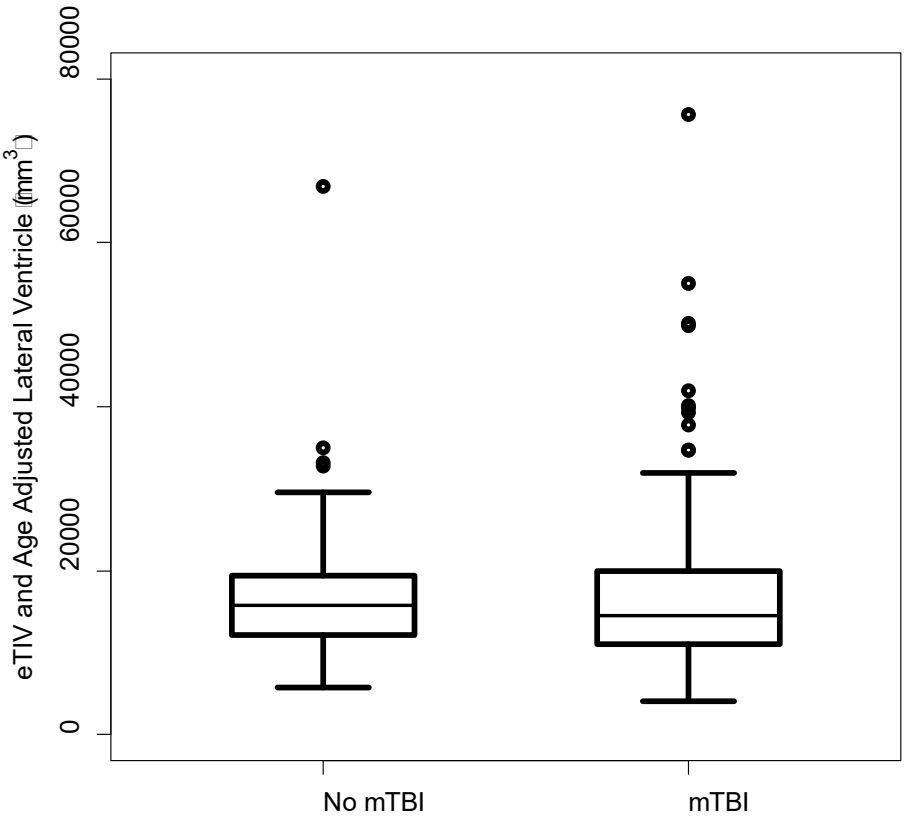

Figure 3: eTIV and age Adjusted Lateral Ventricle by mTBI. Lateral Ventricle adjusted for eTIV and Age using the regression technique (See Table 2 for mean and standard error of the mean values; mTBI/no group standard deviation = 9,704 mm3 ; mTBI group standard deviation 8,571 mm3).

Site differences are an issue within any multi-site study (Nencka et al., 2017) and there are clearly site differences noted across the four acquisition sites, each with different MRI system platforms from three MRI vendors. As reflected in Figures 1 and 2 along with mention in Table 4, TIV and TBV significantly varied by site whereas height, weight and BMI did not. There are multiple factors that likely relate to site differences. The service populations differ in terms of age and type of service member being seen. Accordingly, demographic differences contribute to site variability. Also, despite similar to identical image acquisition protocols, differences likely

relate to local influences of different MR platforms on image contrasts that subtlety impact how segmentation and classification occurs (Wilde et al., 2016). In a previous CENC investigation, we have shown how site differences result in different volumetric output even in the same individual scanned across different platforms with ostensibly the same MR sequences (Wilde et al., 2016). In a practical sense, this represents a limitation only for reporting and comparing absolute volumes across different acquisition sites, but does not necessarily influence the relationship value of a measure with an outcome variable. Note that although there were absolute differences in TIV and TBV size across the different sites, their relationship with age was not. In the absence of height and weight differences across sites, it is unlikely that there would be a systematic difference in correlational values using TIV or TBV, even though absolute volumes may differ by site. The fact that TIV and TBV did vary by site implies measurement differences were influenced by the MR platform, yet the age and TIV or TBV relations showed similar relationships regardless of site. Accordingly, for correlational analyses, minor differences in site likely has minimal to no effect on the correlation. Additionally, where site differences exist such differences likely represent a constant that could be statistically computed for harmonization of volumetric differences across sites (Manley et al., 2017; Nencka et al., 2017)

However, expanding the clinical application of MRI-based volumetrics may need to simply embrace the "noise" from different scanners and platforms and not even attempt to correct for site differences. Because the endpoint of CENC is the utilization of neuroimaging findings in clinical decision making, as part of a 'precision medicine' approach, current informatics and morphometric approaches using volumetric data from multiple sites may actually need to disregard site differences. In generating the normative comparison data for widespread usage, it would be unwieldy to always attempt to correct for scanner differences. Rather, it may simply require incorporating the greater variability that comes with multiple site differences into clinical 'cut-points' separating what may or may not be pathological. For example, a normative date set based on multi-site acquisitions would incorporate inherent scanner differences in the overall normative data acquired, when sufficient sample size was included across the different sites. Based on such a diverse dataset, if a cut-point were defined to meet or exceed a ~ 2.0 standard deviation difference from the comparison mean, this accounts for the variability and likewise uses a rigorous cut-point. This approach is exemplified by the

currently available NeuroQuant method in the clinical application of volumetric image analysis for an individual subject, which does not correct for type of scanner (Farid et al., 2012; Stelmokas et al., 2017; Wang et al., 2016). While adjusting and accounting for site differences would reduce between site variance, that approach would not be feasible for broader use, as not all sites would necessarily have sufficient samples to generate their own normative data. Site differences also occur with software upgrades as well as changing out hardware, which can possibly affect the longitudinal assessment of data and need to be followed in any longitudinal trial. As such, there could be a never-ending array of potential adjustments necessary for individual comparisons related to a multisite database. This merely underscores that site of acquisition needs to be one of those variables examined in CENC investigations.

Another important factor from a precision medicine standpoint would be not just the individual to a normative group comparison, but potential change over time (Ross, Castelvecchi, & Ochs, 2013; Ross et al., 2012). There is a known rate of "normal" change over time and as shown in Figure 1 and 2 there is a progressive brain volume loss with aging. As shown by the current investigation, the known rate of age-mediated changes can be calculated and factored in when examining longitudinal changes in the individual patient. Knowing such factors and using the patient as their own control in a within subject comparison eliminates site variability issues, and may provide the best method for tracking neuroimaging factors relevant to mTBI and PTSD, and whether there are adverse long-term effects.

Conclusions

Initial methods and MRI volumetric findings from the *Neuroimaging Core* of CENC have been overviewed. While there were no coarse ROI volumetric differences associated with mTBI, there were differences in cortical thickness. Age and body size differences in relation to TIV and TBV were observed, which have relevance for future cross-sectional as well as longitudinal CENC mTBI investigations. The implications for how best to use basic volumetric data from the CENC *Neuroimaging Core* is discussed along with future implications of issues that need to be addressed when investigating the longitudinal effects of mTBI and multi-site acquisition of scan data.

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Appendix 31

TBI Severity and Risk of Suicide and Unintended Death by Overdose and Firearms: A Chronic Effects of Neurotrauma Consortium Study

Word Count for Text: 2,997

TBI Severity and Risk of Suicide and Unintended Death by Overdose and Firearms

A Chronic Effects of Neurotrauma Consortium Study

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Key Points

Question: What is the association between severity of traumatic brain injury and risk of suicide and unintended death by drug overdose and firearms?

Findings: In more than 1.5 million veterans with and without traumatic brain injury, mild, as well as moderate to severe, traumatic brain injury increased risk of suicide and unintended death by drug overdose and firearms, with higher risk for overdose death observed with age. Results remained above and beyond competing risk of death and common comorbidities.

Meaning: All levels of traumatic brain injury increase risk of preventable death by overdose and firearms across the life course.

ABSTRACT

Importance: Evidence guiding suicide prevention efforts in vulnerable patients with traumatic brain injury (TBI) is extremely important. Better understanding the association between TBI and risk of suicide-related outcomes like death by drug overdose and firearms is vital and supports such efforts.

Objective: To determine the association between severity of TBI and risk of suicide and unintended death by drug overdose and firearms in veterans.

Design: Using Fine-Gray proportional hazards regression, accounting for competing risk of death, we analyzed veterans with and without TBI in the Veterans Health Administration health care system from October 1, 2001 to December 31, 2014 with data linked to the National Suicide Data Repository.

Setting: Department of Veterans Affairs medical centers in the United States.

Participants: A total of 1,524,921 veterans 18 years and older, including all patients with a TBI diagnosis (n=240,506) and a random sample without a TBI (n=1,284,415).

Main Outcome Measure: Death by drug overdose and firearms, including suicide and unintentional injury, were defined by the *International Classification of Diseases, Tenth Revision* codes using the National Suicide Data Repository.

Results: After adjusting for demographics, comorbidities, and accounting for competing risk of other deaths, adjusted hazard ratios for death by drug overdose were 1.51 (95% CI, 1.34-1.70) for mild TBI and 1.71 (95% CI, 1.53-1.91) for moderate to severe TBI, while adjusted hazard ratios for death by firearms were 1.20 (95% CI, 1.01-1.42) for mild TBI and 1.50 (95% CI, 1.30-1.72) for moderate to severe TBI. Both mild and moderate to severe TBI predominantly increased risk of suicide and unintended death by overdose and firearms. A significant

interaction was found with TBI severity and diagnosis age predicting death by overdose ($P <$ .001). No interaction was found predicting death by firearms ($P = .22$). Differences in increased risk of overdose death due to TBI severity were largely observed for middle and older age groups.

Conclusions and Relevance: These findings highlight that drug overdose and firearms are imperative to consider in suicide prevention and intervention efforts for patients with mild, as well as moderate to severe, TBI across the life course and into late life.

INTRODUCTION

Traumatic brain injury (TBI) is a serious and real artifact of war. Approximately, 15-20% of Iraq and Afghanistan veterans experience combat-related TBI[1,2] with the majority of TBIs documented as mild.[3] Preventable deaths such as suicide and unintended death by drug overdose and firearms are also particularly salient in veterans.[4-12] Moreover, drugs and firearms are important targets of means restriction for intervention and prevention of premature death.[10,13-15] Thus, a greater understanding of the extent to which severity of TBI is associated with suicide and unintended death by drug overdose and firearms is imperative. However, little is known about the association between TBI and such preventable deaths.

Although prior research shows that traumatic brain injury increases risk of suicide,[16] only a few studies have considered mild TBI.[17,18] Even more so, to our knowledge, next to nothing is known if death by drug overdose and firearms, including suicide and unintentional death, are associated with severity of TBI. Determining the relationship of mild and moderate/severe TBI to risk of death by drug overdose and firearms is highly significant to suicide prevention efforts, especially when considering: 1) overdose and firearms are leading means of suicide-related death;[13,19] 2) there is frequent misclassification of suicide-related overdose deaths as accident or undetermined;[19-22] and 3) mild TBI is very common, composing up to 82% of total TBIs in military personnel[3] with nearly similar estimates in the general population.[23] If a relationship is observed with mild TBI, implications for prevention of premature deaths could be enormous.

The purpose of our study was to determine the association between severity of TBI and risk of suicide and unintended death by drug overdose and firearms among U.S. veterans. We hypothesize that mild TBI, as well as moderate/severe, will be associated with an increased risk of death by drug overdose and firearms across the life course, and above and beyond major medical conditions and psychiatric disorders.

METHODS

Data and Participants

Data for this retrospective cohort study were obtained from the Department of Veterans Affairs (VA) National Patient Care Database (NPCD) linked to the National Suicide Data Repository (SDR).[24] The NPCD captures all inpatient and outpatient services within the VA. The SDR includes all cause-specific deaths. Records were extracted for veterans 18 years and older who had been seen at either inpatient or outpatient VA healthcare facilities between October 1, 2001 through December 31, 2014. The current study sample included 1,524,921 patients; comprising all patients who received a TBI diagnosis during this time period (n=240,506) and those without TBI (n=1,284,415) determined from a 2% random sample of all patients. Patient baseline was determined by the index date, i.e., first date of TBI diagnosis or random selection date (between 10/1/2001 and 12/31/2014) for those without TBI.

The institutional review boards of the University of California, San Francisco and the San Francisco Veterans Affairs Medical Center, and the Research Protection Office of the U.S. Army Medical Research and Materiel Command approved this study.

Measures

Traumatic Brain Injury

TBI diagnoses were determined using the Defense and Veterans Brain Injury Center (DVBIC) and the Armed Forces Health Surveillance Branch (AFHSB) for TBI surveillance 2012 criteria.[25] DVBIC/AFHSB criteria is based on a comprehensive and standardized list of *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes in the VA NPCD. In addition, we utilized the Comprehensive Traumatic Brain Injury Evaluation (CTBIE) database,

an accruing national database that includes Iraq and Afghanistan-era veterans who have separated from military service, enrolled in VA healthcare, and received a comprehensive TBI evaluation. The CTBIE database includes detailed information on final determination of TBI status as well as duration of loss of consciousness (LOC), alteration of consciousness (AOC) and post-traumatic amnesia (PTA). We identified all Iraq and Afghanistan Veterans who received a TBI diagnosis through CTBIE from October 2007 to 2014.

TBI severity. TBI severity was classified as no TBI, mild, or moderate/severe. In veterans whose TBI was diagnosed through CTBIE, mild and moderate/severe TBI were defined using the more stringent DOD criteria (i.e., mild TBI: LOC 0-30 minutes, AOC a moment to 24 hours and PTA 0-1 day; and moderate/severe TBI: LOC > 30 minutes, AOC > 24 hours, or PTA > 1 day).[26] However, this definition does not directly correspond to *ICD-9* codes, in which 'brief' LOC is defined as ≤1 hour rather than ≤30 minutes and AOC and PTA are not specified. Therefore, in veterans whose TBI was diagnosed through the NPCD using *ICD-9* codes, mild and moderate/severe TBI were defined using DVBIC 2012 Criteria.[25] In veterans with more than one TBI, TBI severity was classified based on most severe injury reported during index year. Patients whose TBI severity could not be classified were excluded.

Death by Drug Overdose and Firearms

Death by drug overdose and death by firearms were determined using non-homicide *ICD-10* codes for primary underlying cause of death and date of death in the VA SDR. Death by drug overdose was defined by *ICD-10* codes X60-64 (suicide), X40-X44 (unintentional), and undetermined (Y10-Y14). Death by firearms was defined by *ICD-10* codes X72-74 (suicide), X32-X34 (unintentional), and undetermined (Y22-Y24).

Baseline Characteristics

Demographic Variables. VA database records had available information on age, gender, and race/ethnicity (categorized as non-Hispanic white, non-Hispanic black, Hispanic, and other/unknown). We used 2000 U.S. Census Data to classify veterans as living in broad educational and income strata according to zip code tabulation areas (ZCTA).[27] Education was defined as a two-level variable categorized according to whether veterans were living in a ZCTA where $\leq$25% versus >25% of the adult population had completed a college education (bachelor's degree or higher). Income was defined as a three-level variable categorized in tertiles of median ZCTA income for adults <75 or $\geq$75 years old.

Comorbidities. Medical and psychiatric disorders were coded as comorbid at baseline if they were coded at veteran's index date or during previous two years using standard *ICD-9* codes. Major medical disorders included diabetes mellitus, hypertension, myocardial infarction, cerebrovascular disease, dementia, sleep disorder (sleep apnea, insomnia, hypersomnia, parasomnia, or circadian rhythm disorders), and chronic pain[28] (head, neck, or back pain). Psychiatric conditions included mood disorders [i.e., depression (major depression or depression not otherwise specified), dysthymia, or bipolar disorder], posttraumatic stress disorder (PTSD), other anxiety disorders (i.e., generalized anxiety disorder, panic, or phobia), and substance use disorders (i.e., alcohol abuse/dependence or drug abuse/dependence), and tobacco dependence.

Statistical Analyses

To describe the sample, baseline characteristics were summarized using means and standard deviations or frequencies and proportions for veterans with no TBI, mild TBI, and moderate/severe TBI. Statistical significance of differences between the three groups were tested by F tests for continuous variables and chi-square tests for categorical variables. Cumulative incidence of death by drug overdose and death by firearms as a function of age and TBI severity were examined graphically. Fine-Gray proportional hazards regression was used to examine time to death, with age as the time scale while accounting for competing risk of other deaths.[29] Hazard ratios were estimated for the association between TBI severity and risk of death by drug overdose and death by firearms in models adjusted for demographics, any medical comorbidities, and any psychiatric conditions. Furthermore, sensitivity analyses were performed stratified based on TBI data source (CTBIE versus NPCD). Finally, to determine if there were different patterns of risk by severity of TBI diagnosis across the life course, we calculated death rates (deaths per 10,000) over the 13 years by TBI diagnosis/index age groups (18-29, 30-39, 40-49, 50-59, and ≥ 60 years). To statistically test if associations were different across age groups, interaction terms with TBI severity and age group (and main effects) were examined in Fine-Gray proportional hazards regression analyses. *P* values were 2-sided with statistical significance defined as $P < .05$. All analyses were performed using SAS version 9.4 software (SAS Institute Inc, Cary, North Carolina) and STATA version 14.2 (StataCorp, College Station, Texas).

RESULTS

The final cohort was 68.5% non-Hispanic white, 12.0% non-Hispanic black, 1.3% Hispanic, and 18.2% other/unknown, with mean (SD) baseline age of 59.6 (17.3) years and 8.7% female veterans. There were 240,506 veterans diagnosed with TBI (> 50% mild TBI). Study participants were followed for a mean (SD) of 5.0 (3.7) years until death or their last clinical visit. Of the more than 1.5 million veterans, 310,212 (20%) died (n=13,237 mild TBI and n=23,065 moderate/severe TBI). Veterans with mild TBI and moderate/severe TBI were younger on average than those with no TBI (45-52 vs 62 years old; $P < .001$; Table 1). Veterans with moderate/severe TBI had more comorbid myocardial infarction, cerebrovascular disease, and dementia than those with mild or no TBI, while veterans with mild TBI had more sleep disorders and chronic pain. Veterans with any TBI diagnosis had more comorbid psychiatric conditions than those with no TBI.

In Table 2, among drug overdose decedents, 13.4% were suicide, 79% were unintentional, and 7.5% undetermined. Among firearm decedents, 97% were suicide, 2.1% were unintentional, and < 1% undetermined. Of veterans who died over the study, death by suicide and unintended death by drug overdose and firearms were highest among decedents with mild TBI ($P < .001$ across all TBI severity groups). Throughout follow-up mortality rates for death by drug overdose (Figure 1) and death by firearms (Figure 2) were consistently higher for patients with mild and moderate/severe TBI than those with no TBI. After adjusting for demographic factors, medical and psychiatric comorbidities, and accounting for competing risk of other deaths, the adjusted hazard ratio (HR) for death by drug overdose was 1.51 (95% CI, 1.34-1.70) for mild TBI and 1.71 (95% CI, 1.53-1.91) for moderate/severe TBI (Table 2). The adjusted HR for death by firearms was 1.20 (95% CI, 1.01-1.42) for mild TBI and 1.50 (95% CI, 1.30-1.72)

for moderate/severe TBI. In general, severity of TBI was shown to be associated with suicide and unintended death by drug overdose and firearms. Results were similar in sensitivity analyses examining the NPCD data source; however, there were insufficient cause-specific mortality outcomes in the CTBIE cohort alone to conduct sensitivity analyses.

Finally, Figure 3 shows the sample across the life course, presenting death rates (deaths per 10,000) by TBI severity and TBI diagnosis/index age groups over the 13 years. A statistically significant interaction of TBI severity by diagnosis age was found for risk of death by overdose ($P < .001$); none was found for firearm death ($P = .22$). Although rates of death by drug overdose were considerably high across most age groups and severity levels of TBI, statistically significant differences in risk due to TBI severity were largely observed for middle and older age. Differences were seen for moderate/severe vs. no TBI for those 30-39 year (57.5 vs. 29.5 per 10,000; adjusted HR, 1.47; 95% CI, 1.10-1.95) and 40-49 years (81.5 vs. 46.9 per 10,000; adjusted HR, 1.33; 95% CI, 1.08-1.63). For veterans 50-59 years, differences were observed for mild vs. no TBI (67.8 vs. 30.7 per 10,000; adjusted HR, 2.37; 95% CI, 1.93-2.91) as well as moderate/severe vs. no TBI (68.1 vs. 30.7 per 10,000; adjusted HR, 1.98; 95% CI, 1.64-2.38). Although rates of death by drug overdose were lower for those with a TBI diagnosis 60 years and older, significant differences were still evident by TBI severity (mild vs. no TBI: 9.9 vs. 4.1 per 10,000; adjusted HR, 2.67; 95% CI, 1.81-3.92; and moderate/severe vs. no TBI: 13.6 vs. 4.1 per 10,000; adjusted HR, 2.87; 95% CI, 2.10-3.93).

DISCUSSION

In this study of more than 1.5 million veterans, mild and moderate to severe TBI were related to a higher risk of suicide and unintended death by drug overdose and firearms compared with no TBI over 13 years; risk of overdose death was particularly salient in middle and older age. Our findings indicate that most non-homicide firearm deaths were suicides (> 90%) across all levels of TBI severity, while drug overdose deaths were largely documented as unintentional (> 75%). With mounting evidence of misclassification of drug-related suicides as accidental or undetermined overdose deaths,[19-22] some of these overdose deaths are likely suicides. Study findings were not accounted for by psychiatric and medical disorders, including chronic pain, or competing risk of other deaths.

Although some prior studies have investigated premature death due to intentional and unintentional injury and its relationship to TBI,[30-32] to our knowledge, no study has examined severity of TBI and its association with death by drug overdose and firearms. In one population-based prospective case-control, record-linkage study of 737 head injury cases admitted to the hospital and 2196 general population controls from Finland,[33] the authors found that head trauma without TBI, mild TBI, and moderate-to-severe TBI significantly increased risk of premature death (i.e., intentional and unintentional traumatic death) by 3- to 21-fold over 15 years compared with controls. However, they did not consider death by drug overdose and firearms separately, had a relatively small sample size compared to our very large sample size, weren't U.S. based, only matched on demographics (age, gender, and residence) and, thus, did not adjust for important comorbidities, and did not account for competing risk of other deaths. Our results take all of this into consideration.

Although it is known that use of drugs such as opioids increase risk of suicide[8] and drug overdose death[9,34,35] in those with and without chronic pain, less is known about how this relates to patients with TBI. Work from our group has recently shown that severity of TBI in veterans with chronic pain increased risk of receiving opioid therapy compared with veterans not reporting TBI sequelae;[36] however, mild TBI alone was not independently associated with opioid therapy initiation. Taking this and our current observation that mild TBI is associated with increased risk of suicide-related overdose and death by unintentional drug overdose, independent of other medical and psychiatric disorders including chronic pain, suggests that drug-related overdose death in veterans with mild TBI is more than about opioid use. Furthermore, VA/DoD clinical practice guidelines advise against using opioids in patients with documented TBI;[38,39] thus, other medications may be salient targets of suicide intervention and prevention.

Our age specific results for death by drug overdose observed a particularly high rate in those diagnosed with mild and moderate/severe TBI in middle and older age, which parallels national trends. Drug-related death rates have risen substantially for middle- and older-aged individual,[39] with the largest increase in rate of opioid-related deaths between 1999 and 2015 occurring among those age 55 to 64 years.[40,41] Moreover, between 2014 and 2015, the percent change in the rate of heroin-related deaths was highest among those 55 years and older.[41] These increases are linked, in part, to increase in opioid prescriptions for pain that began in late 1990s.[42] Relatedly, over the past two decades in the U.S., suicide rates among persons age 65 years and older have been consistently high, with middle-aged persons recently experiencing the highest increase in suicide rates of any age group.[43] Among veterans, there has been consistent evidence of a high burden of suicide in middle-aged and older adults. It has been documented that nearly 70% of veteran suicides are in those 50 years and older; increasing to nearly 80% for

veterans who use VA health services.[4,5] In terms of TBI, further research is needed to determine where TBI and TBI severity fall on the pathway from drug use to suicide and unintended death by drug overdose in these age groups.

Considering current study findings, targeted means restriction programs are indicated for patients diagnosed with mild and moderate/severe TBI. Multiple studies have found that firearm access is a significant and strong risk factor for suicide.[13,44,45] Furthermore, restriction of lethal means is one of the only suicide-prevention policies that has been effective.[14,46] All this is pertinent for military personnel and veterans, given their increased knowledge of and ownership of firearms compared to those without a history of military service.[10,47] Compounding things for veterans with TBI, particularly mild TBI, is greater potential of engaging in risky lifestyle behaviors that may be related to both sustaining a TBI and attempting suicide.[16,48] The current work supports recommendations that rehabilitation clinicians engage in suicide screening and prevention efforts among those with TBI at intake and continue with regular follow-up.[16] Such engagement has been found acceptable, particularly with suicide risk, by patients and family members.[49,50] Similarly, monitoring of medications by providers is highly indicated by these current findings. It is important for healthcare providers to educate patients and caregivers and promote appropriate storage and reduction of prescription drugs and over-the-counter medications in veterans[13] with a mild, as well as moderate/severe, TBI diagnoses.

Our study has several important strengths, including application of a longitudinal study design in a large, national sample of patients aged 18 years and older. The VA data provided detailed records of medical and psychiatric disorders, an advantage over self-report data that is subject to recall bias. Moreover, the data allowed for documentation of suicide and unintended death by drug overdose and firearms, and assessment of age-specific risk. We also were able to

adjust for confounding from medical and psychiatric comorbidities and account for competing risk of other deaths. Finally, this study is the first, to our knowledge, that has reported that mild TBI increases risk of suicide by drug overdose and firearms.

Limitations of our study are also important to mention. Our study population included mainly male veterans. Thus, we need to determine if our findings generalize to female veterans and non-veterans. In addition, validity of diagnoses could not be confirmed. Finally, although we were able to adjust for important potential confounders, we did not have information regarding lifestyle and social support factors, which may confound the relationship of TBI with death by drug overdose and firearms.

Conclusion

When considering the current epidemics of drug overdose and firearms[13,39-42,50] and heightened suicide risk for those with TBI,[16-18] providing evidence for tangible targets of intervention and prevention in this highly vulnerable population with multiple levels of trauma severity is extremely important. The findings of the current study emphasize this importance and the need to closely monitor all levels of traumatic brain injury for risk of suicide and unintended death by firearms and drug overdose.

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Table 1. Baseline Characteristics of 1,524,921 Veterans by TBI Severity

	No. (%)			
	No TBI (N=1,284,415)	**Mild TBI (n=129,795)**	**Moderate/Severe TBI (n=110,711)**	***P* value[a]**
Demographic				
Age, mean (SD), y	61.80 (15.9)	44.91 (18.9)	51.67 (19.4)	<.001
Age groups				<.001
18-29	60,208 (4.7)	39,896 (30.7)	21,475 (19.4)	
30-39	77,080 (6.0)	24,429 (18.8)	14,608 (13.2)	
40-49	136,957 (10.7)	18,636 (14.4)	15,452 (14.0)	
50-59	263,580 (20.5)	16,661 (12.8)	20,847 (18.8)	
60+	746,590 (58.1)	30,173 (23.3)	38,329 (34.6)	
Female	113,847 (8.9)	11,140 (8.6)	8,194 (7.4)	<.001
Race				
Non-Hispanic White	895,679 (69.7)	77,614 (59.8)	70,449 (63.6)	
Non-Hispanic Black	153,858 (12.0)	14,632 (11.3)	14,110 (12.7)	
Hispanic	15,099 (1.2)	2,382 (1.8)	3,011 (2.7)	
Other[*]	219,779 (17.1)	35,167 (27.1)	23,141 (20.9)	
>25% college-educated in zip code[b]	623,410 (48.5)	67,063 (51.7)	54,439 (49.2)	<.001
Median income tertile in zip code[b]				<.001
Low tertile (<$24,516)	422,010 (32.9)	33,235 (25.6)	33,418 (30.2)	
Middle tertile	412,085 (32.1)	41,831 (32.2)	34,726 (31.4)	
High tertile (>$32,486)	399,687 (31.1)	49,105 (37.8)	37,157 (33.6)	
Medical				
Diabetes mellitus	90,335 (7.0)	4,478 (3.5)	4,780 (4.3)	<.001
Hypertension	206,472 (16.1)	13,717 (10.6)	13,465 (12.2)	<.001
Myocardial infarction	22,893 (1.8)	1,586 (1.2)	2,283 (2.1)	<.001
Cerebrovascular disease	40,060 (3.1)	4,282 (3.3)	10,678 (9.6)	<.001
Dementia	91,300 (7.1)	10,662 (8.2)	16,776 (15.2)	<.001
Sleep disorder	24,576 (1.9)	7,722 (6.0)	5,305 (4.8)	<.001
Chronic Pain	143,146 (11.1)	50,422 (38.9)	32,590 (29.4)	<.001
Any medical disorder	458,279 (35.7)	72,002 (55.5)	62,205 (56.2)	<.001
Psychiatric				
Mood disorder[c]	120,789 (9.4)	34,532 (26.6)	26,076 (23.6)	<.001
PTSD	42788 (3.3)	36554 (28.2)	21280 (19.2)	
Other Anxiety disorder[d]	51,541 (4.0)	19,582 (15.1)	12,730 (11.5)	<.001
Substance use disorder[e]	52,619 (4.1)	15,656 (12.1)	12,334 (11.1)	<.001
Tobacco dependence	84,963 (6.6)	16,811 (13.0)	13,096 (11.8)	<.001
Any psychiatric disorder	252,603 (19.7)	68,554 (52.8)	50,295 (45.4)	<.001

[a]P value based on F test for continuous variables and chi-squared test for categorical variables comparing across TBI severity.

[b]Zip code tabulation area from 2000 census.

[c]Mood disorder includes depression, dysthymia, bipolar disorder.

[d]Other Anxiety disorder includes generalized anxiety disorder, panic, phobia.

[e]Substance use disorder includes alcohol abuse/dependence or drug abuse/dependence.

[*]% decline/unknown race = 258,402 (16.95%).

Table 2. Adjusted Risk of Death for Drug Overdose and Firearms by TBI Severity (N = 1,524,921)

Cause of Death	Among 310,212 decedents, No. (%)[c]			Adjusted Hazard Ratios (95% CI)[d]	
	No TBI (n=273,910)	Mild TBI (n=13,237)	Mod/Sev TBI (n=23,065)	Mild TBI (n=129,795)	Mod/Sev TBI (n=110,711)
Drug overdose[a]	2,109 (0.8)	455 (3.4)	494 (2.1)	1.51 (1.34-1.70)	1.71 (1.53-1.91)
Suicide	302 (0.1)	58 (0.4)	51 (0.2)	1.65 (1.18-2.29)	1.36 (0.98-1.90)
Unintentional	1,644 (0.6)	362 (2.7)	411 (1.8)	1.50 (1.31-1.72)	1.81 (1.60-2.04)
Undetermined	163 (0.1)	35 (0.3)	32 (0.1)	1.36 (0.88-2.11)	1.31 (0.85-2.00)
Firearms[b]	1,883 (0.7)	201 (1.5)	264 (1.1)	1.20 (1.01-1.42)	1.50 (1.30-1.72)
Suicide	1,838 (0.7)	193 (1.5)	247 (1.1)	1.18 (0.99-1.40)	1.45 (1.25-1.67)
Unintentional	34 (0.01)	6 (0.1)	10 (0.04)	1.85 (0.85-4.03)	3.25 (1.80-5.59)[e]
Undetermined	11 (0.004)	2 (0.02)	7 (0.03)		

[a]*ICD-10* codes for death by drug overdose = suicide (X60-X64) + unintentional (X40-X44) + undetermined (Y10-Y14).
[b]*ICD-10* codes for death by firearms = suicide (X72-X74) + unintentional (W32-W34) + undetermined (Y22-Y24).
[c]No. (%) based on absolute values over study period.
[d]No TBI is the reference group; HRs adjusted for demographics (gender, race, education, income), any medical conditions, and any psychiatric disorders.
[e]HRs are based on combined unintentional and undetermined due to small cell sample sizes.

Figure 1. Cumulative Incidence of Death by Drug Overdose by TBI Severity (N=1,524,921)

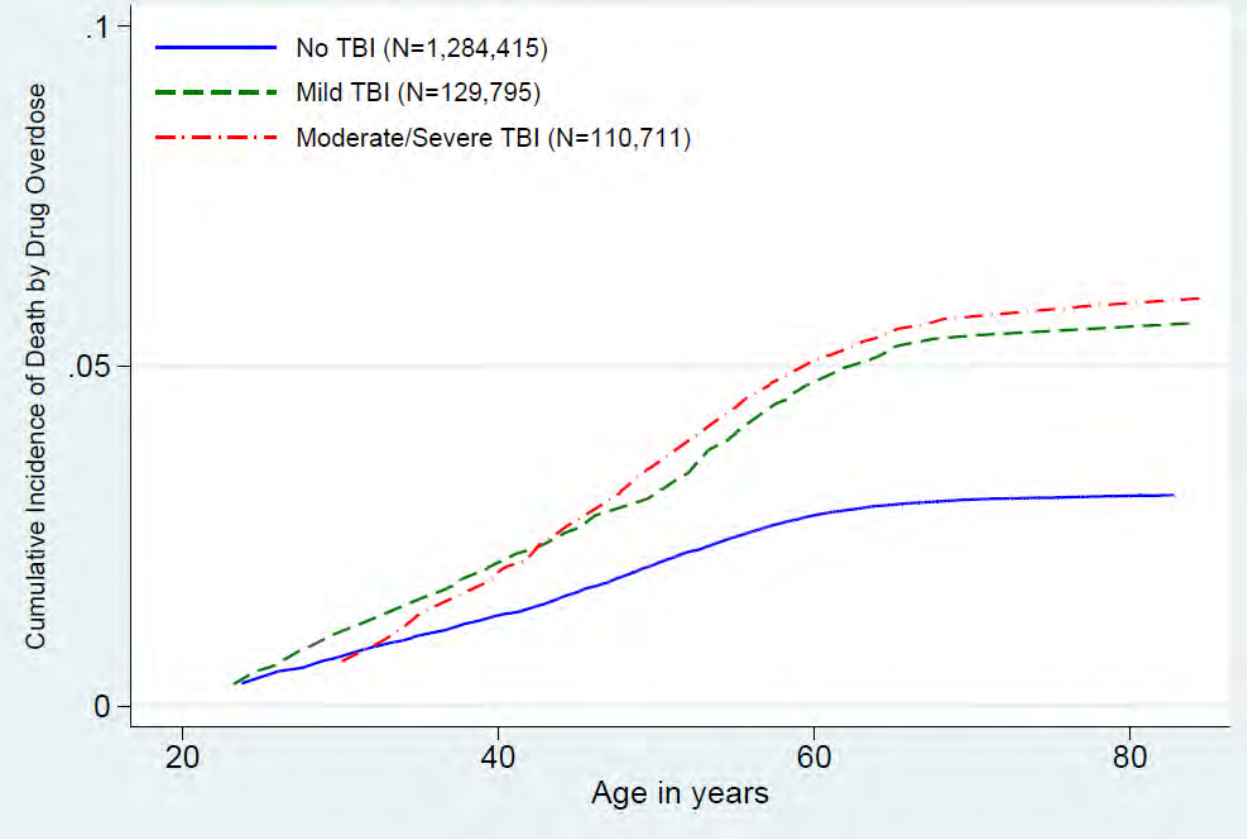


Figure 2. Cumulative Incidence of Death by Firearms by TBI Severity (N=1,524,921)

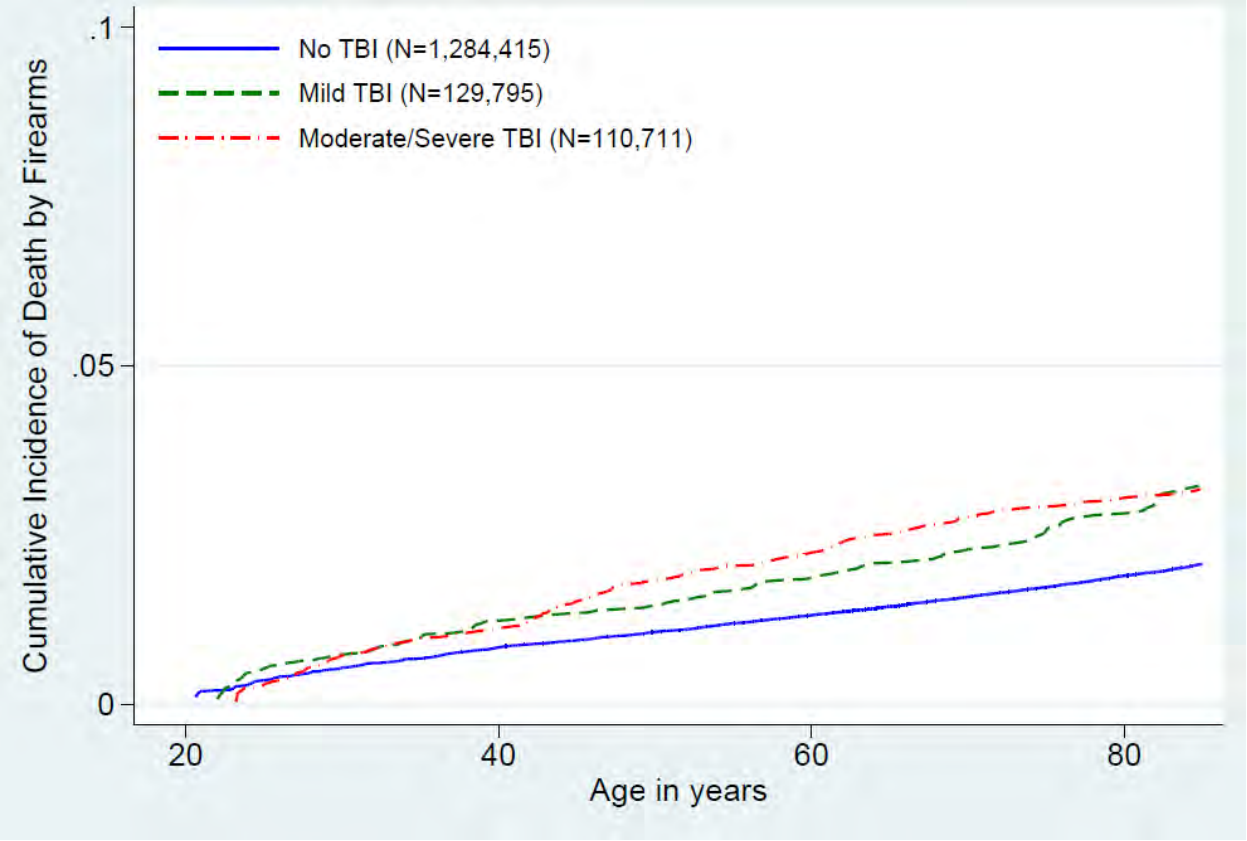
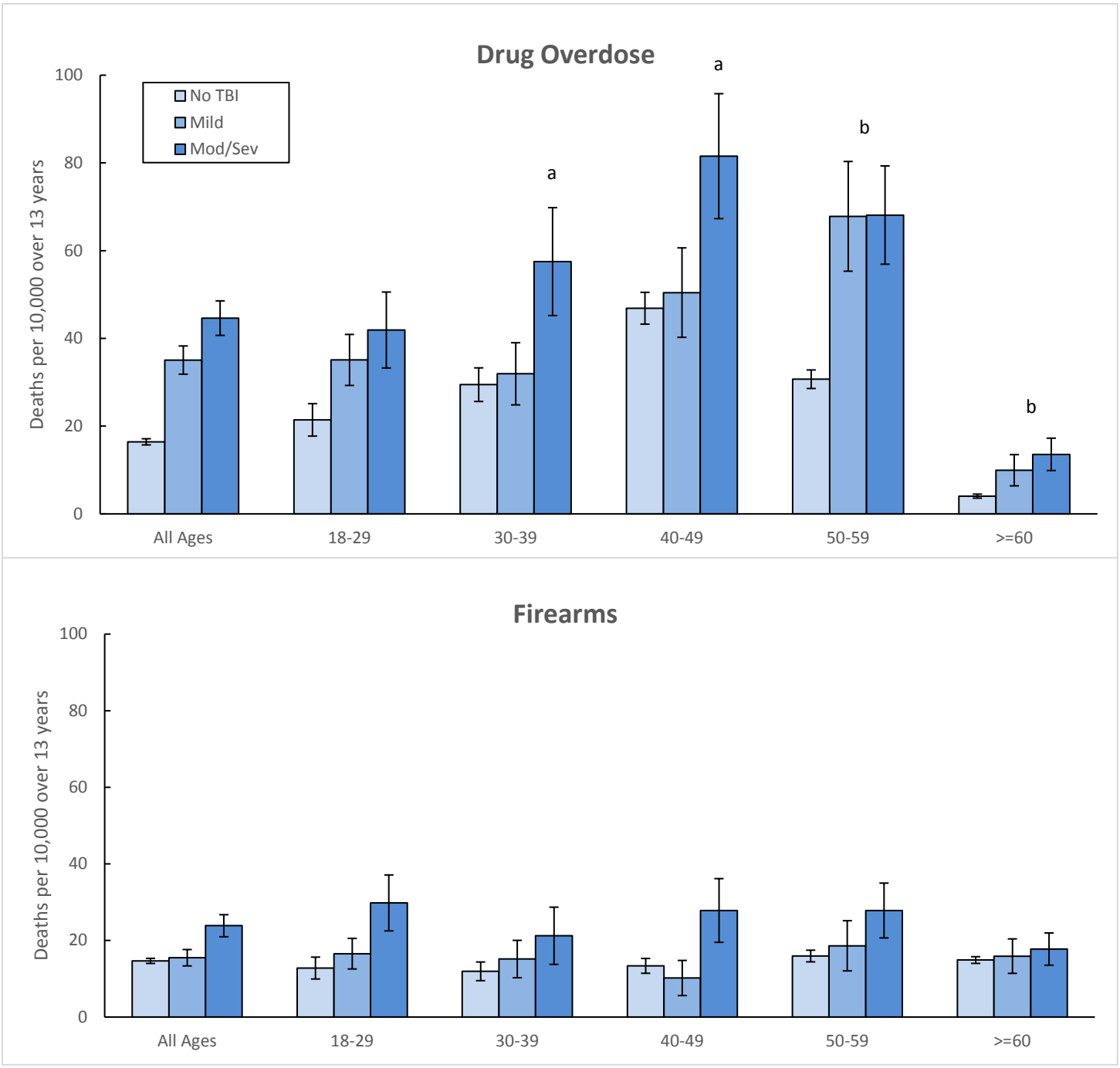


Figure 3. Death Rates (Deaths per 10,000) over 13 Years by TBI Diagnosis/Index Age



The error bars indicate 95% CIs.

[a]Mod/Sev TBI vs. No TBI, $P < .05$ (based on adjusted Fine-Gray proportional hazards analyses).

[b]Mild TBI vs. No TBI and Mod/Sev TBI vs. No TBI, $P < .001$ (based on adjusted Fine-Gray proportional hazards analyses).

Appendix 32

Impact of Otolith Dysfunction on Postural Stability and Quality of Life: A Chronic Effects of Neurotrauma Consortium Study

Title: Impact of Otolith Dysfunction on Postural Stability and Quality of Life: A Chronic Effects of Neurotrauma Consortium Study

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Background: Until recently, clinical vestibular function assessment was limited to measurement of horizontal semicircular canal pathways. Vestibular evoked myogenic potentials are becoming more widely used to supplement the vestibular test battery by providing information about the otolith organs and their pathways; yet, the clinical significance of otolith organ dysfunction is unclear. The purpose of this study was to determine the functional consequences of otolith organ dysfunction on postural stability and quality of life.

Methods: A prospective case-control study of Veterans (n=130) was completed. Comprehensive vestibular site-of-lesion testing was performed and participants were grouped according to patterns of vestibular test findings. Three vestibular groups included individuals complaining of dizziness/imbalance with: (1) otolith organ dysfunction only (Otolith Only, n=21), (2) semicircular canal and otolith organ dysfunction (Canal+Otolith, n=19), and (3) semicircular dysfunction only (Canal Only, n=12). Two control groups included individuals with normal vestibular function and (1) complaining of dizziness/imbalance (Dizzy Control, n=52) or (2) with no complaints of dizziness/imbalance (Healthy Control, n=26). Self-report questionnaires and physical performance measures of balance and gait assessed postural stability and quality of life. MANOVAs were performed to determine significant group differences ($p < 0.05$) for balance and gait and quality of life outcome measures. As appropriate, post hoc analyses of covariance and pairwise comparisons were performed to identify specific group differences ($p < 0.05$).

Results: There were no significant group differences for age, race, ethnicity, gender or occupational status. MANOVAs indicated significant group differences for both gait and balance and quality of life measures. The Otolith+Canal group performed significantly worse than both control groups and the Otolith Only and Canal Only groups on the Sensory Organization Test. The Otolith+Canal group also performed significantly worse than both control groups on the Functional Gait Assessment.

The Otolith Only group performed significantly worse than the Healthy Control group on a measure of the impact on activities, the Activities-specific Balance Confidence scale (ABC), and the Dizziness Handicap Inventory (DHI). The Otolith+Canal group performed significantly worse than the Healthy Control on a measure of the impact on activities, the ABC, DHI, and Vestibular Activities and Participation measure.

Conclusions: Otolith organ dysfunction negatively impacts quality of life, and in conjunction with semicircular canal dysfunction negatively impacts balance and gait. The findings of this study have important implications for developing effective clinical protocols for the diagnosis and management of individuals with dizziness related to otolith organ dysfunction.

Appendix 33

Comparability of iPad and Web-Based NIH Toolbox Cognitive Battery Administration in Veterans

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Comparability of iPad and Web-Based NIH Toolbox Cognitive Battery Administration in Veterans

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Abstract

Objective: The purpose of this study was to evaluate the comparability of National Institutes of Health Toolbox Cognitive Battery test scores across iPad application and web-based personal computer administration platforms. Original test norms were developed using a personal computer-based administration and no previous studies assessing platform comparability have been published.
Method: Participants ($N = 62$; final analyzed sample $n = 49$) were combat-exposed post-deployment veterans without neurologic disorder, severe mental illness, current substance use disorder, or a history of moderate or severe traumatic brain injury. All participants completed both iPad and web-based versions of tests on the same day in an experimental within-subjects crossover design. Standalone validity measures were incorporated to exclude invalid performance. Outcome measures included the Dimensional Change Card Sort Test, Flanker Inhibitory Control and Attention Test, List Sorting Working Memory Test, and Pattern Comparison Processing Speed Test.
Results: Score differences between platforms were found on the Flanker Inhibitory Control and Attention Test. Scores were moderately correlated across tests, with the exception of low correlations for the Pattern Comparison Processing Speed Test. Most participants preferred iPad to web administration, regardless of administration order.
Conclusions: Results suggest caution when interpreting iPad-acquired scores, particularly for the Flanker Inhibitory Control and Attention Test. iPad-based testing offers valuable improvements; however, the development of iPad-specific norms may be necessary to ensure valid interpretation of acquired data.

Keywords: Cognition; Assessment; Toolbox; mHealth; Telehealth; Tablet

The National Institutes of Health Toolbox (NIHTB) is a compilation of computerized measures developed to provide an efficient assessment of neurological, cognitive, and behavioral function that promotes translation of research findings across diverse settings (Gershon et al., 2013). The NIHTB cognitive test battery (NIHTB-CB) measures key domains of brain function: language, processing speed, attention, episodic memory, and executive function. Four NIHTB-CB tests were normed for ages three through eighty-five: Picture Vocabulary Test, Flanker Inhibitory Control and Attention Test (Flanker), Dimensional Change Card Sort Test (Card Sort), and Picture Sequence Memory Test. Three additional tests were normed for ages seven through eighty-five: List Sorting Working Memory Test (List Sorting), Pattern Comparison Processing Speed Test (Pattern

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Comparison), and Oral Reading Recognition Test. Weintraub and colleagues (2014) confirmed the test–retest reliability of each individual NIHTB-CB measure (r = .73–.90), and data reported by Heaton and colleagues (2014) indicated high reliability for battery composite scores (r = .86–.92). Moderate convergent validity with existing neuropsychological tests has also been suggested (Weintraub et al., 2013).

The normative sample for the NIHTB-CB was acquired through a local personal computer (PC) administration. The battery was then deployed with minimal changes to PCs in a web-based form (Gershon et al., 2013). Recently, the NIHTB-CB measures were translated to an iPad app-administered format which has made their use more convenient for both clinical and research settings (Clay, 2016; Northwestern University, 2017). Although iPad administration has clear advantages (e.g., portability, simplicity, offline access, immediate scoring), many factors may affect test comparability across administration modalities including hardware characteristics (e.g., display size, device speed/memory, speaker quality), administration differences (e.g., instructions, timing), and participant/administrator comfort and familiarity with the administration modality used (Brearly et al., 2017; Cernich, Brennana, Barker, & Bleiberg, 2007; Grosch, Gottlieb, & Cullum, 2011; Luxton, Pruitt, & Osenbach, 2014).

There are several key differences between the PC web-based and iPad versions of the NIHTB-CB including: logistical requirements, user interface, number of test trials, and test prompts/instructions. First, the web-based version requires a relatively complex hardware configuration including a dual-screen computer, speakers, keyboard, and an external mouse. One screen is used to manage administration by the examiner and one screen is used to present stimuli to the examinee. Compared to the iPad version, where the participant and examiner share one screen, portability is limited and there are multiple avenues for computer peripheral variation or failure. Second, tactile differences in user interfaces require separate sets of training instructions for iPad and web-based versions of the Flanker, Pattern Comparison, and Card Sort. During web-based administration, participants are instructed to use keyboard directional keys when responding to test items, whereas iPad administration requires participants to return their finger to a standardized reference point (*home base*) on the table in front of them between each touchscreen response (National Institutes of Health and Northwestern University, 2017a). Further, differences in screen size and type may affect the viewing of test stimuli. Although the iPad screen is higher resolution than many computer monitors, it is also much smaller. There are fewer Pattern Comparison trials on the iPad than on the web version, rendering the raw scores between the two tests incompatible. Finally, iPad administration relies on displayed test instructions accompanied by audio of the instructions, whereas web-based administration requires the examiner to verbally repeat all test instructions that are displayed on-screen (National Institutes of Health and Northwestern University, 2017a; Northwestern University, 2017).

The importance of accounting for administration nuances specific to electronic administration of tests has been formalized in a joint consensus statement released by the American Academy of Clinical Neuropsychology and the National Academy of Neuropsychology. The consensus statement calls for developers of electronically administered tests to "provide users with sufficient technical information to ensure that [the test] will provide data that can be accurately compared to that which exists in the test's normative database" (Bauer et al., 2012, p. 183). The NIHTB-CB was developed with the goal of allowing modification and updates in the future without losing the comparability of previously collected data (Gershon et al., 2013). However, in accord with consensus statement precautions, an internal investigation described by e-mail to test users in 2016 reported incongruence between most norm-referenced scores produced by the web and iPad-based tests (Gershon & Diaz, personal communication, October 7, 2016). Specifically, iPad norm-referenced scores were reported as inappropriate for use with the Card Sort, Flanker, Pattern Comparison, and Picture Sequence Memory Test. The norm-referenced scores for the remaining cognitive tests (List Sorting, Picture Vocabulary, and Oral Reading Recognition) administered by iPad were reported to be accurate and comparable to web administration. Test developers have attempted to address this issue in two ways. First, a new scoring process was developed for the iPad data and previously collected data stored on iPads were rescored by application update in December 2016, to foster iPad compatibility with existing norms for all tests. Second, a Python-based program was released by test developers in March 2017 to allow for calculation of web-based norm-referenced scores that would be comparable across platforms (Casaletto et al., 2015; National Institutes of Health and Northwestern University, 2017b).

Most research on the NIHTB-CB has not utilized the iPad-administered form (Carlozzi, Goodnight, et al., 2017; Carlozzi, Tulsky, et al., 2017; Holdnack et al., 2017; Tulsky, Carlozzi, et al., 2017; Tulsky, Holdnack, et al., 2017). Therefore, it is important that independent validations of test rescoring be conducted to facilitate confident integration of iPad-collected data into existing protocols and clinical work. There are currently no published studies validating the iPad administration and the scores it produces, or comparing scores acquired by iPad to those acquired by web-based administration. The aim of the current study was to address this need by comparing iPad and web-based test scores using an experimental crossover design.

Methods

Participants

Study participants were Iraq and Afghanistan combat veterans ($N = 62$) recruited to participate in a larger Chronic Effects of Neurotrauma Consortium (CENC) study at the Salisbury Veterans Affairs Medical Center investigating the structural neurobiological and functional sequelae of primary blast forces. This study was approved as an addition to the parent study by the local Institutional Review Board. All participants provided informed consent prior to participation. Eligibility criteria included at least one Iraq or Afghanistan deployment with combat exposure, English speaking, 18 years of age or older, able to comply with instructions to complete study tasks, and able to provide informed consent. Exclusion criteria included a history of moderate or severe traumatic brain injury (TBI); penetrating head injury; non-deployment-related TBI with loss of consciousness; presence of neurologic disorder, severe mental illness, dementia, current substance abuse, psychotic symptoms, or any contraindication for neuroimaging. Participants were initially screened by phone call and then completed an in-person assessment visit confirming full eligibility before being enrolled in an imaging visit. Data for the current study were obtained during the in-person assessment visit.

Nine participants included in the current analyses disclosed a history of non-deployment TBI with loss of consciousness during the in-person assessment visit. Nine participants were excluded from current analyses due to performance below established cutoffs on standalone performance validity measures; seven failed the Medical Symptom Validity Test and two failed the b Test (Boone et al., 2000; Green, 2005). Two additional participants were excluded from analyses, one due to reported and observed fatigue during the second condition and one due to interruption of the study protocol. Two final participants were removed from analyses due to missing data. The final sample size for analysis was $n = 49$ participants.

Measures

Full descriptions and video illustrations of administered tests as well as references for reliability and validity data can be found in NIHTB-CB online manuals (National Institutes of Health and Northwestern University, 2017a; Northwestern University, 2017, 2018). List Sorting, a measure of immediate recall and sequencing, presents a series of stimuli (visually and verbally) that participants are required to immediately verbally re-order according to a particular characteristic. The Card Sort is described as a measure of cognitive flexibility and requires examinees to match a stimulus picture with one of two response options after being presented with a matching rule. For this test, examinees are also required to return their finger to a standardized position in front of the iPad (*home base*) between each response on that platform. Scores for List Sorting and Card Sort are generated based on the total items correctly completed. The Flanker is a timed measure of attention and inhibitory control requiring participants to indicate the direction of an arrow while inhibiting responding to "flanking" distractor arrows across a series of trials. This task, like the Card Sort, requires examinees to return their finger to *home base* between each trial to standardize measurement of response time. Finally, the Pattern Comparison measures speed of processing by requiring participants to quickly evaluate a series of picture pairs by providing a response indicating whether each pair of pictures are the same or different. The difficulty of items on both the Pattern Comparison and Flanker is limited and speed of responding is emphasized given the cognitive abilities these tasks are purported to measure. For this reason, computed scores that account for both accuracy and speed of responding are provided as an alternate measure to the raw correct response score.

Procedures

Participants completed NIHTB-CB tests in both web and iPad formats on the same day. NIHTB-CB tests were selected based on their inclusion in the primary study protocol. A randomized crossover design was employed. Condition order was counter-balanced by participant sequence to account for practice and order effects. Participants completed either the web-based or iPad version first, at the onset of the assessment visit, and the second administration was completed approximately 6 h later at the visit's conclusion. A battery of neurocognitive tests (including standalone performance validity measures), interviews, and self-report measures was completed between administrations per the primary study protocol. Standardized procedures outlined in NIHTB-CB test manuals were followed. To better understand participant perspectives regarding NIHCB-TB administration types, qualitative responses regarding administration preference were collected after the second condition for 35 participants ("Which administration format did you prefer?"). Testing was conducted by trained masters- or doctoral-level research staff.

Data Analysis

Chi-squared analyses were conducted to ensure demographic comparability between condition order groups. ANOVA/correlational analyses were run for each demographic characteristic (i.e., age, education, race/ethnicity) and each associated norm-referenced score to ensure that demographic effects were adequately addressed across platforms. Analyzed test data included raw, computed, and norm-referenced scores. Standardized scores adjust for age ($M = 100$, $SD = 15$) and T scores adjust for age, sex, education, and race/ethnicity ($M = 50$, $SD = 10$). Analyzed web data included raw or computed scores (for tests with both a speed and accuracy component), standardized scores (*Age-Corrected Standard Scores*), and T scores (*Fully Corrected T Scores*). The norm-referenced scores were produced from NIHTB-CB web data by the Python program recommended by test developers in March 2017 (National Institutes of Health and Northwestern University, 2017b; Casaletto et al., 2015). Analyzed iPad data included raw or computed scores, standardized scores (*Age-Corrected Standard Scores*), and T scores (*Fully Corrected T Scores*) produced by iPad after the December 2016 scoring update. Web-based scores were calculated using the recommended Python program. For the Pattern Comparison, raw web scores were compared to computed iPad scores per developer recommendations (National Institutes of Health and Northwestern University, 2017b).

RStudio was used to conduct statistical analyses (RStudio Team, 2018). Shapiro–Wilk normality tests indicated that scores on each of the included tests did not meet the normality assumptions for *t*-tests. Performance across modalities was compared using Wilcoxon signed-rank tests. Control of false discovery rate was used to account for multiple comparisons with a family-wise error rate of $\alpha = 0.05$ (Benjamini & Hochberg, 1995). Concordance correlation coefficients (CCC) were calculated to evaluate the reliability of scores acquired across modalities (Lin, 1989). The CCC accounts not only for precision, indicated by the distance data points fall from the line of best fit (i.e., Pearson's correlation coefficient), but also the accuracy of measurement reflected by how far that line falls from the 45-degree line of perfect agreement between scores (Watson & Petrie, 2010). Post-hoc Mann–Whitney *U* tests were used to compare combined raw/computed scores and score differences for carryover and period (practice or fatigue) effects by applying the procedure described by Tudor and Koch (1994).

Results

There were no demographic differences between condition order groups (Table 1). Demographically-corrected scores accounted for population specific relationships observed in raw/computed scores suggesting that norm-referenced scores adequately address demographically associated variability for both iPad and web platforms. Significant differences between conditions were found across scores on the Flanker that remained following correction for multiple comparisons (Table 2). List Sorting scores were not significantly different after correction for multiple comparisons. There was no statistical difference between median iPad and web scores for the Card Sort or Pattern Comparison. Raw/computed, standardized, and T scores were moderately correlated for the Card Sort, Flanker, and List Sorting across modalities. Pattern Comparison scores were poorly correlated, with relatively low precision across modalities (Table 2). There were no differential carryover or period effects for the Flanker, further supporting the presence of a true difference in test platforms with web scores being higher than iPad scores ($U = 122$, $p < .001$, $r = .51$). A period (practice) effect was found for List Sorting ($U = 107$, $p < .001$, $r = .56$) and Pattern Comparison ($U = 7$, $p < .001$, $r = .84$) with test scores improving significantly during the second administration. A carryover effect on Pattern Comparison ($U = 180$, $p < .05$, $r = .34$) indicated that scores during the second period improved more when this condition was web-based.

Thirty-five participants were queried regarding their administration preference: 19 completed web-administration first and 16 completed iPad administration first. Condition preference did not significantly differ by administration order, $\chi^2 = 5.03$, $p = .08$, $\varphi = .38$. Of those completing the web-based administration first, 47.4% (9/19) preferred web administration, 42.1%

Table 1. Demographic characteristics by condition order (Web first/iPad first)

Characteristic	Web First ($n = 24$) *M* (*SD*) or *n* (%)	iPad First ($n = 25$) *M* (*SD*) or *n* (%)	t/χ^2	*p*
Age	41.63 (9.02)	39.04 (9.24)	0.99	.327
Education (years)	14.63 (1.91)	14.16 (1.60)	0.92	.359
Race/Ethnicity			0.64	.571
Black	8	11		
Hispanic	1	2		
White/Asian	15	12		

Note: Race/ethnicity follows NIH Toolbox normative categorization.

Table 2. Wilcoxon Signed-Rank Comparisons and Correlation Coefficients of Administration Modality Scores

Score	PC/Web			iPad						*z*		
	Mean (*SD*)	Median	Range	Mean (*SD*)	Median	Range	*W*	*p*	*r*	*CCC*	ρ	χ_a
DCCS Computed	8.24 (0.74)	8.22	6.50–9.74	8.33 (1.07)	8.21	4.88–10.00	529	.409	0.08	.59	.63	.93
DCCS Standardized	100 (14)	98	72–136	103 (21)	104	67–146	495	.247	0.12	.51	.56	.91
DCCS T	50 (9)	50	30–70	52 (14)	52	27–79	472	.165	0.14	.46	.51	.90
FICAT Computed	8.58 (1.14)	8.86	3.75–9.91	8.16 (0.99)	8.37	4.75–9.67	974	<.001	0.36	.46	.50	.92
FICAT Standardized	100 (19)	103	41–134	90 (16)	89	57–121	996	<.001	0.39	.47	.56	.85
FICAT T	51 (11)	52	21–69	44 (10)	45	22–62	990	<.001	0.38	.46	.55	.83
LSWM Raw	19 (3)	19	12–26	18 (3)	18	12–26	642	.041*	0.21	.42	.45	.94
LSWM Standardized	107 (15)	108	73–138	101 (16)	98	73–138	824	.036*	0.21	.41	.44	.94
LSWM T	55 (9)	55	33–73	52 (10)	49	33–74	832	.028*	0.22	.40	.43	.93
PCPS Raw/Computed**	58 (14)	57	32–85	60 (13)	61	21–87	503	.386	0.09	.23	.24	.99
PCPS Standardized	100 (23)	97	62–158	103 (21)	106	40–143	520	.360	0.09	.23	.23	.99
PCPS T	50 (14)	51	24–80	53 (12)	54	20–72	506	.295	0.11	.21	.21	.97

Note: CCC = Concordance Correlation Coefficient, DCCS = Dimensional Change Card Sort Test, FICAT = Flanker Inhibitory Control and Attention Test, LSWM = List Sorting Working Memory Test, PCPS = Pattern Comparison Processing Speed Test, ρ = Pearson's correlation coefficient (precision), χ_a accuracy coefficient. Casaletto and colleagues (2015) adjustment is recommended only for web scores, thus standardized iPad scores were consistent across most comparisons. All non-computed scores are rounded to the nearest whole number post-analysis as per interpretive guidelines.

*Not significant after controlling false discovery rate.

**Current developer guidance indicates that for PCPS the web raw score should be compared to the iPad computed score, in contrast to other tests.

(8/19) preferred iPad administration, and 10.5% (2/19) reported no administration preference. Among those who completed the iPad condition first, 12.5% (2/16) preferred web administration, 75.0% (12/16) preferred iPad administration, and 12.5% (2/16) reported no administration preference. Across orders, 31.4% (11/35) of participants preferred web administration, 57.1% (20/35) preferred iPad administration, and 11.4% (4/35) denied any preference.

Discussion

The present study examined the comparability of iPad-administered NIHTB-CB test scores with the PC web-administered version of the tests in a sample of Iraq and Afghanistan combat veterans. Utilized scores were updated and calculated according to final developer recommendations released in March 2017, meant to ensure comparability between test modalities. The current study did not support the adequacy of these adjustments for any Flanker scores, where mean norm-referenced iPad scores fell nearly one standard deviation below those acquired using the web-administered version. Differences between web and iPad scores were not found across the Card Sort, List Sorting, or Pattern Comparison (although differences on List Sorting were significant prior to correction for multiple comparisons). Concordance correlations between modalities were low to moderate. Low correlation was found for Pattern Comparison, along with a moderate carryover effect for this test in our sample. Observed large practice effects on List Sorting and Pattern Comparison suggested a need for caution when re-administering either of these tests after a short delay. An unpublished investigation by test developers did not indicate discrepancies between the iPad and web versions of the Flanker, as observed in the current study. This may be due to differences between within-subjects and cross-sectional comparisons. The present analysis utilized a within-subjects crossover approach, whereas the test developers compared between-subjects using demographically similar groups (personal communication, April 7, 2016).

Patterns in findings hinted that specific test characteristics may be explanatory. In addition to the significant web-score advantage on the Flanker, the identification of a crossover effect on Pattern Comparison suggested a similar web-advantage when this test was administered after the iPad version (although overall median scores on Pattern Comparison were comparable). This is notable because both the Flanker and Pattern Comparison rely on accurate perception of small visual details to a greater extent than the other two included tests. It could be that stimuli are less clearly perceived on the smaller iPad screen compared to a PC. This hypothesis is consistent with the lack of identified differences on the Card Sort, given that it is arguably the non-verbal test least likely to be affected by display differences because the test relies on differentiating between only two distinct colors and shapes. The relative comparability of scores on the Card Sort also suggests that differences in outcomes cannot be fully attributed to use of the *home base* unique to the iPad administration which is also required for the Flanker. Finally, it seems reasonable that practice effects would be found for List Sorting and Pattern Comparison, both of which present a series of colorful and visually distinct stimuli that arguably would be most vulnerable to recognition benefit

during the second administration of the test, where the presented stimuli remain consistent. Of course, these hypotheses would need to be verified by future work.

Limitations of this study include sample size, the use of data collected within the context of a larger study (limiting the number of NIHTB-CB tests administered), and lack of control over demographic characteristics. All participants were combat veterans indicating a need for caution when generalizing study results to other populations. It is possible that intervening study activities may have differentially affected participants across conditions; although, it should be noted that the NIH Toolbox normative sample completed a 47-instrument battery (Gershon et al., 2013). Strengths of this study include a crossed and randomized design to account for practice and order effects, and the use of standalone performance validity measures to account for invalid responding. This is the first research study to examine the comparability between web-based and iPad administrations of NIHTB-CB tests. Results indicate a clear need for replication, particularly in non-veteran and non-adult samples. Future studies should also investigate additional NIHTB-CB tests not included here.

The continued incorporation of modern, efficient, and accessible measures into the collection of neurocognitive data is important for the evolution of neuropsychology, and the development of an iPad version of the NIHTB-CB was an important step towards this end (Miller & Barr, 2017). Although unique challenges such as frequent technology and software updates create inherent difficulties, the advantages of reduced administrative burden and apparent participant preference indicate the importance of continued development and implementation of the iPad version of the test. However, the NIHTB-CB should not be exempt from the iterative development and validation required of well-established measures. Further work is indicated, and current normative issues suggest a need for caution when interpreting the results of the iPad NIHTB-CB Flanker test, particularly when combining with previously collected web data. These results suggest the potential value of developing iPad-specific normative data for the NIHTB-CB, just as it was gathered for the PC.

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Any opinions, findings, conclusions or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the views of the U.S. Government the Department of Defense, or the U.S. Department of Veterans Affairs, and no official endorsement should be inferred.

Conflict of Interest

None declared.

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Appendix 34

Association of Diagnosed Depression With Inpatient, Outpatient and Pharmacy VA Costs in Veterans Diagnosed with Traumatic Brain Injury

Association of Diagnosed Depression With Inpatient, Outpatient and Pharmacy VA Costs in Veterans Diagnosed with Traumatic Brain Injury

Dismuke-Greer CE, Gebregziabher M, Hunt K, Taber D, Axon N, Egede LE.

BACKGROUND: In an Institute of Medicine (IOM) report, the IOM reviewed existing literature and concluded that there is sufficient evidence of an association between Traumatic Brain Injury (TBI) and depression. Based on this finding, the VA established depression as a secondary service connection condition if manifest within 3 years of the incurrence of moderate or severe TBI and within 12 months of mild TBI. The IOM study reviewed four primary and five secondary studies of major depression following TBI and showed a higher rate of major depression 6 months or more after TBI, when compared to appropriate comparison groups. Currently the association of depression with health care costs of Veterans diagnosed with TBI, while using Veterans Health Administration (VHA) facilities is unknown. We examine the association of a diagnosis of depression with total, inpatient, outpatient and pharmaceutical costs in VHA from 2000-2014 for all Veterans and a subset of Operation Enduring Freedom (OEF)/Operation Iraqi Freedom (OIF) Veterans diagnosed with TBI between 2000 and 2010.

METHODS: We examined differences in Veteran demographics, TBI severity, and other comorbidities by depression status using chi-square for categorical variables and t-tests for continuous variables. We examined unadjusted differences in VA total, inpatient, outpatient, and pharmacy costs by depression status using student t tests. We estimated adjusted total, inpatient, outpatient, and pharmacy VHA costs associated with depression among Veterans diagnosed with TBI for all Veterans and a subset of OEF/OIF Veterans, using generalized linear models and seemingly unrelated regression models. We used box plots to examine visually the association of a depression diagnosis with total, inpatient, outpatient, and pharmaceutical VHA costs for all Veterans diagnosed with TBI and a subset of OEF/OIF Veterans diagnosed with TBI. We used the Consumer Price Index (CPI) to adjust all VHA costs to 2017 values.

RESULTS: Of 113,339 all era Veterans diagnosed with TBI between 2000 and 2010, 72.91% were found to have a diagnosis of depression. Of 34,391 OEF/OIF Veterans diagnosed with TBI between 2000 and 2010, a higher percentage, 87.46% were found to have a diagnosis of depression. For all era Veterans, those diagnosed with depression had significantly higher ($p<0.05$) unadjusted mean total VHA costs per year ($13,911) relative to Veterans without a depression diagnosis ($9,990). For the subset of OEF/OIF Veterans diagnosed with TBI between 2000 and 2010, those diagnosed with depression also had significantly higher unadjusted total VHA costs per year ($8,550) relative to OEF/OIF Veterans without a depression diagnosis ($4,659). After adjustment for demographic, TBI severity, survival and comorbidities, depression was significantly associated with an additional $1,771 in total costs, $1,590 in outpatient costs, and $273 in pharmaceutical costs per year for all era Veterans and $1,196 in total costs, $1,667 in outpatient costs and $192 in pharmacy costs in OEF/OIF Veterans, relative to Veterans without a depression diagnosis. Interestingly, for OEF/OIF Veterans, depression was significantly associated with lower inpatient ($663) costs while depression was not significantly associated with inpatient costs for all era Veterans. Based on the numbers of Veterans affected and predicted VHA costs per year per Veteran, we estimated that the VHA financial burden associated with depression has been approximately $1,101,412,592 per year for all era Veterans and $247,016,960 for OEF/OIF Veterans.

CONCLUSIONS: Depression has been established as a secondary service connection condition in Veterans diagnosed with TBI. We estimated the VHA financial burden in all era

Veterans diagnosed with TBI and depression to exceed $1 billion per year. The VHA has evidence based treatment for depression so future research needs to be conducted to examine VHA cost differences in Veterans diagnosed with TBI and depression based on receiving mental health treatment for depression.

Appendix 35

NINR: Precision Health: Smart Technologies, Smart Health: Accessing and using VINCI data from the VA

NINR: Precision Health: Smart Technologies, Smart Health: Accessing and using VINCI data from the VA

Clara E. Dismuke-Greer, PhD

Charleston Health Equity and Rural Outreach Innovation Center, Ralph H. Johnson VA Medical Center, U.S. Department of Veterans Affairs

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- VINCI Databases
- What questions can be answered using VINCI – Large Database Studies or Clinical Studies
- VINCI's Clinical Trial Recruitment Services
- What Veteran health questions are most important to NINR researchers?
- How to Start? Without Compensation (WOC) status for non VA employees
- The DART (regulatory process) for requesting VINCI Data
- VINCI's analysis tools
- Real-world application using a study on the VA costs associated with depression in Veterans diagnosed with Traumatic Brain Injury
- VINCI Leadership and VA Nursing Research Contacts

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About VINCI

The VA Informatics and Computing Infrastructure (VINCI) is a Health Services Research & Development (HSR&D) Resource Center that provides researchers a nation-wide view of high value VA patient data. VINCI is a research and development partnership and operational platform for health services research, epidemiology, decision support, and business intelligence. Partners are VHA's HSR&D program, VHA's Office of Informatics and Analysis, and OI&T's Business Intelligence Service Line. All participating groups desire that their contributions be managed as an integrated organization, the impact of which will be much greater than the sum of its parts.

While VINCI brings together data sources and provides the analytical environment for performing studies, data stewards such as VHA National Data Systems (NDS), VA Information Resource Center (VIReC), and others authorize research access to patient data. New research projects are granted access to dynamic views or snapshots of data that can be updated as needed. In addition to data storage, VINCI includes a cluster of servers set aside for tasks like analysis, data processing, and extracting information from text. This means that VA researchers will have access to data and the applications they need to select, transform, and analyze patient data in a central, secure location accessible from the VA intranet.

Joint IT, Research, and Medical-Care Mission, Vision, and Value
VINCI's mission is to provide high-quality data, openly extensible information technology, and supporting services to generate and integrate new knowledge, methods, and technologies for research and medical-care communities to assess and improve Veterans' healthcare. VINCI's 5-year vision is to be part of a vital private-public community in which open-source and open-standards technologies provide a foundation for generation of new content and technologies to promote transparent and reproducible health science and business intelligence.

VINCI Research Program's Mission, Vision, and Value
VINCI Research Program's mantra is innovation and translation for dual research and medical-care benefit. HSR&D recognizes that for a sustainable, relevant, and vibrant program, the Program must serve a dual mission that supports health services research and innovative business intelligence. The following statements of mission, vision, and value are from the perspective of research. For a broader perspective, researchers could be interchanged with business-intelligence innovators and practitioners. VINCI Research Program's mission is to provide services to help researchers appropriately access data and use tools, to conduct research addressing key gaps in VINCI's offerings, and to manage the interface with IT partners for translating research innovations into deployed tools for general use. VINCI Research Program's 5-year vision is an enticing, cooperative scientific infrastructure that provides a majority of HSR&D-funded projects with transparent methods and reusable tools resulting in reproducible results.

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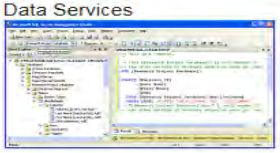

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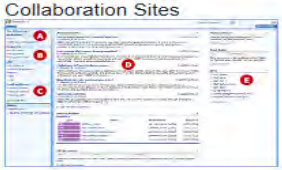

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Computing Cloud

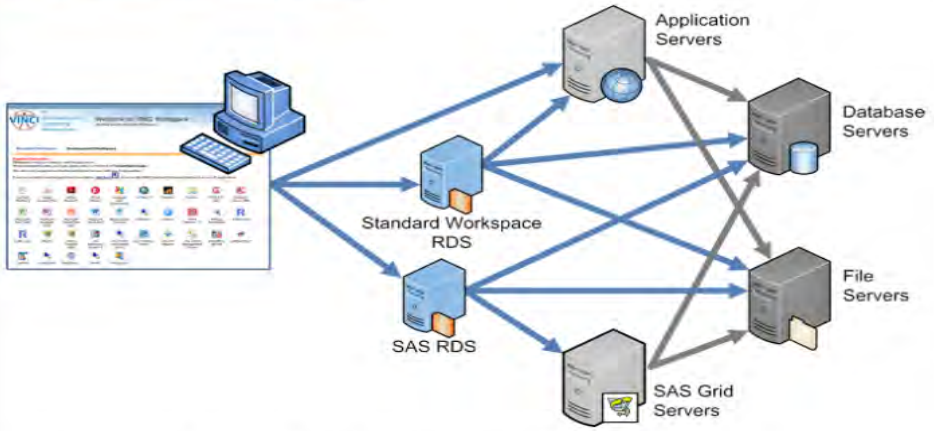
The VINCI Computing Cloud consists of extensive storage area networks, drives, file shares, databases, SharePoint farm for collaboration and correspondence sites, SAS/Grid, and racks upon racks of servers containing virtual machines with an extensive collection of software called the VINCI Workspace.

VINCI Standard Workspace

The VINCI Standard Workspace is a secure, virtual computing environment.

The VINCI Standard Workspace is a secure, virtual computing environment. The robust system is designed to carefully balance the data access needs of researchers with the Veteran Administration's requirement to maintain security and privacy of the data while providing the resources and tools necessary to conduct studies and analyze data. So whether you are starting a new study, have an existing study, or just need a place to analyze data, VINCI has the workspace for you. If you intend to use the VINCI Workspace, be sure to specify it in your study's IRB.

Click here to request a VINCI Standard Workspace



- Windows Server 2012 Enterprise R2 x64 SP2 Operating System
- 4 Logical Processors (shared)
- 16GB RAM (shared, can request more)
- 10GB H-drive Personal Network Storage
- 100GB P-drive Shared Project Folder Network Storage (can request more)
- Limited Internet access (where justified)
- No Administrative Permissions
- See a list of pre-loaded software

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- Launch Workspace
- VINCI Workspace User Guide
- VINCI Database User Guide
- VINCI File Transfer Guide
- All SAS Grid Guides

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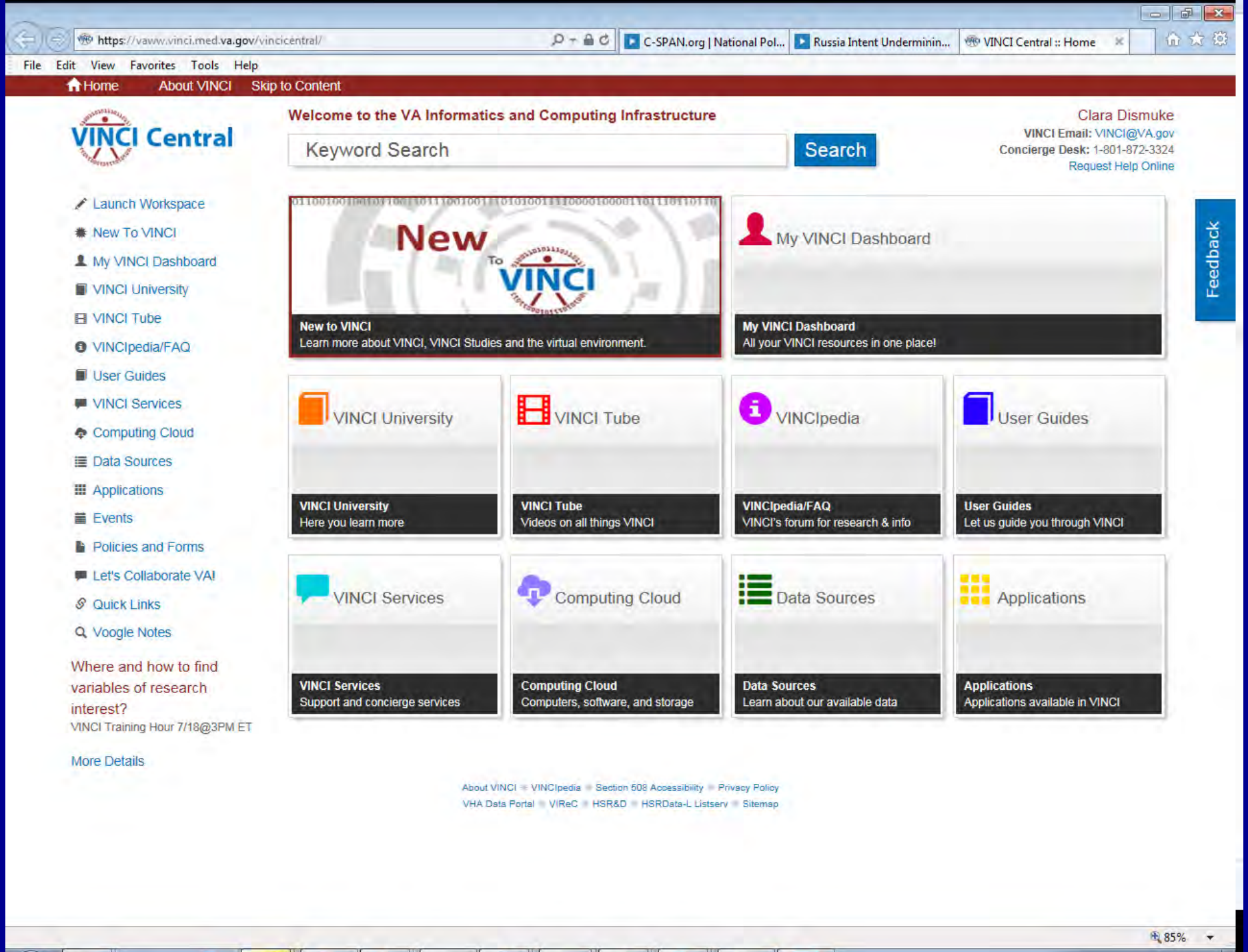
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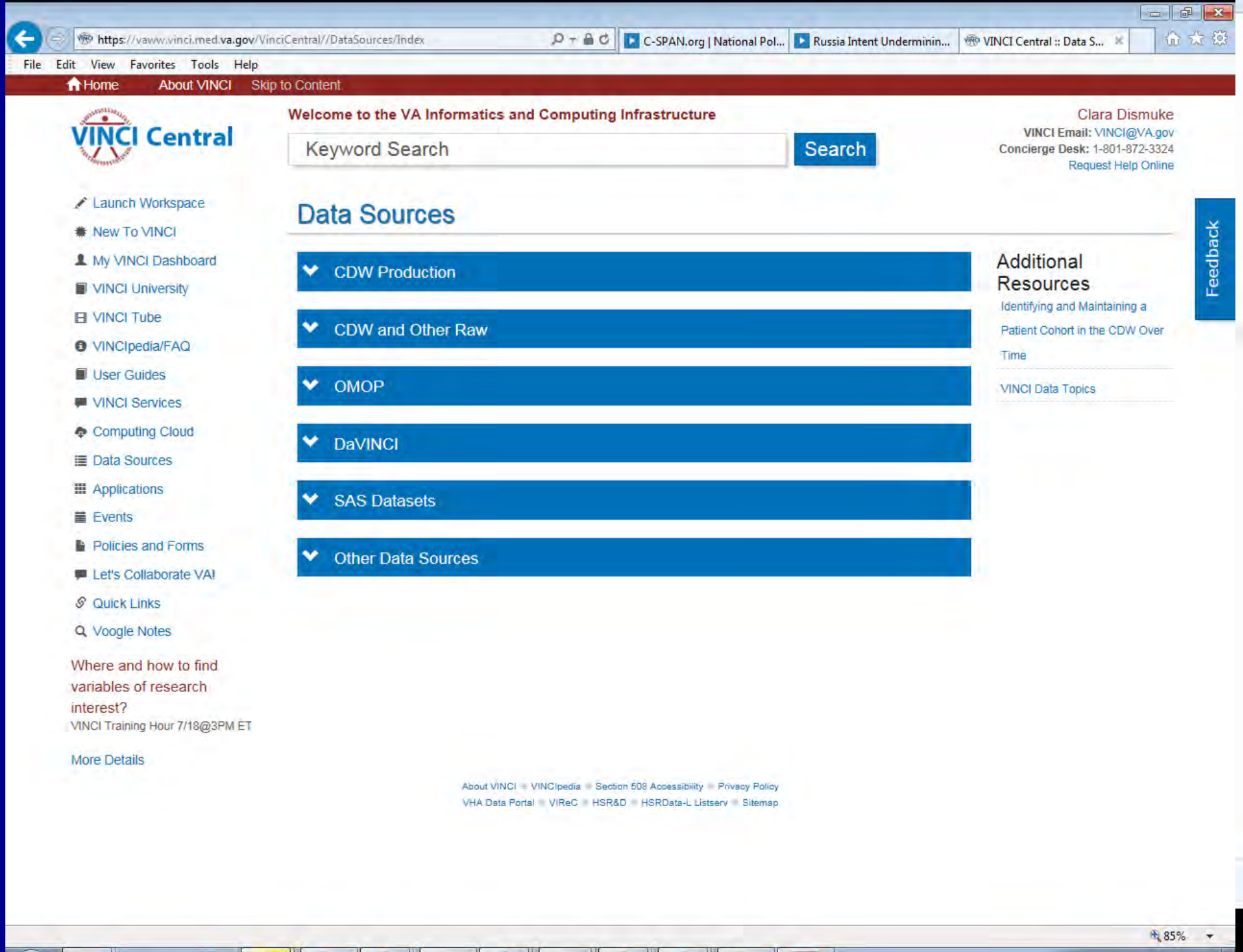
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CDW Production

The Veterans Administration's Corporate Data Warehouse (CDW) is a national repository comprising data from several Veterans Health Administration (VHA) clinical and administrative systems. The objective of CDW is to provide data and tools to support management decision making, performance measurement and research objectives. Its premise is that incorporating data from multiple differing data sets throughout the VHA into one standard database structure will facilitate reporting and data analysis at the enterprise level. The CDW operates within the VA Office of Information & Technology Field Operations Business Intelligence Service Line.

CDW data are stored in a relational database. Multiple VA data sources are being merged so that cohorts will be definable by attributes such as ICD-9, ICD-10, and CPT codes from both inpatient and outpatient encounters or from abnormal values of vital signs like blood pressure, weight and height, within a target time period. Data are kept current by refreshing on a nightly basis and is available beginning October 1, 1999. CDW is considered to be the best model data.

See CDW MetaData Reports Page on the CDW site.
See VIReC's CDW Documentation.

Available CDW Production data domains in VINCI

- Allergy
- Appointment
- Consult
- CPRS Orders
- Dental
- Emergency Department Integration Software (EDIS)
- Health Factors
- Immunization
- Inpatient
- Integrated Billing
- Lab Chemistry
- Lab Microbiology
- Mental Health Assessment
- Non-VA Meds
- Outpatient
- Outpatient Workload
- Patient
- Patient Associated
- Patient Enrollment
- Patient Insurance
- Primary Care Management Model (PCMM)
- Pharmacy Bar Code Medication Management (BCMA)
- Pharmacy Outpatient
- Pharmacy Patient
- Purchased Care (Formerly Fee)
- Pyramid GIS
- Radiology
- Recall Reminders
- Reengineered Primary Care Management Module (RPCMM)
- SPatient
- Staff
- SStaff
- Surgery INTRA Table
- Surgery PRE Table
- Surgery POST Table
- Text Document Titles
- Travel
- VistA Compensation & Pension
- VistA Waitlist
- Vital Signs

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CDW Production

CDW and Other Raw

The purpose of VINCI's CDW Raw is to hold domains that have not been obtained through the normal CDW process. The Raw extractor allows us to obtain data quickly and to make changes as subject area experts refine their requirements. Certain domains will be promoted to CDW Production and others will not. Raw data domains have limited documentation, entail additional provisioning time, and are more difficult for studies to utilize.

The Raw extraction data are not as refined as the CDW Production data set. They are extracted directly from the VistA sites through a process as data snapshots, rather than continuously as does CDW. The Raw extractions are therefore not kept current. Extractions may be repeated as needed.

See CDW-Raw Domains Page on CDW site.
See VIReC's CDW Documentation.

Available CDW and Other Raw data domains in VINCI

- Decision Support System (DSS)
- Echocardiogram
- Equipment Inventory
- Fee Basis Claim System (FBCS)
- Health Economics Resource Center (HERC)
- Intravenous Meds (IV)
- MedSAS
- Oncology
- Prosthetics
- PSSG Geocoded Files
- Pulmonary Function Test (PFT)
- RxUD (Unit Dose)
- Travel
- Veterans Choice Program Eligibility (VACAA)
- Veterans Services Network Corporate Mini Master File (VETSNET)
- Vital Status

Raw Data Refresh Schedule

Raw domains are refreshed on 3rd Friday at 7:00 PM CST of every month based on the below schedule. The Raw domains that are being refreshed may not be available during the weekend.

Showing 1 to 10 of 17 entries Filter:

Domains	Frequency	Refresh Months	Additional Information	Last Updated
DSS	Monthly	Every Month	DSS	2018-06-15
Echocardiogram	Quarterly	March, June, September, December	Echocardiogram	2018-06-16

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OMOP

For this link to work, you must have a VA Pulse account that you are signed into with "Keep me logged in" checked.
See the VINCI OMOP Users Group Page on VA Pulse.

Researchers understand no single observational data source provides a comprehensive view of the clinical data a patient accumulates while receiving healthcare and it takes multiple sources to sufficiently meet all expected outcome analysis needs. This explains the need for accessing and analyzing multiple data sources concurrently using a common data standard. This standard is provided by the OMOP Common Data Model (CDM). While OMOP may not meet all the needs of all VINCI users, we anticipate that the majority of all projects performed in VINCI may be able to meet their needs exclusively using OMOP data and that every project will at least be able to take advantage of the data mappings and standardization created as a result of the OMOP work.

VINCI OMOP is designed to support the conduct of research to identify and evaluate associations between interventions (drug exposure, procedures, healthcare policy changes etc.) and outcomes caused by these interventions (condition occurrences, procedures, drug exposure etc.). Outcomes can be efficacious (benefit) or adverse (safety risk). Often times, specific patient cohorts (e.g., those taking a certain drug or suffering from a certain disease) may be defined for treatments or outcomes, using clinical events (diagnoses, observations, procedures, etc.) that occur in predefined temporal relationships to each other. The CDM, combined with its standardized content via the Standardized Vocabularies, will ensure that research methods can be systematically applied to produce meaningfully comparable and reproducible results. In addition, there is a growing desire for investigators to share analytic code and run it within different environments, and a need to reduce the level of deep and idiosyncratic understanding of the source data required to conduct an analysis on healthcare data. Common data models for health care data have been developed in order to address some of these needs.

The OMOP CDM defines table structures for each of the data domains in a Person and Provider-centric model. Almost all tables have foreign keys to the Person table and a date. This allows for a longitudinal view on all the healthcare-relevant events. In addition, Providers carrying out health care are linked to many of the events as well. Both are linked to healthcare organizations (hospitals, independent physician associations), care sites (doctor's offices, hospital departments etc.) and physical locations (addresses, station). The CDM aims to provide data organized in a way optimal for analysis rather than for the purpose of operational needs of health care providers or payers. The domains are modeled in a person-centric relational data model where for each record, the identity of the person and a date is captured as a minimum.

To standardize the content of those records, the CDM relies on Standardized Vocabularies containing all necessary and appropriate corresponding standard healthcare concepts. If possible, these concepts are leveraged from national or industry standardization or vocabulary definition organizations or initiatives, such as the National Library of Medicine, the Department of Veterans' Affairs, the Center of Disease Control and Prevention, etc.
VINCI OMOP is technology neutral. It can be realized in any relational database, such as Oracle, MySQL etc., or as SAS analytical datasets. The CDM is optimized for data processing and computational analysis to accommodate data sources that vary in size, including databases with up to hundreds of millions of persons and billions of clinical observations. All changes from previous CDMs are clearly delineated. Older versions of the CDM can be easily created from this CDMv5, and no information is lost that was present previously.

Available Data Domains in OMOP:

- CDW Appointment (Status)
- CDW Dental (Tobacco Use Only)
- CDW Dim (Abused Substance, Clinical Procedure, CPT, Device, Facility Type, Institution, Location LOINC, MajorConceptMap, SNOMED, etc.)
- CDW Fee Basis/Purchased Care- Outside of VA Care (Pending)
- CDW ICD 9CM and ICD 10CM

Time
VINCI Data Topics
Feedback

https://vaww.vinci.med.va.gov/VinciCentral//DataSources/Index

VINCI Central :: Data Sources

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Home About VINCI Skip to Content

VINCI Central

Welcome to the VA Informatics and Computing Infrastructure

Keyword Search Search

Clara Dismuke
VINCI Email: VINCI@VA.gov
Concierge Desk: 1-801-872-3324
Request Help Online

- Launch Workspace
- New To VINCI
- My VINCI Dashboard
- VINCI University
- VINCI Tube
- VINCIpedia/FAQ
- User Guides
- VINCI Services
- Computing Cloud
- Data Sources
- Applications
- Events
- Policies and Forms
- Let's Collaborate VA!
- Quick Links
- Voogle Notes

Where and how to find variables of research interest?
VINCI Training Hour 7/18@3PM ET

More Details

Data Sources

CDW Production

CDW and Other Raw

OMOP

DaVINCI

The Military Health System Data Repository (MDR) is the most comprehensive source of data available for researchers and is the source of data being sent to the VA through DAVINCI. This source contains records on all health care events (that are required to be reported) paid for by the MHS, regardless of setting. This system also contains robust historical beneficiary data, including coverage information, service-related information and demographics. The MDR incorporates important clinical data such as vital signs, Body Mass Index, tobacco usage, radiology results, and chemistry, microbiology, and pathology lab results. Most of the clinical data is only available for Fiscal Year (FY) 2009 and forward, while most other administrative data sources go back many more years, some as far as FY 1989. For records from FY 2000+, the MDR contains a unique person identifier allowing person-level files to be linked across data sources. MDR files are useful for cohort definition, in that all event and beneficiary data are available in one system. The MDR is generally considered the most reliable source for MHS data.

DaVINCI Data Dictionary
DoD Dataset Descriptions

SAS Datasets

Other Data Sources

Additional Resources

Identifying and Maintaining a Patient Cohort in the CDW Over Time

VINCI Data Topics

Feedback

85%

VINCIpedia/FAQ
User Guides
VINCI Services
Computing Cloud
Data Sources
Applications
Events
Policies and Forms
Let's Collaborate VA!
Quick Links
Voogle Notes

Where and how to find variables of research interest?
VINCI Training Hour 7/18@3PM ET

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DaVINCI Data Dictionary
DoD Dataset Descriptions

SAS Datasets

The SAS data sets are national administrative data for VHA-provided health care utilized primarily by veterans, but also by some non-veterans (e.g., employees, research participants). The data sets are provided in SQL format by fiscal year (Oct. 1 - Sept. 30). These data are extracted from the National Patient Care Database (NPCD) maintained by the VHA Office of Information at the Austin Information Technology Center (AITC), the central repository for VA data. Having historically been monitored by AITC mainframe, VINCI has acquired a complete copy of those data sets.

In all of the SAS data sets, each patient has a unique identifier referred to as the Scrambled SSN, which is a formula-based encryption of the Social Security Number. The identifier is consistent for a given patient across data sets and fiscal years.

Please note that VINCI consolidated the pre-2005 DSS data from the mainframe SAS files that were available at Austin (AITC). Since VINCI is not the data owner, no attempt was made by VINCI to modify, enhance, or change the data other than consolidating the original individual SAS files and making the data available as SQL Server tables. DSS is now known as MCA. Please visit the VIReC site to find more information on MCA data.

See VIReC's site on MCA NDE data.
See VIReC's site on MedSAS data.

Other Data Sources

Patient Cohort in the CDW Over Time
VINCI Data Topics

Please note that VINCI consolidated the pre-2005 DSS data from the mainframe SAS files that were available at Austin (AITC). Since VINCI is not the data owner, no attempt was made by VINCI to modify, enhance, or change the data other than consolidating the original individual SAS files and making the data available as SQL Server tables. DSS is now known as MCA. Please visit the VIReC site to find more information on MCA data.

See VIReC's site on MCA NDE data.
See VIReC's site on MedSAS data.

Other Data Sources

VINCI has several other data sets available.

Care Assessment Need (CAN) Score - The Care Assessment Need (CAN) score reflects the estimated probability of hospital admission or death within a specified time frame (90 days (or 1 year). The score is expressed as a percentile, ranging from 0 (lowest risk) to 99 (highest risk) and indicates how a given patient compares with other VA patients in terms of likelihood of hospitalization or death. Patients with a very high score (e.g., 99) are have a risk of admission or death that approaches 72% at one year while for those with a low score (e.g., 5) that risk is only about 3%. The CAN score is generated using sophisticated statistical prediction models that utilize demographic data (e.g., age, gender) and clinical information (e.g., medical conditions, use of VA health care, vital signs, medications and laboratory tests) from VHA administrative data. In addition to the CAN score, the report displays the actual probability of an event associated with that CAN Score. The report also displays a count of the patient's diagnoses, care management resources already in use, and utilization, including the date of the last primary care visit. It is critical to recognize that the CAN scores represent probabilities and although these scores are very accurate for large groups of patients, they may be inaccurate for an individual patient. In the highest risk group, those with a CAN score of 99, more than a quarter of patients would NOT be expected to die or be hospitalized while even some of those in very low risk groups will experience one of these events. The goal is to identify groups of patients at high risk for whom care coordination may be valuable.

Typical Use of Data would be dependent upon the nature of the user: Studies have shown that it is difficult for providers to accurately predict which patients are at highest risk of becoming sicker or dying. The CAN Score Report is intended to help identify the sickest patients in a primary care panel so attention and resources can be focused accordingly. The CAN score is not a performance measure to try to "improve" like hemoglobin A1c for a patient with diabetes. A high score does not mean that a patient is receiving less than the highest quality care, nor does a low score (like 5 or 10) mean that you can ignore a patient. A score does not indicate a specific clinical action and needs to be considered in concert with all other available clinical information. A care manager, for example, might scan this report to identify their highest risk patients. The care manager can review care management resources already in use and identify other available local resources, such as telehealth or specialty care, that might be indicated clinically to ensure that high risk patients are receiving all the information they need.
See Care Needs Assessment (CAN) Score Report Data Definitions.

Health Economics Resource Center (HERC) Average Cost, V21, and Nosos Risk Scores Data. See the VHA Data Portal for description.

Patient Aligned Care Team (PACT) Implementation Index (Pi2). See the VHA Data Portal for description.

Vital Status File. See VIReC's page on Vital Status File for description. See VIReC's page on Vital Status File for description.

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What kind of questions can be answered by VINCI?

Epidemiology and Economic Large Database Cohort Studies using ICD codes, Procedure Codes, CPT codes, Clinic Stop Codes, Laboratory Values, etc. as the basis for formation

Clinical Studies – providing VINCI with a cohort of Veterans being followed in a Clinical Study.

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- Source: Jeff Scehnet, PHD, MSRegSci, CIPP/G, VINCI Services Manager

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- Source: Jeff Scehnet, PHD, MSRegSci, CIPP/G, VINCI Services Manager

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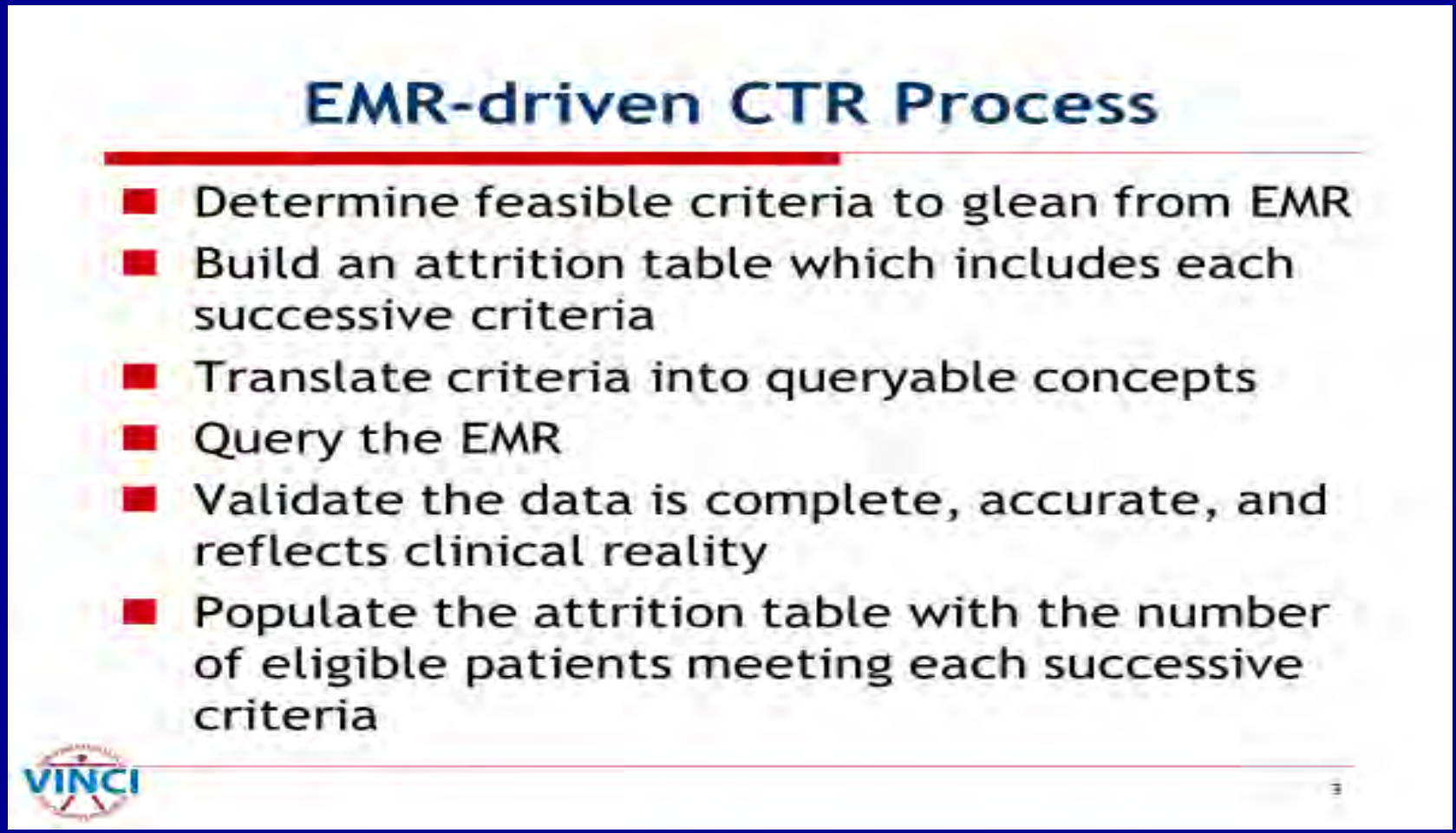

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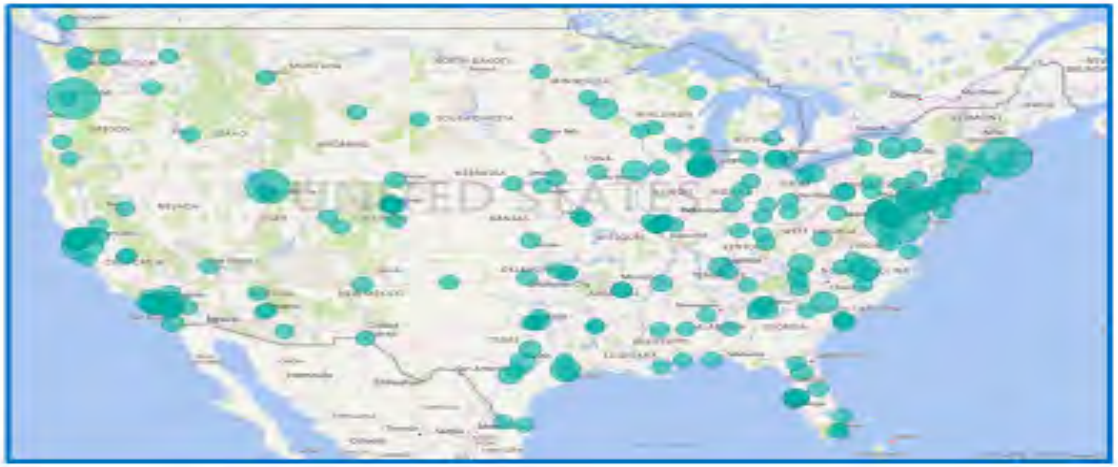
- Source: Jeff Scehnet, PHD, MSRegSci, CIPP/G, VINCI Services Manager

CTR Deliverables

- Before…
  - Feasibility counts in order to justify project development and site selection



VINCI

- Source: Jeff Scehnet, PHD, MSRegSci, CIPP/G, VINCI Services Manager

CTR Deliverables

- During…
  - list of potentially eligible Veterans with upcoming appointments who meet the study inclusion and exclusion criteria
  - list of Veterans and their contact information who meet the study inclusion and exclusion criteria

- Source: Jeff Scehnet, PHD, MSRegSci, CIPP/G, VINCI Services Manager

CTR Deliverables

- After…
  - any additional associated Veteran's data that meets the study inclusion and exclusion criteria approved by an IRB/R&D Committee and appropriate data steward

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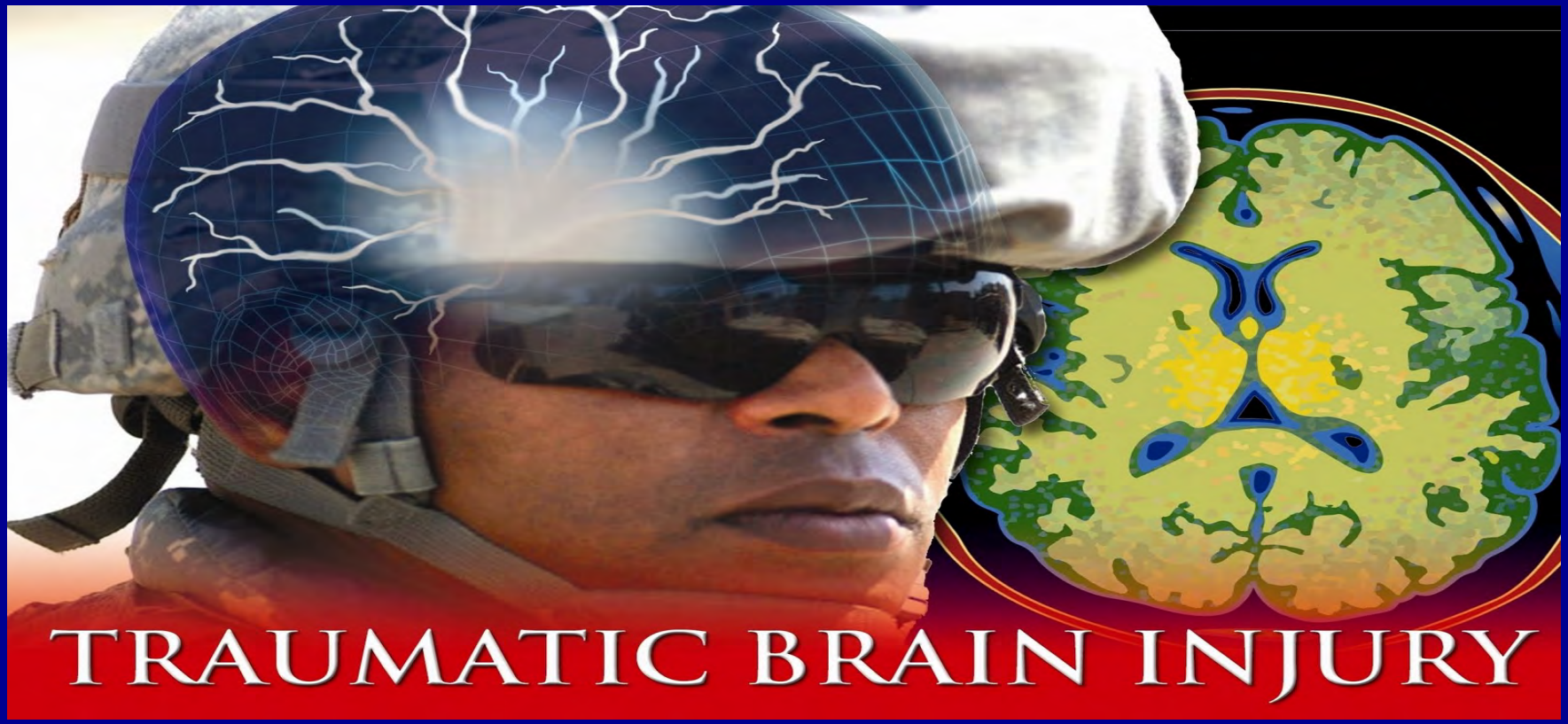
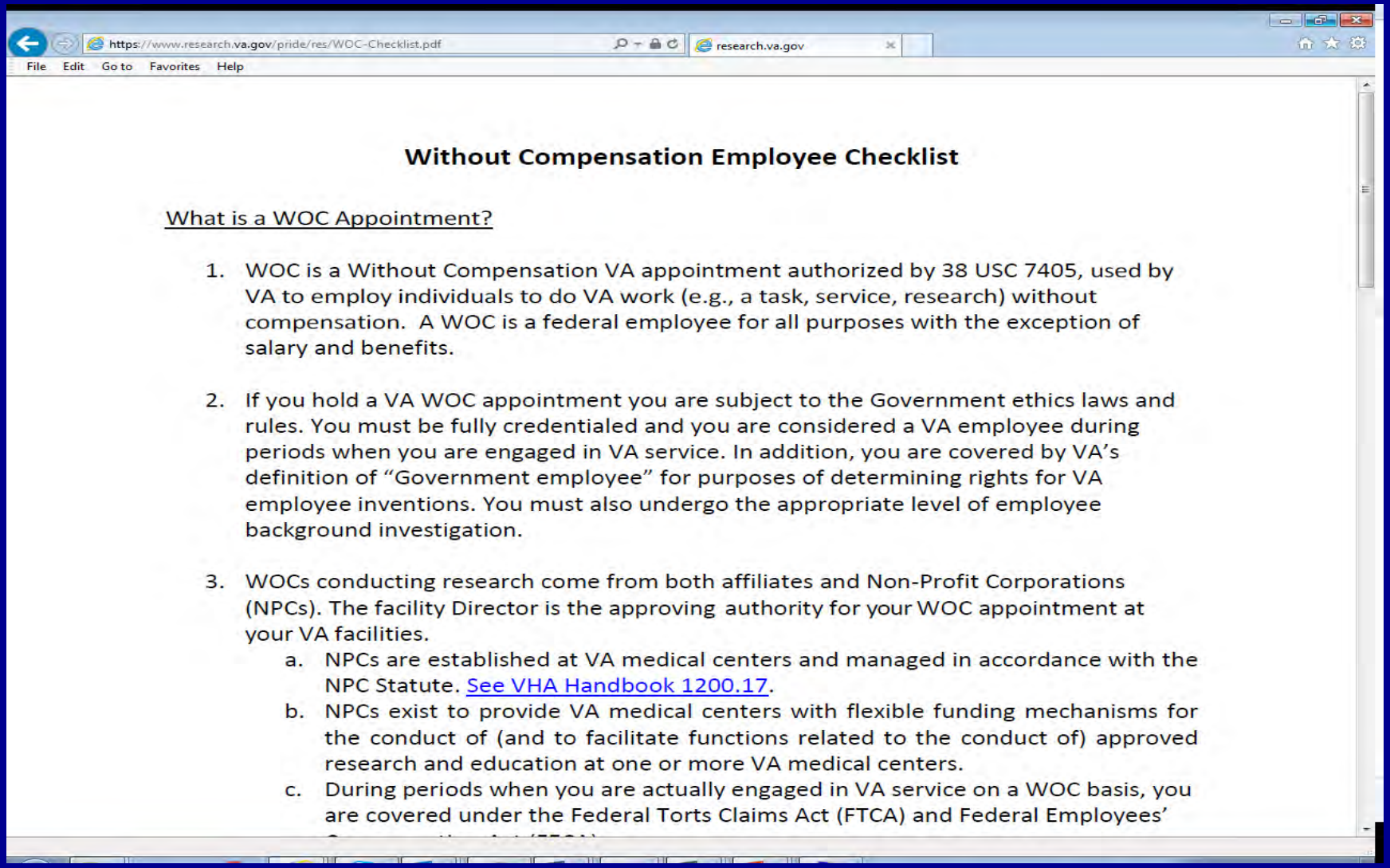
What Questions Regarding Veteran Health Are Of Interest to NINR Researchers? This is Mine:





https://www.research.va.gov/pride/res/WOC-Checklist.pdf

research.va.gov

File Edit Go to Favorites Help

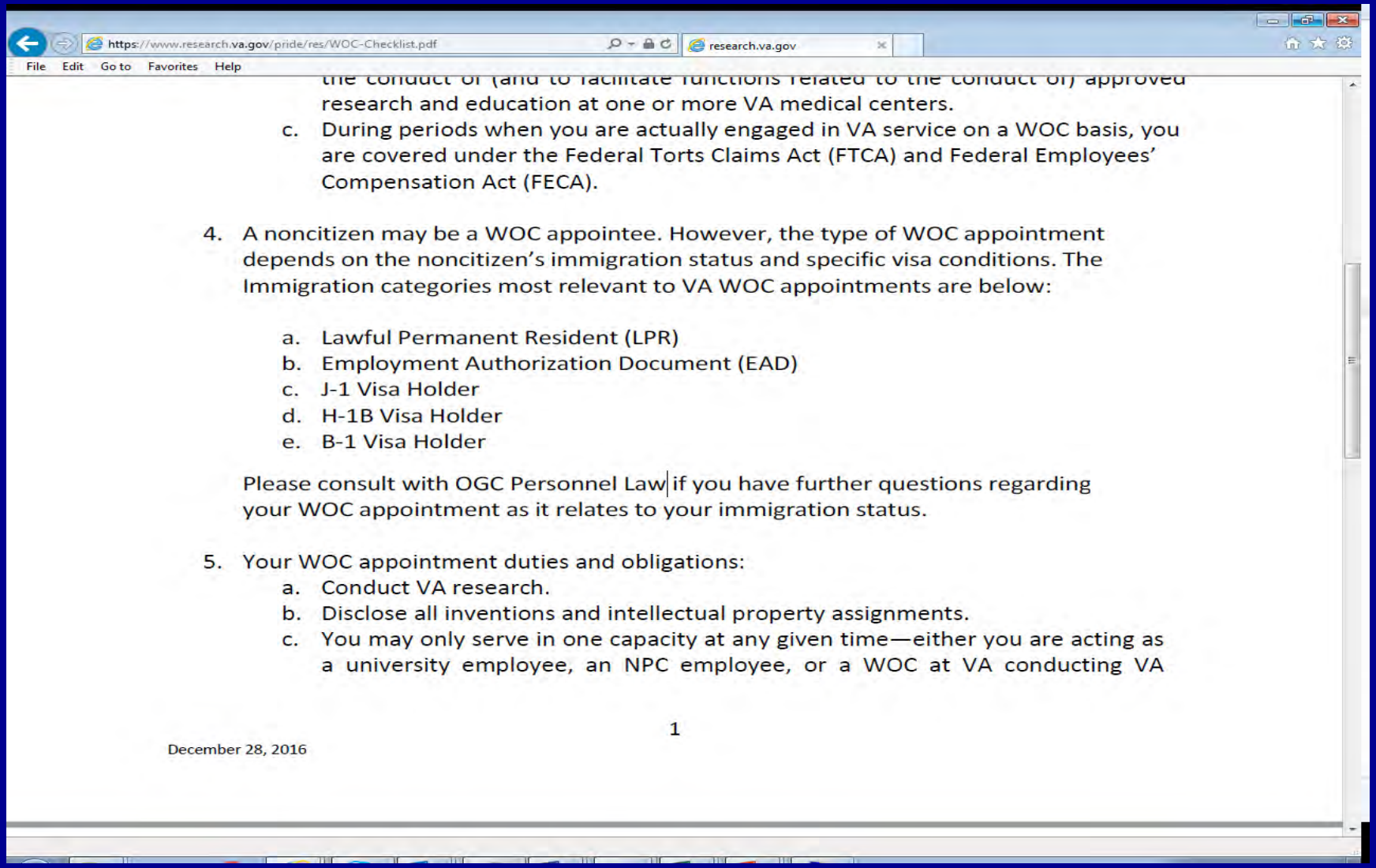
Without Compensation Employee Checklist

What is a WOC Appointment?

1. WOC is a Without Compensation VA appointment authorized by 38 USC 7405, used by VA to employ individuals to do VA work (e.g., a task, service, research) without compensation. A WOC is a federal employee for all purposes with the exception of salary and benefits.

2. If you hold a VA WOC appointment you are subject to the Government ethics laws and rules. You must be fully credentialed and you are considered a VA employee during periods when you are engaged in VA service. In addition, you are covered by VA's definition of "Government employee" for purposes of determining rights for VA employee inventions. You must also undergo the appropriate level of employee background investigation.

3. WOCs conducting research come from both affiliates and Non-Profit Corporations (NPCs). The facility Director is the approving authority for your WOC appointment at your VA facilities.
    a. NPCs are established at VA medical centers and managed in accordance with the NPC Statute. See VHA Handbook 1200.17.
    b. NPCs exist to provide VA medical centers with flexible funding mechanisms for the conduct of (and to facilitate functions related to the conduct of) approved research and education at one or more VA medical centers.
    c. During periods when you are actually engaged in VA service on a WOC basis, you are covered under the Federal Torts Claims Act (FTCA) and Federal Employees'



the conduct of (and to facilitate functions related to the conduct of) approved research and education at one or more VA medical centers.

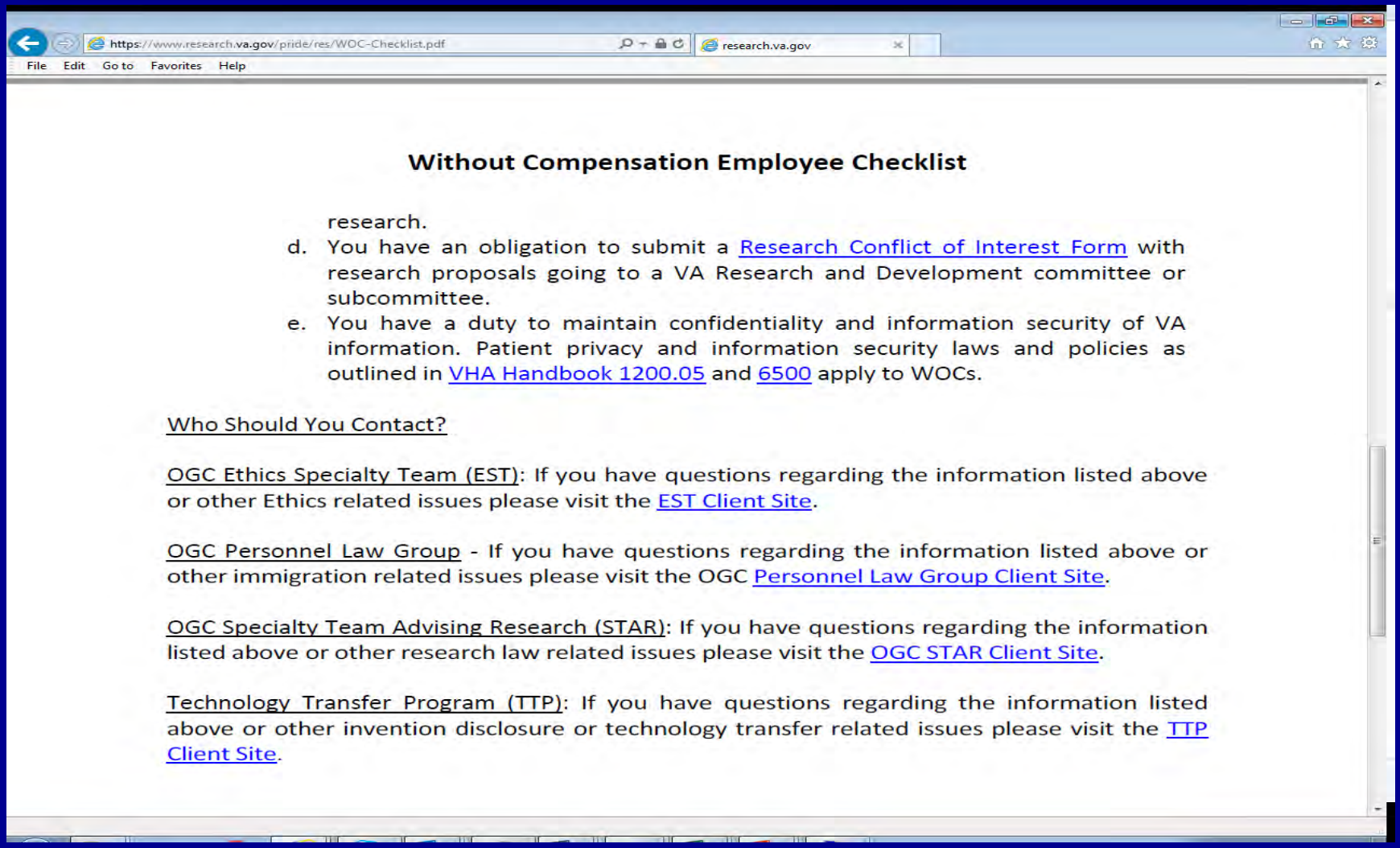
c. During periods when you are actually engaged in VA service on a WOC basis, you are covered under the Federal Torts Claims Act (FTCA) and Federal Employees' Compensation Act (FECA).

4. A noncitizen may be a WOC appointee. However, the type of WOC appointment depends on the noncitizen's immigration status and specific visa conditions. The Immigration categories most relevant to VA WOC appointments are below:

   a. Lawful Permanent Resident (LPR)
   b. Employment Authorization Document (EAD)
   c. J-1 Visa Holder
   d. H-1B Visa Holder
   e. B-1 Visa Holder

   Please consult with OGC Personnel Law if you have further questions regarding your WOC appointment as it relates to your immigration status.

5. Your WOC appointment duties and obligations:
   a. Conduct VA research.
   b. Disclose all inventions and intellectual property assignments.
   c. You may only serve in one capacity at any given time—either you are acting as a university employee, an NPC employee, or a WOC at VA conducting VA



Without Compensation Employee Checklist

research.

d. You have an obligation to submit a Research Conflict of Interest Form with research proposals going to a VA Research and Development committee or subcommittee.
e. You have a duty to maintain confidentiality and information security of VA information. Patient privacy and information security laws and policies as outlined in VHA Handbook 1200.05 and 6500 apply to WOCs.

Who Should You Contact?

OGC Ethics Specialty Team (EST): If you have questions regarding the information listed above or other Ethics related issues please visit the EST Client Site.

OGC Personnel Law Group - If you have questions regarding the information listed above or other immigration related issues please visit the OGC Personnel Law Group Client Site.

OGC Specialty Team Advising Research (STAR): If you have questions regarding the information listed above or other research law related issues please visit the OGC STAR Client Site.

Technology Transfer Program (TTP): If you have questions regarding the information listed above or other invention disclosure or technology transfer related issues please visit the TTP Client Site.

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Source: Ron D. Simpson, BSF, VINCI Lead Concierge Specialist

Data Access Request Tracker (DART) 4.0

Ron D. Simpson, BSF
VINCI Lead Concierge Specialist

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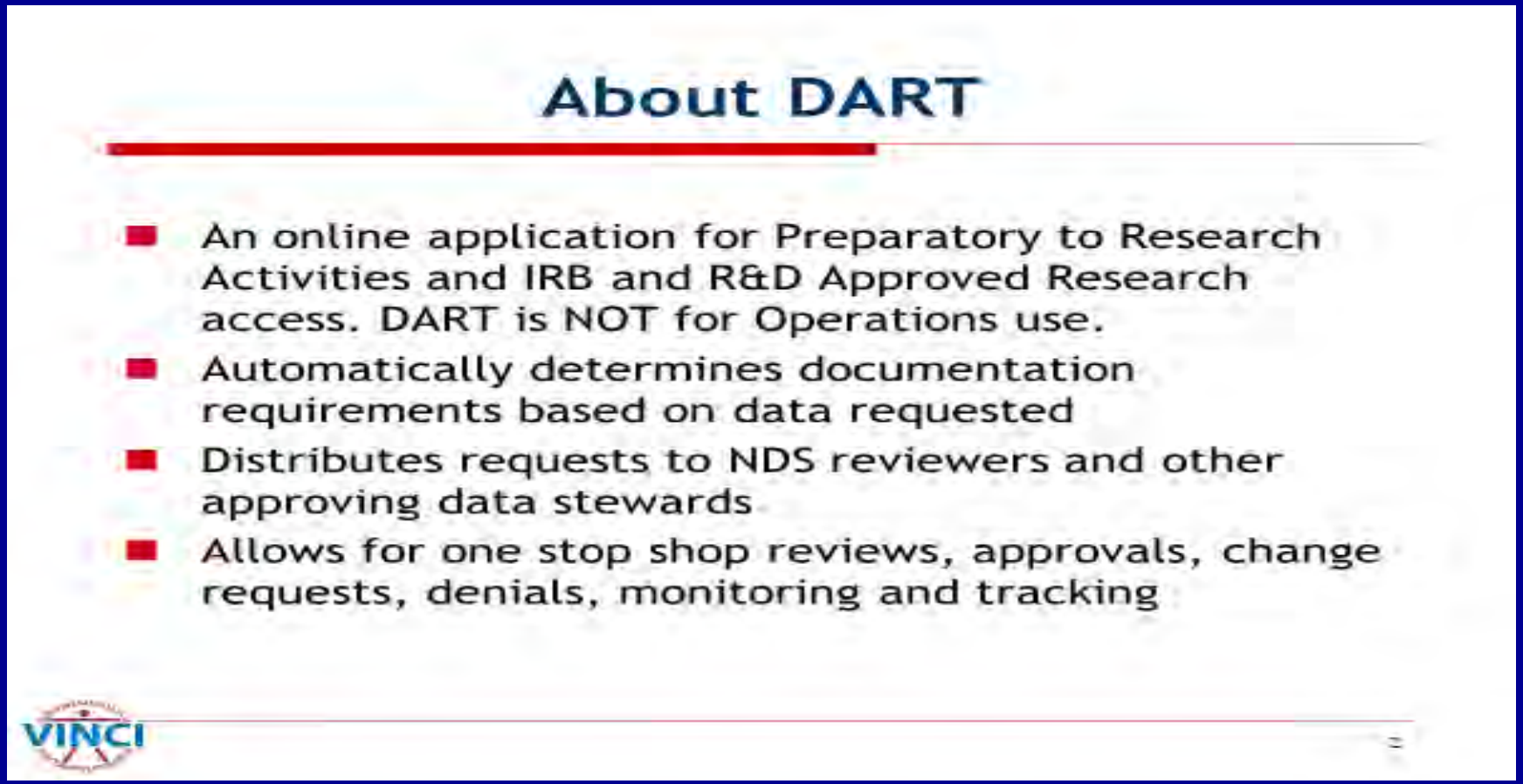

Source: Ron D. Simpson, BSF, VINCI Lead Concierge Specialist

Why Use DART

- Once stop shop for Research Activities
- Access to VHA National data for Research
- *NEW Access to Preparatory to Research
- Access to CAPRI/Joint Legacy Viewer for Research
- Incorporated a centralized secure environment with single sign-on and integrated services

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DART Features

- The Communication tool within DART allows for questions and answers between the Requestors and Approvers
- The History tool date and timestamps every event that takes place
- The DART Dashboard allows for display of approval times
- VA email notifications as the request progresses and ultimately approved
- The updated DART User Guide is now on every page for your convenient reference

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Source: Ron D. Simpson, BSF, VINCI Lead Concierge Specialist

DART Required Documents

- Research Request Memo
- IRB Approval Letter
- Research and Development Committee Approval Letter
- Research Protocol
- HIPAA Informed Consent/Authorization or Waiver
- Real SSN Access Request Form (if needed)
- CDW Domain Checklist
- Any additional data source specific forms
- Forms can be found on the VHA Data Portal:

http://vaww.vhadataportal.med.va.gov/DataAccess/DARTRequestProcess.aspx

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Research Request Memo

Department of Veterans Affairs

Memorandum

Date:

From: Principal Investigator: [Insert Name of Principal Investigator]

Subj: Research Data Request Memo re: [Tracking Number - Name of Protocol]

To: Director, National Data Systems

The following information is required and all signatures must be obtained before any access of this request can take place:

Are all participants requesting access a VA employees or WOC employees? ☐Yes ☐No
Is this request for data use for a VA research study (includes pilot studies)? ☐Yes ☐No
Is this request for activities preparatory to research? ☐Yes ☐No
Select the type(s) of data needed: ☐Real SSN ☐Scrambled SSN ☐HHI but No SSN
Is access to CAPRI / VistAWeb being requested? ☐Yes ☐No
Is AITC Main Frame access being requested? ☐Yes ☐No
Is access to VSSC and/or MCA Web Reports being requested? ☐Yes ☐No
Will any requested data be transferred outside of the VA? ☐Yes ☐No
Will the data be stored on the VINCI Environment? ☐Yes ☐No ☐Both

Please describe the data you are requesting. The data requested must reflect data disclosed in the protocol or HIPAA waiver if applicable and selected in DART.
Provide a high level summary of how the requested data will be used in the research study.
If Real SSN access is requested, please provide a justification.
List the participants names and whether they are: VA Employee, Contractor, or Without Compensation (WOC).

Estimated time the data will be needed for:

Approval

As the Principal Investigator, I certify that the data will be transferred, retained, utilized, and destroyed in accordance with VA and VHA policy including the following: VA Handbook 5011-5, Chapter 4 (Alternative Workplace Arrangements); VA Directive and Handbook 6500, Information Security Program; VA Directive and Handbook 6502, Privacy Program; and VHA Directive 1605, VHA Handbook 1200.05, 1605.1, and 1605.2. The data being requested will only be used in accordance with the protocol listed above.

I acknowledge and affirm that I am the responsible party should there be any data incidental breaches involving downloaded data from this request.

[Name of Principal Investigator] [Date]

[Name of Co-Investigator] [Date]

February 2008

VINCI

Source: Ron D. Simpson, BSF, VINCI Lead Concierge Specialist

IRB Approval Letter

- Can come from the CIRB or locally
- IRB letters are not standardized across the VA
- Key Items needed:
  - PI Name
  - Study Name
  - Approval Date
  - Expiration Date
  - Signed by the Chair of the IRB

Source: Ron D. Simpson, BSF, VINCI Lead Concierge Specialist

Research and Development Committee Approval Letter

- Each VA facility has a local Research and Development Committee
- All IRB Approved Research studies in DART must have and R&D approval letter for each location participating in the study

Source: Ron D. Simpson, BSF, VINCI Lead Concierge Specialist

Research Protocol

- Introductory paragraph
- Statement of the Problem
- Purpose
- Significance of the Study
- Research Questions and/or Hypotheses and/or Null Hypotheses
- Background
- Methodology
- Procedure and time frame
- Analysis plan
- Scope and limitations

Source: Ron D. Simpson, BSF, VINCI Lead Concierge Specialist

HIPAA Informed Consent/Authorization or Waiver

- HIPAA Waivers are not standardized across the VA
  - VA Facility Name
  - Station Number
  - Title of Study
  - PI Name
  - Brief description of PHI used for IRB
  - Must have Chair of IRB Signature
- Form 10-0521 is available for use

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Source: Ron D. Simpson, BSF, VINCI Lead Concierge Specialist

Real SSN Access Request Form

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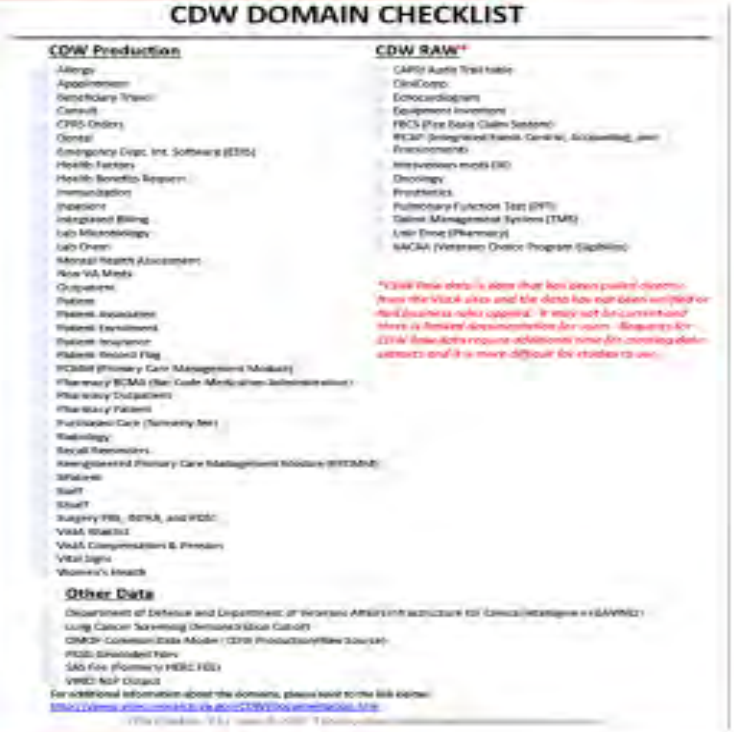
Source: Ron D. Simpson, BSF, VINCI Lead Concierge Specialist

CDW Domain Checklist



CDW DOMAIN CHECKLIST

CDW Production

- Allergy
- Appointment
- Beneficiary Travel
- Consult
- CPRS Orders
- Dental
- Emergency Depc. Int. Software (EDIS)
- Health Factors
- Health Benefits Reports
- Immunization
- Inpatient
- Integrated Billing
- Lab Microbiology
- Lab Chem
- Mental Health Assessment
- New VA Meds
- Outpatient
- Patient
- Patient Association
- Patient Enrollment
- Patient Insurance
- Patient Record Flag
- PCMM (Primary Care Management Module)
- Pharmacy BCMA (Bar Code Medication Administration)
- Pharmacy Outpatient
- Pharmacy Patient
- Prosthetics Care (Tenant Set)
- Radiology
- Recall Reminders
- Reengineered Primary Care Management Module (RPCMM)
- Sharing
- Staff
- Visit
- Surgery PIV, RPRA, and PDC
- VIMM Waiting
- Visit Compensation & Pension
- Vital Signs
- Women's Health

CDW RAW*

- CAPRI Audit Trail table
- ClinExpo
- Echocardiograms
- Equipment Inventory
- FBCS (Fee Basis Claim System)
- IFCAP (Integrated Funds Control, Accounting, and Procurement)
- Interventions made (IM)
- Oncology
- Prosthetics
- Pulmonary Function Test (PFT)
- Talent Management System (TMS)
- Unit Dose (Pharmacy)
- VACAA (Veterans Choice Program Eligibility)

*CDW Raw data is data that has been pulled directly from the VistA sites and the data has not been verified or had business rules applied. It may not be consistent and there is limited documentation for users. Requests for CDW Raw data require additional time for running data extracts and it is more difficult for readers to use.

Other Data

- Department of Defense and Department of Veterans Affairs Infrastructure for Clinical Intelligence (DAVINCI)
- Lung Cancer Screening Demonstration Cohort
- OMOP Common Data Model (CDW Production/Raw Source)
- PDSS: Stratified Files
- SAS Files (Formerly HERC FD)
- VINCI NLP Output

For additional information about the domains, please send to the link below:

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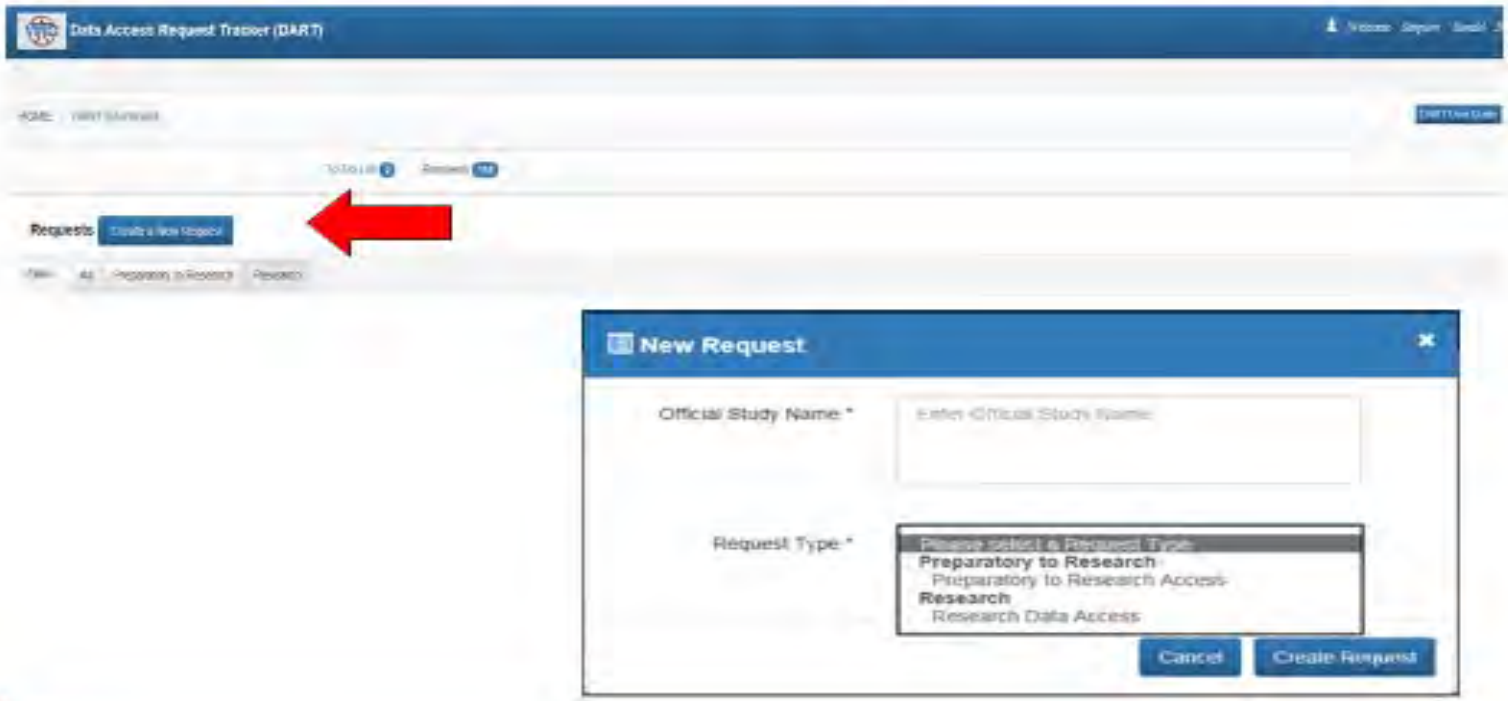
Source: Ron D. Simpson, BSF, VINCI Lead Concierge Specialist

Demo Time - IRB Research Study



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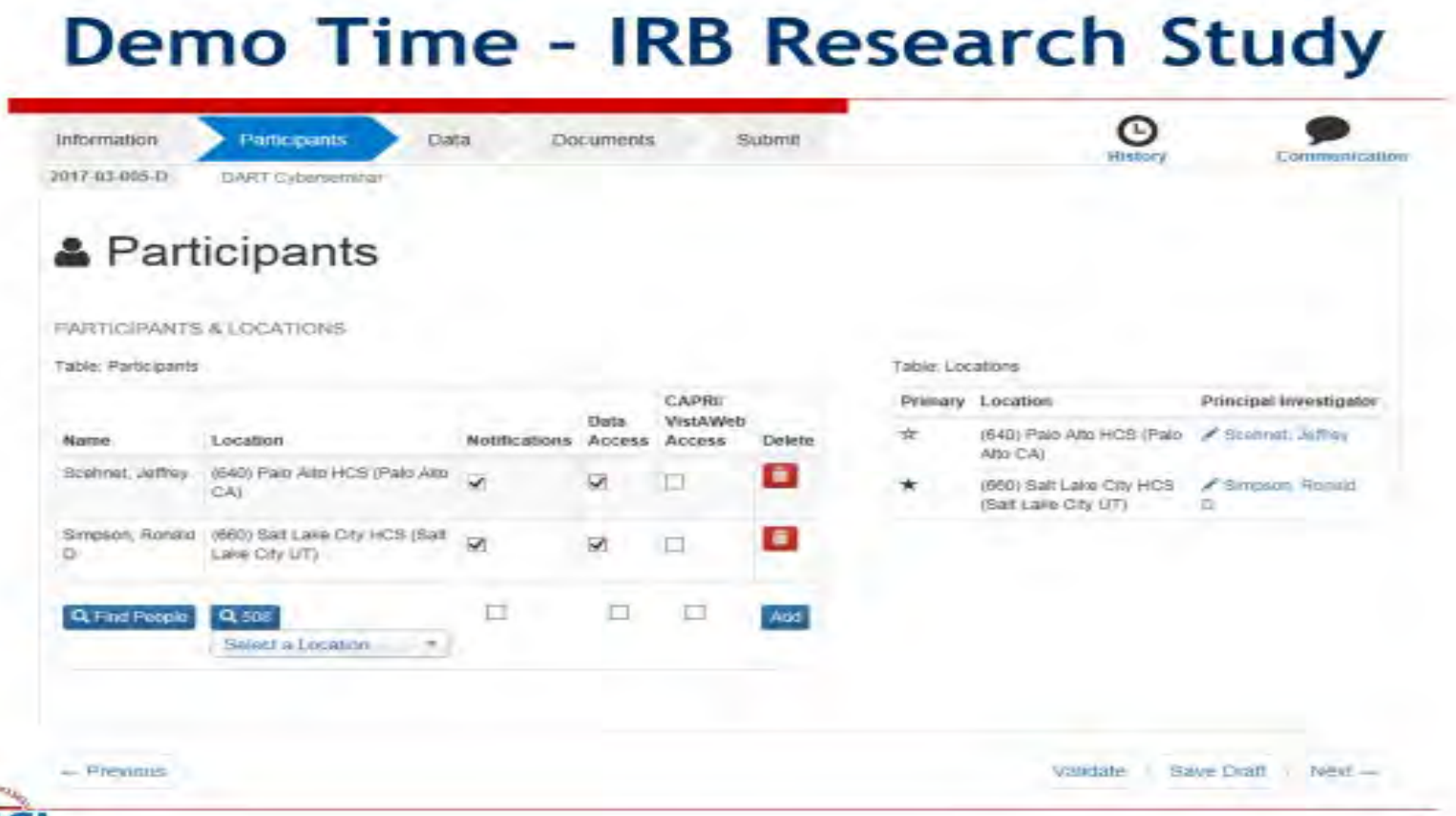

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- VHA Data Portal – DART - http://vaww.vhadataportal.med.va.gov/DataAccess/DARTRequestProcess.aspx
- CDW Metadata Documentation on Data Sources - https://vaww.cdw.va.gov/metadata/Metadata%20Documents/Forms/AllItems.aspx
- CDW Documentation on Data Sources from VIReC - http://vaww.virec.research.va.gov/CDW/Documentation.htm

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- Depression is a secondary service connected condition to traumatic brain injury (TBI) in the Veterans Health Administration (VHA).
- We asked the Question: What are the total, inpatient, outpatient and pharmaceutical costs to the VHA associated with depression in Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) and Pre OEF/OIF veterans diagnosed with TBI?

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- Every day, 153 people in the United States die from injuries that include TBI. Effects of TBI can include impaired thinking, memory, movement, vision, hearing, and emotional functioning, manifested in personality changes and depression.
- There has been an increasing amount of research on TBI focused on military personnel, as nearly 380,000 US military, across all branches worldwide, have been diagnosed with TBI since the year 2000 with the beginning of OEF/OIF. However, veterans may also be at higher risk for TBI once they leave active duty.

- An Institute of Medicine (IOM) report reviewed existing literature and concluded that there was sufficient evidence of an association between TBI and depression, which the VA now considers a secondary condition for the VA to establish depression as a secondary service connected condition if manifest within 3 years of the incurrence of moderate or severe TBI, or within 12 months of mild TBI.
- Though there are estimates of VHA inpatient and outpatient costs for OEF/OIF veterans with TBI as well as outpatient only costs of OEF/OIF veterans with comorbid TBI-PTSD, evidence is lacking concerning VHA costs associated with comorbid TBI-depression.

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- We estimated the annual marginal impact and predicted per veteran total, inpatient, outpatient and pharmaceutical VHA cost burden associated with comorbid TBI-depression by OEF/OIF status, FY2000-FY2014.
- After receiving IRB, VA R&D approvals and submitting the DART, we requested a cohort of veterans diagnosed with TBI from VINCI between 2000-2010 and followed their costs until 2014.
- Diagnosis and TBI severity were based upon International Classification of Diseases, Ninth Revision (ICD-9) codes for TBI, post-concussive syndrome, and TBI-related late effects, according to the Military Health System and Defense Health Agency Traumatic Brain Injury (TBI) DoD Standard Surveillance Case Definition for TBI Adapted for AFHSB Use.

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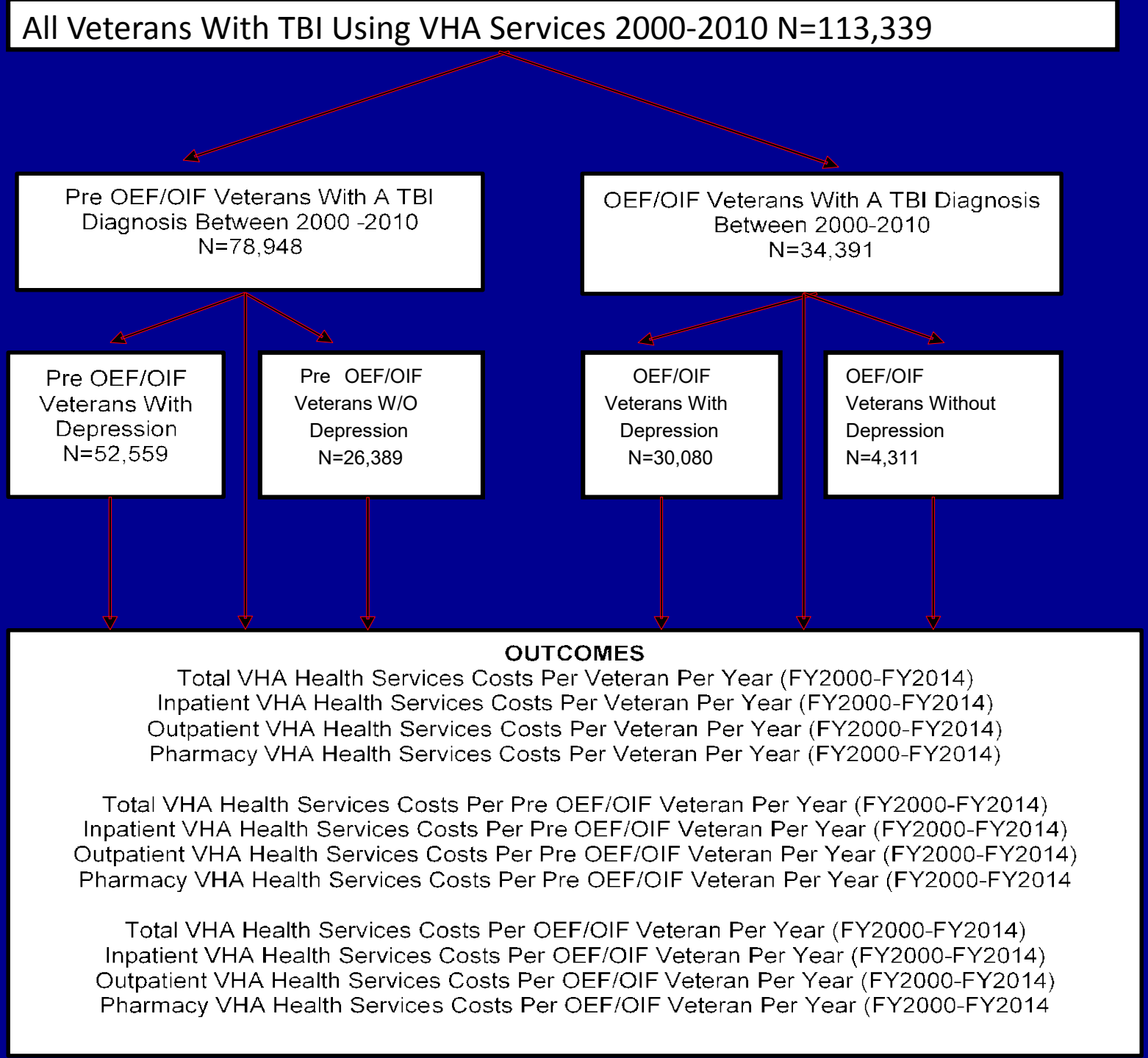
- We supplied VINCI with the diagnosis codes contained in the DoD Standard Surveillance Case Definition and we requested Patient Treatment Files inpatient and outpatient (PTF) containing veteran demographics and ICD codes as well as Health Economics Resource Center (HERC) costs FY2000-FY2014 for each veteran.
- We merged the files which VINCI provides in SQL and we read into STATA for cleaning and analysis, by scrambled SSN. Depression was identified based on the Elixhauser Algorithm from ICD codes in the VINCI PTFs.
- All costs were converted to 2017 dollar values using the US Department of Labor Inflation Calculator.


All Veterans With TBI Using VHA Services 2000-2010 N=113,339
Pre OEF/OIF Veterans With A TBI Diagnosis Between 2000 -2010 N=78,948
OEF/OIF Veterans With A TBI Diagnosis Between 2000-2010 N=34,391
Pre OEF/OIF Veterans With Depression N=52,559
Pre OEF/OIF Veterans W/O Depression N=26,389
OEF/OIF Veterans With Depression N=30,080
OEF/OIF Veterans Without Depression N=4,311
OUTCOMES
Total VHA Health Services Costs Per Veteran Per Year (FY2000-FY2014)
Inpatient VHA Health Services Costs Per Veteran Per Year (FY2000-FY2014)
Outpatient VHA Health Services Costs Per Veteran Per Year (FY2000-FY2014)
Pharmacy VHA Health Services Costs Per Veteran Per Year (FY2000-FY2014)
Total VHA Health Services Costs Per Pre OEF/OIF Veteran Per Year (FY2000-FY2014)
Inpatient VHA Health Services Costs Per Pre OEF/OIF Veteran Per Year (FY2000-FY2014)
Outpatient VHA Health Services Costs Per Pre OEF/OIF Veteran Per Year (FY2000-FY2014)
Pharmacy VHA Health Services Costs Per Pre OEF/OIF Veteran Per Year (FY2000-FY2014
Total VHA Health Services Costs Per OEF/OIF Veteran Per Year (FY2000-FY2014)
Inpatient VHA Health Services Costs Per OEF/OIF Veteran Per Year (FY2000-FY2014)
Outpatient VHA Health Services Costs Per OEF/OIF Veteran Per Year (FY2000-FY2014)
Pharmacy VHA Health Services Costs Per OEF/OIF Veteran Per Year (FY2000-FY2014

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- First, the unadjusted frequency of OEF/OIF status, service connected disability status, TBI severity, and socio-demographics by depression status was tested using chi-square tests for all veterans. Second, number of non-depression Elixhauser comorbidities, unadjusted total, inpatient, outpatient, and pharmaceutical annual VHA costs per veteran by depression status were tested using student t tests for all veterans and by OEF/OIF status.
- In order to estimate the covariate adjusted association of depression with annual total VHA costs per veteran diagnosed with TBI, a generalized linear model with Gaussian family and identity link was estimated for all veterans and cohorts subset by OEF/OIF status.

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- Predicted marginal annual VHA cost impact of comorbid TBI-depression was estimated by multiplying the marginal effect on cost of depression per veteran times the number of veterans with depression, by OEF/OIF status. Predicted annual VHA cost burden of comorbid TBI-depression was estimated by multiplying the predicted mean cost per veteran times the number of veterans with depression, by OEF/OIF status.
- All analyses were performed using STATA version 15.0 in VINCI.
- Statistical significance was determined at $P<0.05$.

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- For estimation of the separate but related inpatient, outpatient and pharmacy cost categories, seemingly unrelated regression (SUR), which allows for correlation between cost categories, was used. Intuitively, this makes sense as decisions regarding inpatient, outpatient and pharmaceutical health services are likely to be coordinated by providers within the VHA.
- All models were adjusted for gender, race/ethnicity, location, marital status, service connected disability, TBI severity, and number of non-depression Elixhauser comorbidities, while the all veteran model was additionally adjusted for OEF/OIF status.

Table 1. Demographics and VHA Health Services Costs 2000-2014 by Depression Diagnosis in All, Pre OEF/OIF and OEF/OIF Veterans With TBI Between 2000-2010 (N=113,339)

	All Veterans N=113,339		Pre OEF/OIF Veterans N=78,948		OEF/OIF Veterans N=34,391	
Variables	**Without Depression**	**With Depression**	**Without Depression**	**With Depression**	**Without Depression**	**With Depression**
N	**30,700**	**82,639**	**26,389**	**52,559**	**4,311**	**30,080**
Age at Baseline						
18-34	17.62%*	33.49%*	8.00%*	10.36%*	76.50%*	73.91%*
35-50	18.03%*	25.92%*	17.62%*	27.41%*	20.48%*	23.31%*
51-61	21.20%*	23.00%*	24.18%*	34.64%*	2.92%*	2.65%*
62+	43.16%*	17.59%*	50.19%*	27.59%*	0.09%*	0.13%*
Gender						
Male	94.91%*	92.90%*	94.92%*	91.94%*	94.85%	94.57%
Female	5.09%*	7.10%*	5.08%*	8.06%*	5.15%	5.43%
Race						
White	76.34%*	76.98%*	75.82%*	76.40%*	79.56%*	77.99%*
Black/ African American	14.22%*	12.95%*	14.97%*	14.48%*	9.60%*	10.28%*
Hispanic	6.54%*	6.50%*	6.69%*	6.26%*	5.64%*	6.93%*
Other	2.90%*	3.56%*	2.52%*	2.86%*	5.20%*	4.80%*
Location						
Urban	68.67%*	69.59%*	68.15%*	69.77%*	71.84%*	69.27%*
Rural/ Highly Rural	28.01%*	28.17%*	28.26%*	27.57%*	26.47%*	29.21%*
U.S. Territory	3.33%*	2.24%*	3.59%*	2.66%*	1.69%*	1.52%*
Married						
Married	54.56%	56.50%	53.74%*	58.67%*	59.59%*	52.71%*
Non-Married	45.44%	43.50%	46.26%*	41.33%*	40.41%*	47.29%*
Service Connected Disability						
Less Than 50%	85.08%*	70.31%*	84.36%*	70.36%*	89.47%*	70.22%*
Greater or Equal to 50%	14.92%*	29.69%*	15.64%*	29.64%*	10.53%*	29.78%*

TBI Severity						
Mild	18.73%*	27.48%*	14.26%*	17.58%*	46.09%*	44.77%*
Moderate/Severe /Penetrating	74.15%*	61.00%*	78.95%*	72.75%*	44.82%*	40.47%*
Unknown	7.12%*	11.52%*	6.79%*	9.67%*	9.09%*	14.76%*
Elixhauser Co-Morbidities						
Mean Per Veteran	3.83*	4.08*	4.34*	5.56*	0.68*	1.50*
(95% CI)	(3.79:3.87)	(4.05:4.10)	(4.30:4.38)	(5.53:5.59)	(0.65:0.71)	(1.48:1.51)
Unadjusted Total Costs						
Mean Per Veteran	$9,988*	$13,908*	$10,858*	$16,975*	$4,658*	$8,550*
(95% CI)	(9786:10190)	(13,778:14,039)	(10636:11080)	(16789:17161)	(4218:5098)	(8418:8682)
Median	$4,683	$8,074	$5,352	$10,575	$2,343	$5,102
Unadjusted Inpatient Costs						
Mean Per Veteran	$4,996*	$5,980*	$5,550*	$8,096*	$1,609*	$2,284*
(95% CI)	(4821:5171)	(5871:6090)	(5358:5742)	(7936:8256)	(1208:2010)	(2185:2382)
Median	$84	$647	$468	$2,004	$0	$0
Unadjusted Outpatient Costs						
Mean Per Veteran	$3,928*	$6,441*	$4,114*	$6,942*	$2,792*	$5,565*
(95% CI)	(3869:3987)	(6400:6483)	(4047:4180)	(6885:7000)	(2699:2884)	(5513:5618)
Median	$2,744	$4,914	$2,903	$5,362	$2,118	$4,202
Pharmacy Costs						
Mean Per Veteran	$1,062*	$1,486*	$1,194*	$1,935*	$256*	$700*
(95% CI)	(1028:1096)	(1470:1502)	(1154:1233)	(1913:1958)	(231:281)	(684:716)
Median	$484	$812	$612	$1,250	$76	$316

Table 2. Adjusted Estimated Marginal Effects of Depression, Predicted Mean Comorbid TBI-Depression Costs in All, Pre OEF/OIF and OEF/OIF Veterans, FY2000-FY2014

	All Veterans		Pre OEF/OIF Veterans		OEF/OIF Veterans	
	Marginal Effect of Depression	**Marginal Effect on VHA**	**Marginal Effect of Depression**	**Marginal Effect on VHA**	**Marginal Effect of Depression**	**Marginal Effect on VHA**
Total (95% CI)	$1,775* (1527:2022)	$146,684,225	$1,847* (1563:2131)	$97,076,473	$1,228* (736:1719)	$36,938,240
Inpatient (95% CI)	-$93 (-304:117)	Not significant	$1.16 (-263:265)	Not significant	-$648* (-944:-353)	-$19,491,840
Outpatient (95%CI)	$1,596* (1518:1673)	$131,809,205	$1,558* (1464:1652)	$81,886,922	$1,685* (1553:1818)	$50,684,800
Pharmacy (95% CI)	$272* (238:306)	$22,477,808	$287* (244:330)	$15,084,433	$191* (148:233)	$5,745,280
	Predicted Mean Per Veteran Per Year	**Predicted VHA Impact Per Year**	**Predicted Mean Per Veteran Per Year**	**Predicted VHA Impact Per Year**	**Predicted Mean Per Veteran**	**Predicted VHA Impact Per Year**
Total						
With Depression	$13,327	$1,101,329,953	$15,548	$817,187,332	$8,216	$247,137,280
Without Depression	$11,552	$354,646,400	$13,701	$361,555,689	$6,988	$30,125,268
Inpatient						
With Depression	$5,689	$470,133,271	$7,245	$380,789,955	$2,118	$63,709,440
Without Depression	$5,782	$177,507,400	$7,244	$191,161,916	$2,767	$11,928,537
Outpatient						
With Depression	$6,193	$511,783,327	$6,518	$342,579,562	$5,429	$163,304,320
Without Depression	$4,597	$141,127,900	$4,959	$130,863,051	$3,743	$16,136,073
Pharmacy						
With Depression	$1,445	$119,413,355	$1,784	$93,765,256	$668	$20,093,440
Without Depression	$1,172	$35,980,400	$1,496	$39,477,944	$477	$2,056,347

*Significant at P<0.05

Adjusted for age, OEF/OIF status (in all Veteran model), gender, race/ethnicity, location, marital status, service connected disability, TBI severity, and number of non-depression Elixhauser co-morbidities.

Note: Marginal Effect on VHA consists of the marginal effect per veteran multiplied times number of veterans. Predicted impact on VHA consists of the predicted mean per veteran multiplied times number of veterans.

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- Conclusions:
- All Veterans with comorbid TBI-depression incur VHA costs exceeding 1 billion dollars per year.
- OEF/OIF Veterans incur VHA costs exceeding a quarter of a billion dollars per year.
- Interestingly, depression is associated with lower inpatient VHA costs in OEF/OIF Veterans.
- This is likely due to mandatory TBI and depression screening for OEF/OIF Veterans.
- We recommend the VHA consider screening for TBI and Depression in all veterans.

Association of Clinically Diagnosed Depression With VHA Costs in Veterans Diagnosed with Traumatic Brain Injury: A CENC Study

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- In addition, he is a certified Privacy Professional by the International Association of Privacy Professionals (IAPP) focusing on U.S. government privacy laws, regulations and policies, privacy compliance and auditing, records management and agency reporting obligations.

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- Special thanks to Jeff Scehnet, Associate Director of VINCI, for invaluable support in creating this presentation.
- Also thank you to Ron Simpson of VINCI for use of his slides.

- Questions?

Appendix 36

A Single Concussion May Increase Risk of Parkinson's Disease

AMERICAN ACADEMY OF NEUROLOGY®

Press Release

EMBARGOED FOR RELEASE UNTIL 4 P.M. ET, WEDNESDAY, APRIL 18, 2018

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A Single Concussion May Increase Risk of Parkinson's Disease

MINNEAPOLIS – People who have been diagnosed with a mild traumatic brain injury, also known as a concussion, may have a 56 percent increased risk of developing Parkinson's disease, according to a study published in the April 18, 2018, online issue of *Neurology*®, the medical journal of the American Academy of Neurology.

"Previous research has shown a strong link between moderate to severe traumatic brain injury and an increased risk of developing Parkinson's disease but the research on mild traumatic brain injury has not been conclusive," said study author Raquel C. Gardner, MD, of the University of California, San Francisco and a member of the American Academy of Neurology. "Our research looked a very large population of U.S. veterans who had experienced either mild, moderate or severe traumatic brain injury in an effort to find an answer to whether a mild traumatic brain injury can put someone at risk."

Moderate to severe traumatic brain injury was defined as a loss of consciousness for more than 30 minutes, alteration of consciousness of more than 24 hours or amnesia for more than 24 hours. Mild traumatic brain injury was defined as loss of consciousness for zero to 30 minutes, alteration of consciousness of a moment to 24 hours or amnesia for zero to 24 hours.

For the study, researchers identified 325,870 veterans from three U.S. Veterans Health Administration medical databases. Half of the study participants had been diagnosed with either a mild, moderate or severe traumatic brain injury and half had not. The study participants, who ranged in age from 31 to 65, were followed for an average of 4.6 years. At the start of the study, none had Parkinson's disease or dementia. All traumatic brain injuries were diagnosed by a physician.

A total of 1,462 of the participants were diagnosed with Parkinson's disease at least one year and up to 12 years after the start of the study. The average time to diagnosis was 4.6 years.

A total of 949 of the participants with traumatic brain injury, or 0.58 percent, developed Parkinson's disease, compared to 513 of the participants with no traumatic brain injury, or 0.31 percent. A total of 360 out of 76,297 with mild traumatic brain injury, or 0.47 percent, developed the disease and 543 out of 72,592 with moderate to severe traumatic brain injury, or 0.75 percent, developed the disease.

After researchers adjusted for age, sex, race, education and other health conditions like diabetes and high blood pressure, they found that those with any kind of traumatic brain injury had a 71 percent increased risk of Parkinson's disease, those with moderate to severe traumatic brain injury had an 83 percent increased risk, and those with mild traumatic brain injury had a 56 percent increased risk of Parkinson's disease.

Researchers also found that those with any form of traumatic brain injury were diagnosed with Parkinson's disease an average of two years earlier than those without traumatic brain injury.

"This study highlights the importance of concussion prevention, long-term follow-up of those with concussion, and the need for future studies to investigate if there are other risk factors for Parkinson's disease that can be modified after someone has a concussion," said Gardner. "While our study looked at

veterans, we believe the results may have important implications for athletes and the general public as well."

One limitation of the study was that medical codes were used to identify people with traumatic brain injury and some cases may have been missed. In addition, mild traumatic brain injury may be underreported in those serving in combat.

The study was supported by the U.S. Army Medical Research and Material Command and the U.S. Department of Veterans Affairs, the National Institute of Neurological Disorders and Stroke, the National Institute on Aging and the American Federation for Aging Research.

To learn more about concussion, visit www.aan.com/concussion.

The American Academy of Neurology is the world's largest association of neurologists and neuroscience professionals, with over 34,000 members. The AAN is dedicated to promoting the highest quality patient-centered neurologic care. A neurologist is a doctor with specialized training in diagnosing, treating and managing disorders of the brain and nervous system such as Alzheimer's disease, stroke, migraine, multiple sclerosis, concussion, Parkinson's disease and epilepsy.

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Appendix 37

Greater Attentional Resources are Required in Older Veterans With More Severe mTBI: An fMRI Study

ABSTRACT PREVIEW

Abstract ID: 401703

Greater Attentional Resources are Required in Older Veterans With More Severe mTBI: An fMRI Study

Abstract Category: Oral Papers

Primary Submission Category: Research

Abstract Status: Complete

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Role: Author

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traumatic brain injury and its treatment, therapeutic interventions for preserving vision in blinding eye diseases, and investigating structure-function relationships in the visual system using optical coherence tomography (OCT), ocular blood flow, image analysis, and MRI. Dr. Kardon is actively involved in the development of telemedicine tools for objectively evaluating the status of the visual and neurological systems for testing in remote locations. He is cofounder of MedFace and FaceX, start-up companies that are developing low cost mobile devices for precise video assessment of facial responses to light stimuli to diagnose and monitor treatment of medical, neurological and eye disorders.

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Biographical Sketch
Dr. Lim is a Professor and Vice Chair for Research in the Department of Psychiatry where he holds the Drs. T.J. and Ella M. Arneson Land Grant Chair in Human Behavior. Dr. Lim's research interests are in the use of neuroimaging approaches to study brain disorders and the development of new treatment approaches using neuromodulation to harness brain plasticity to improve function.

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Learning Objectives

1. Describe the importance of executive function for cognition.
2. Explain the use of the Stroop task in assessing attention.
3. Describe the importance that aging has on brain function in a person with an mTBI.
4.
5.

Objectives
To examine the effect age has on executive function in Veterans who have had a mild traumatic brain injury (mTBI) using fMRI.

Design
Case-control cross-section study of military veterans with and without mTBI. Subjects received an fMRI scan at 3T while performing the Color and Word Stroop task to assess executive processing abilities. Severity of mTBI was assessed with the Minnesota Blast Exposure Screening Tool (MN-BEST).

Setting
The Minneapolis Veterans Affairs Clinic (VAMC) and the Center for Magnetic Resonance Research (CMRR) at the University of Minnesota.

Participants
124 veterans with and without mTBI were recruited via posters or clinical staff referral at the VAMC. The mean age of the participants studied was 49.5 years with a range of 23.4 to 65.9 years.

Interventions
Not applicable

Main Outcome Measure(s)
fMRI task activation

Results
A multiple linear regression was performed with fMRI task activation, age, and mTBI severity. Following an ROI-wise permutation analysis (379 ROIs across cortical hemispheres and sub-cortex), the left inferior parietal lobule showed significant interaction effects such that with increasing age and more severe mTBI, greater activation was observed in the left inferior parietal lobule.

Conclusions
This analysis reveals that with an increase in age and MN-BEST scores there is an increase in activation within the left inferior parietal lobule, suggesting that older participants with more severe mTBIs required more attentional resources. This may have implications for the clinical course and care of our aging Veteran population with an mTBI.

Content Topics

Life Stages
Young adult - 19 years to 29 years of age, Adult - 30 years to 66 years of age

Theme 1
Aging with TBI

Theme 2

Theme 3

Key Words

Keyword 1
Aging

Keyword 2
Brain Concussion

Keyword 3
Executive Function

Keyword 4
Magnetic Resonance Imaging

Keyword 5

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Additional Information

Additional Information

Appendix 38

Exosomes in Acquired Neurological Disorders: New Insights into Pathophysiology and Treatment

Molecular Neurobiology
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Exosomes in Acquired Neurological Disorders: New Insights into Pathophysiology and Treatment

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Abstract
Exosomes are endogenous nanovesicles that play critical roles in intercellular signaling by conveying functional genetic information and proteins between cells. Exosomes readily cross the blood-brain barrier and have promise as therapeutic delivery vehicles that have the potential to specifically deliver molecules to the central nervous system (CNS). This unique feature also makes exosomes attractive as biomarkers in diagnostics, prognostics, and therapeutics in the context of multiple significant public health conditions, including acquired neurological disorders. The purpose of this review is to summarize the state of the science surrounding the relevance of extracellular vesicles (EVs), particularly exosomes, to acquire neurological disorders, specifically traumatic brain injury (TBI), spinal cord injury (SCI), and ischemic stroke. In total, ten research articles were identified that examined exosomes in the context of TBI, SCI, or stroke; these manuscripts were reviewed and synthesized to further understand the current role of exosomes in the context of acquired neurological disorders. Of the ten published studies, four focused exclusively on TBI, one on both TBI and SCI, and five on ischemic stroke; notably, eight of the ten studies were limited to pre-clinical samples. The present review is the first to discuss the current body of knowledge surrounding the role of exosomes in the pathophysiology, diagnosis, and prognosis, as well as promising therapeutic strategies in TBI, SCI, and stroke research.

Keywords Acquired neurological disorders · Traumatic brain injury (TBI) · Stroke · Spinal cord injury (SCI) · Exosomes · Extracellular vesicles

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Introduction

Extracellular Vesicles and Exosomes

What They Are and Where They Come From

The term extracellular vesicle (EV) has yet to be definitively standardized [1]. Classification is most often dependent on several key characteristics including the biogenesis, size, composition, and cargo of each vesicle type (Table 1). Broadly, EV refers to a collection of structures (e.g., microvesicles, exosomes) that are formed by, and obtain their membrane from, the plasma membranes of cells. EVs are highly heterogeneous because they are derived from several cell types leading to variation in the markers on the outer membrane as well as the cargo contained within [4]. Likewise, depending on the

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Table 1 Extracellular vesicle types and their corresponding characteristics

EV subtype	Biogenesis	Size	Lipid content	Cargo type/use
Apoptotic bodies	Plasma membrane (blebbing of membrane on a cell undergoing apoptotic cell death)	~500–2000 nm	Phosphatidylserine	Fragmented DNA; cellular organelles; released by cells undergoing programmed cell death
Exosomes	Multivesicular body (MVB), also known as a "late endosome" (fuses with cell membrane to release exosomes)	~30–100 nm	Ceramide	DNA, RNA (mRNA, miRNA, non-coding RNA), and proteins; cargo is transferred horizontally between cells to affect the recipient cell.
Microvesicles (i.e., Ectosomes)	Plasma membrane (outward budding of the membrane)	~50–1000 nm	Phosphatidylserine	DNA, RNA (mRNA, miRNA, non-coding RNA), and proteins; cargo is transferred horizontally between cells to affect the recipient cell
Exosome-like vesicles	Unknown (possibly MVB from other organelles)	~20–50 nm	No lipid rafts	DNA, RNA (mRNA, miRNA, non-coding RNA), and proteins; their cargo is transported to affect various cell types

Comparison of exosomes to other type of extracellular vesicles based on how they are made, their physical properties (size; lipid content), cargo type, and what it is used for. Information in the table is based off information from the following sources: [2] and [3]

cell type from which they are formed and the surrounding microenvironment, exosomes can be detected in various human secretions [5–9]. In addition to the shared mechanism by which EVs are formed, these structures are thought to share a role in cell-to-cell communication by facilitating exchange of DNA, RNA, and proteins between cells.

Exosomes are one type of EVs that are relatively well studied compared to other EV subtypes [1, 10, 11]. Exosomes form when an endocytic, multivesicular body (MVB) fuses with the plasma membrane, and the MVB's contents (*exosomes*) are exocytosed [2]. Fusion with the plasma membrane results in protein markers from the cell of origin integrating into the membrane of the EVs which is useful for determining the source of the exosome [12]. After release into the extracellular milieu, exosomes fuse with other cells, and their cargo (e.g., RNA, enzymes, peptides) is transferred to the recipient cell, where it can participate in signaling processes, thereby orchestrating cellular response [13]. In addition to their characteristic biogenesis, exosomes are distinguished from other types of EVs based on their physical properties (e.g., size, lipid content), as well as their cargo (Table 1).

Exosomal samples can be enriched for exosome-specific protein markers to increase the specificity, as well as the certainty that the exosomes are not contaminated with other EVs or cellular materials. Exosomal protein markers most commonly reported in the acquired neurological disorder literature are ALIX [14], CD9 [15–18], CD63 [18, 19], CD81 [17, 18, 20, 21], and TSG101 [20, 21]; a less commonly reported marker is HSP70 [15]. A variety of standard methods can be used for detection of these marker proteins, including western blot analysis, ELISA, and ultra-sensitive protein quantification techniques. In addition to the common exosomal markers described above, enrichment for certain markers can also be used to isolate exosomes from specific cell types. This is useful when studying acquired neurological disorders, as it is often the goal to identify exosomes secreted from a specific cell type or those generally of central origin. For example, L1CAM, a nerve cell marker, has been used in Alzheimer's disease (AD) research [22]. While this marker is capable of detecting exosomes of nerve-cell origin, it is unable to distinguish between centrally and peripherally derived exosomes since peripheral nerve cells also express L1CAM [22, 23], as do cells of the kidney and soft tissue [24]. More recently, the ionotropic glutamate receptor, GluR2—also referred to as GRIA2 or AMPA2—has been used as an exosomal surface marker for determining central origin in a pre-clinical TBI study [25]. GluR2 is widely expressed within the brain in both neurons and developing oligodendrocytes, with only low levels of expression reported in other tissue types [24]. Another option in histological studies is to use co-staining techniques for specific cell type markers to identify where the cargo is being expressed as a possible source of the exosomal contents. One study that examined miRNA

expression within exosomes after TBI found miR-21 was highly expressed in neuronal cell bodies based on MAP2 co-localization. In this study, miR-21 was not expressed in microglia, based on a lack of co-localization with Iba-1 [15].

A key feature of exosomes and other EV is their small size. A general way to isolate and detect exosomes from a biological specimen is to use one of a variety of size-exclusion methods. For example, electron microscopy can be used to screen particles by size [14], which is often followed up by enriching for an exosomal marker. Other options include a combination of differential centrifugation and filtration [23], or sucrose gradient centrifugation, which separates vesicles based on flotation densities [26]. The abovementioned techniques can be used alone or in combination with commercially available kits that facilitate exosomal isolation. Several commercially available kits have been used in the literature and there is no established gold-standard approach to exosomal isolation in the research community [3, 14, 16–18, 26–31]. However, the methods available for isolating exosomes are rapidly improving.

Why They Are Being Increasingly Researched

EVs and other nanoparticles are increasingly being studied for their potential to improve diagnosis, prognosis, and treatment of various diseases, including acquired neurological disorders [32]. The secretion of EVs occurs across species, suggesting that EV-mediated communication is an evolutionarily conserved process [33–36]; however, the study of EVs is a relatively new area of scientific inquiry, especially as they relate to human health. A recent review found that between 2006 and 2016, there was a tenfold increase in the number of peer-reviewed exosome research publications [2]. However, there remains a great deal to understand, specifically related to acquired neurological disorders. Despite their discovery and characterization in the 1970s and 1980s [37, 38], exosomes have remained largely understudied for decades, in part due to an inability to accurately characterize their activity. Since their initial characterization, several key advances in the scientific understanding of exosomes occurred. Exosomes and other EVs have been isolated from numerous accessible human biological fluids, including blood [5], saliva [7], urine [8], stool [39], semen [40], breastmilk [9], and cerebrospinal fluid [6], making it feasible to study exosomes in patients with a variety of disorders. RNAs and proteins packaged within exosomes are stable because they are protected from nucleases and proteinases found in plasma and other biological tissues; thus, they can be readily assayed in stored samples. In 2007, it was shown for the first time that messenger RNA (mRNA) and microRNA (miRNA) could be transferred between cells using exosome-mediated mechanisms, indicating that genomic signaling occurs from cell to cell in part through exosome activity [28]. The relevance of this RNA transfer was demonstrated in 2008, with the finding that tumor growth in glioblastoma depends in part on exosome-mediated transport of RNA and proteins between cells; this study linked exosomes to the neuropathology associated with cancer progression [29]. Despite this increased interest, the mechanisms by which exosomes are produced and the consequences of exosome-mediated information transfer remain poorly understood. Consequently, the translation of exosome research into clinical research and practice has been limited [2, 11].

This gap in knowledge is especially evident in the context of acquired neurological disorders, a field where biomarker research has lagged behind compared to monogenic or other heritable disorders. Moreover, the inaccessibility of brain tissue for histological testing, and high cost of neurological imaging, results in a dire need for reliable circulating biomarkers for acquired neurological disorders. While all acquired neurological conditions are poorly understood, the decision was made to focus this review on traumatic brain injury (TBI), spinal cord injury (SCI), and stroke, which are especially underrepresented in the EV literature. Further rationale for the decision to focus the discussion to TBI, SCI, and stoke is that all three conditions are characterized by a primary neurological insult, followed by a sustained pattern of secondary injury cascades. Moreover, there is overlap in the types of secondary injury mechanisms triggered by all three conditions, such as inflammation, oxidative stress, and cellular death/regeneration [41–45].

Acquired Neurological Disorders

Acquired neurological disorders represent injuries that affect the central nervous system (CNS) in the form of one or more diverse insults to the brain or spinal cord. Since the CNS controls the functionality of other organs, an array of symptoms and deficits can result, including cognitive, motor, and emotion/behavior issues [46]. Many of these symptoms and deficits are ultimately associated with poorer health and quality of life [47–49], which may influence the ability to return to normal roles (e.g., work, family, athletics) [50, 51]. Considered together, acquired neurological disorders are one of the leading causes of disability. Progress in developing diagnostic tools and effective therapies has been limited by the absence of biomarkers measurable in accessible biological fluids that reflect the pathology in CNS tissue. Since it is rarely practical to biopsy CNS tissues, it has been difficult to assess the relationship between molecules expressed in neural tissues and peripheral biomarker levels. This is of critical importance, since identifying biomarkers of central origin that can be detected peripherally would facilitate a better understanding of the CNS microenvironment in acquired neurological disorders. This would be especially helpful for patients who do not require neurosurgical interventions or shunts, which provide direct access to neural tissue and CSF. Detecting

exosomes in peripheral blood is both practical and clinically relevant. Exosomes are known to readily pass from the brain, through the blood-brain barrier (BBB), and into the peripheral circulation. One study suggests that BBB-derived exosomes associated with amyloid beta (Aβ) can contribute to the Aβ pathology and deposition seen in neurodegenerative diseases such as AD [27]. More recently, efforts have been made to exploit the natural transport mechanisms of exosomes as potential therapeutic delivery vesicles. A 2011 study demonstrated that intravenously administered exosomes containing siRNA could be delivered to mouse brain by crossing the BBB [52]. Thus, it is possible to deliver exosomes to the brain and distribute cargo proven to be a useful therapy to combat the consequences of acquired neurological disorders. Moreover, the ability of exosomes to cross the BBB makes them relevant to conditions other than TBI, SCI, and stroke, though this is beyond of the scope of this review.

This information could guide the development and testing of therapeutics, and may also be relevant to precision medicine initiatives aimed at personalizing therapy based on individual characteristics. Ultimately, the evaluation of exosomal cargo could inform the choice of therapy. In addition, exosomes themselves could be administered therapeutically, since in pre-clinical studies, exogenous administration of exosomes results in beneficial effects on physiological and behavioral endpoints [14, 19].

Exosomes are released from all types of brain cells (Fig. 1) [54], but remain understudied in the context of acquired neurological disorders. Still, exosomes are worth pursuing considering the promising evidence in neurodegenerative conditions which share important features with acquired neurological disorders. Thus, diagnostic or therapeutic approaches addressing neurodegenerative pathologies may be of benefit for TBI, SCI, and stroke patients. For example, exosomes have shown promise in the contexts of AD/dementia [55–57], Parkinson's disease [58–60], amyotrophic lateral sclerosis [61–63], and Huntington's disease [64–66]. Not only does building evidence related to exosomes in TBI, SCI, and stroke adds to the evidence gleaned using traditional biomarkers (e.g., DNA, RNA, protein), it also offers some advantages over these more well-studied alternatives. For example, circulating pro-inflammatory cytokines in serum after brain injury may be peripheral in origin due to the confounding effects of polytrauma or other factors (e.g., exercise) [67, 68]. Likewise, circulating RNA may be of peripheral origin, making it potentially less useful as a diagnostic or prognostic indicator. Double-stranded DNA as well as mitochondrial and chromosomal DNA has also been identified within exosomes [69, 70]. Thus, by identifying exosomes with centrally derived markers on the outside, any protein, RNA, or DNA contained within can be more reliably considered indicative of the CNS microenvironment. Since in CNS disorders, only certain cell types may be affected, identifying evidence of damaged cells peripherally that contain signature cargo reflecting the acquired neurological disorder is promising. Still, there may be diffuse effects that alter exosomes beyond the site of injury. For example, a pre-clinical TBI study using a unilateral CCI model found differentially expressed exosomal miRNA mostly on the ipsilateral (i.e., injured) side of the brain, with only miR-146 dysregulated bilaterally [15].

The purpose of this review is to capture the state-of-the-science surrounding exosomes in the context of acquired neurological disorders. Due to the low number of published studies, each will be summarized and followed by a synopsis of the existing evidence. This review will also suggest areas for future research to improve the clinical treatment of these devastating conditions; but first, an introduction to the acquired neurological disorders of interest in this review (TBI, SCI, and stroke) is provided.

Traumatic Brain Injury

Blunt traumatic brain injury (TBI) is a form of acquired injury to the brain due to an object contacting the skull or sometimes brain tissue with a rotational injury, axonal injury, or a combination. There are many causes of TBI; more common are falls, motor vehicle accidents, assaults, and sports-related head impacts [71]. Typically, a TBI is classified based on its severity (e.g., mild, moderate, severe), as well as the mechanism of injury (e.g., blunt-force, penetrating). TBIs affect individuals across the life span, and represent a significant cause of death and disability worldwide [72]. In the United States (U.S.) alone, there are approximately 2.8 million emergency department visits, 282,000 inpatient hospitalizations, and 56,000 deaths attributable to TBIs each year [73, 74]. In addition to the high prevalence, TBIs are associated with very high direct and indirect costs associated with death, healthcare costs, and the consequences of disability [75]. Moreover, despite high health care utilization, a recent estimate shows that disability after TBI remains common, with 3.2 million individuals living with one or more TBI-related disability in North America alone [76]. Overall, TBI affects countless individuals worldwide every year, many of whom go without diagnosis or treatment. Since some individuals are largely asymptomatic and/or underreport their symptoms, objective markers of injury to support accurate diagnosis and prognosis are needed; exosomes represent a promising avenue for biomarker discovery, as described in detail later. There are no FDA-approved interventions to mitigate TBI pathology and subsequent symptoms. Moreover, given the high degree of variability in TBI symptoms and recovery profiles, exosomes may provide insights regarding which patients to follow more closely as well as inform clinical management to attenuate symptoms and deficits.

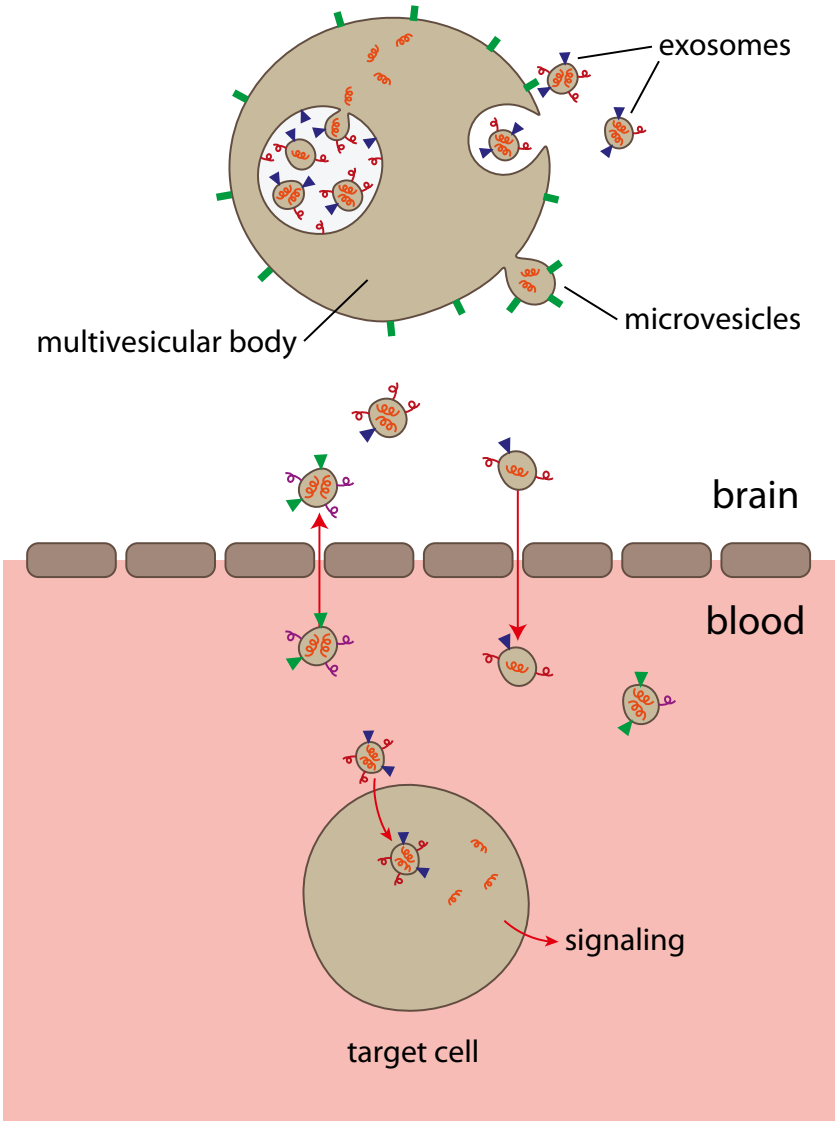

Fig. 1 This figure depicts key features of exosomes, including their release following fusion of a multivesicular body with the plasma membrane (vs. microvesicles which bleb directly off the membrane), ability to cross the blood-brain barrier, and role in cellular signaling. This figure was generated by Nicole Osier and Michael Farmer using Adobe Illustrator based on information from the following sources: [2, 25, 53]

Spinal Cord Injury

Spinal cord injury (SCI) is defined as a form of acquired injury to the spinal cord, which often results in serious disruptions to normal sensorimotor and autonomic functions [77]. SCIs occur due to many of the same causes as TBIs including, but not limited to, motor vehicle accidents, falls, assaults, and sports-related traumas [78]. According to the National SCI Statistical Center, there are approximately 17,000 new SCI cases in the U.S. each year [79]. Subsequently, SCI is associated with significant healthcare costs, the average lifetime expenditure for treating a patient with a SCI ranges between $500,000–$2 million USD [80]. The classification of SCIs is typically based on the location of the injury [the cervical (C), thoracic (T), or lumbar (L) vertebrae affected], as well as the neurological and functional impairments that arise as the result of injury. SCI severity is commonly graded using the guidelines outlined in the American Spinal Injury Association (ASIA) impairment scale [81]. The chronic complications of SCI often include dysfunction in the respiratory, cardiovascular, genitourinary, and gastrointestinal systems, as well as increased spasticity of motor neurons throughout the body. Following SCI, up to 80% of patients report musculoskeletal, visceral, and/or neuropathic pain, which often persist chronically and may require long-term pharmacological and psychotherapeutic intervention [82]. Exosomes may represent an avenue for development of therapeutics capable of improving outcomes of SCI.

Stroke

Stroke occurs when blood flow through a vessel to or within the brain is interrupted, by a blockage or bleed, resulting in dysfunction and death of the affected brain cells. Resulting secondary injury processes can

compromise more distal cells [83]. The American Heart Association reports that approximately 795,000 U.S. citizens suffer a stroke annually, resulting in significant morbidity and mortality [84]; indeed, stroke is the fifth leading cause of death in the U.S. The total direct cost of stroke care in the U.S., including inpatient/outpatient health care services, medications, and home health care, is estimated annually at over $193 billion dollars, over twice the direct costs of cancer [84]. Complications following stroke include decreased mobility and cognitive ability, aphasia/dysarthria, and anxiety and depressive symptoms; complications limit social interactions for survivors [85] and have long-term detrimental consequences on quality of life [86]. There are two major types of stroke [83, 87]: (1) hemorrhagic stroke, which results from bleeding in the brain often caused by a weakened arterial wall (i.e., aneurysm) [87]; and (2) ischemic strokes which lead to brain tissue death caused by a blockage, often due to atherosclerosis or a clot in a cerebral blood vessel supplying oxygen and nutrients to the brain [83]. Ischemic strokes account for the most common type (87%) of strokes [88] and are further subdivided into large vessel disease, small vessel disease, and cardioembolism [89]. As with TBI and SCI, exosomes may represent a promising prognostic biomarker and therapeutic avenue for stroke [90, 91].

Methods

Between October 18, 2016 and April 27, 2016, primary literature searches were conducted using the following online databases: PubMed, PubMed Central (PMC), Google Scholar, and The Cochrane Database. The following search terms and truncations (*) were used, alone, or in combination with standard Boolean operators (AND; OR; NOT): exosomes; exosom*; traumatic brain injury; TBI; brain injury; brain trauma; stroke; ischemia; ischem*; spinal cord injury; SCI; neurological injury; neurodegeneration; neurodegenerat*; cell-free; extracellular vesicles; vesicles. The following Medical Subject Heading (MeSH) terms were also added to the searches: exosomes; brain injuries; neurodegenerative diseases; stroke; cerebrovascular accident; apoplexy; brain ischemia; cerebral ischemia. Secondary literature searches were performed using the bibliographies of relevant manuscripts identified during primary searches. Following preliminary screening of the title and abstract for relevance, over 100 full-text articles were assessed for the following inclusion criteria: (1) studied TBI, SCI, or stroke in either humans or animals; (2) either isolated and assessed exosomes or tested their therapeutic potential; and (3) articles that were originally written in English or subsequently had an English translation published. In total, ten articles were identified that met the abovementioned inclusion criteria, four of which focused exclusive on TBI, one on both TBI and SCI, and five on stroke.

Results

Exosomes in Traumatic Brain Injuries

To date, four studies were published that examined exosomes in the context of TBI. All four were animal studies; one study was performed with rats [14, 25] and three were performed with mice [15, 19]. Published studies differed with respect to methodological considerations, including the method of inducing the TBI, techniques used for exosomal isolation/enrichment, and study goals. Only two studies tested the therapeutic potential of exosomes in the context of TBIs [14, 19]; both showed beneficial effects of EV therapy, including improved cellular outcomes (e.g., attenuated inflammation, increased generation of both newly formed endothelial cells and neurons) [14] and attenuation of post-injury cognitive deficits (e.g., reduced sensorimotor deficits on the foot fault test, improved spatial learning on the Morris water maze) [14, 19].

One study exposed C57BL/6 mice to TBI modeled using the controlled cortical impact (CCI) model or sham (control) surgery resulting in what would be considered to be a moderate to severe brain injury; mice were sacrificed 7 days after surgery and exosomes were isolated from the cerebellum, brain stem, and both hemispheres based on the presence of exosomal markers (CD9, CD63, CD81, HSP70, and TSG101) [15]. This study was the first to profile miRNA in exosomes isolated from harvested brain tissue after a TBI [15]. Specifically, RNA-sequencing revealed miR-212 was downregulated, whereas miR-21, 146, 7a and 7b were upregulated, with the largest fold increase being in miR-21 after CCI [15]. The authors of this study were especially interested in the upregulation of miR-21 which has known neuroprotective roles. A key finding of this study was that microglia may be activated by the entry of neuronally derived exosomal cargo [15]; this finding warrants ongoing inquiry to better understand the origins and consequences of exosomes.

A second mouse study sought to test a novel point-of-care tool to isolate and detect brain-derived exosomes with a smartphone-based μ MED chip [25]. In this study, exosomes were obtained from three sources: (1) a cell culture model of murine cortical neurons, (2) a pre-clinical model of mice exposed to mild TBI induced using CCI (or sham control), and (3) a pre-clinical model of mice exposed to mild TBI induced using blast (or sham control) [25]. In cell culture, a stretch model of injury demonstrated increased levels of GluR2+ exosomes in injured cortical neurons, as compared to non-injured neurons ($p = 0.003$). The smartphone-based tool was effective at isolating and detecting exosomes, which were enriched for Glutamate receptor 2 (GluR2), a protein primarily

expressed in the brain making it a good central marker [25]. This protein was also found to be endocytosed after brain trauma leading to further cellular injury; thus, this protein is implicated in TBI pathology [92, 93]. Exosomes from the two mouse models were isolated from serum; GluR2+ exosomes were elevated in both injury models compared to the respective sham control groups [25]. In addition to being the first to study exosomal GluR2+ levels, this study was strengthened by its methodological advancements. Exosome sample preparation typically takes over 24 h using standard methods; however, the point-of-care tool tested in this study reduces the wait time to less than 1 h from the time of sample collection until the time of obtaining results [25]. Monitoring the counts and cargo of GluR2-containing exosomes may provide insights into the acute and chronic pathology associated with TBIs [25]. Future directions include expanding the platform to examine exosomal cargo and potential opportunities for clinical translation [25].

The therapeutic potential of exosomes has also been explored in the context of TBIs. A third study induced TBI in Wistar rats using the CCI model and examined the therapeutic effects of cell-free exosomes on outcomes related to neurovascular remodeling and functional recovery [14]. The TBI-exposed group was further subdivided based on whether they were administered exosomes derived from mesenchymal stem cells (MSC) or phosphate buffered saline (PBS) control solution 24 h after CCI or sham induction [14]. The key findings in this study were that the administration of MSC-derived exosomes led to physiological changes, including increased angiogenesis, vascular density, and neurogenesis within the dentate gyrus [14]. EV therapy also leads to decreased neuroinflammation; however, there was no effect of exosomes on the cortical lesion volume, compared to PBS control [14]. The physiological changes in the exosome-treated group were associated with enhanced spatial learning on the Morris water maze and better sensorimotor outcomes assessed using the neurological severity score [14]. These findings may lay the foundation for development of novel therapeutic approaches for treatment of TBIs. Future studies should attempt to identify the specific constellation of miRNAs and growth factors that contribute to the therapeutic benefits. Considerations for individualizing exosomal therapies and/or tailoring the therapeutic regimen should also be explored.

The final TBI study identified was the second to test MSC-derived EVs as a TBI therapy (vs. control solution) in mice. A novel in vitro protocol, capable of producing large numbers of EVs with anti-inflammatory properties, was developed and the therapeutic EVs were tested in an in vivo CCI model using 7–8-week-old male C57BL/6J mice [19]. In this study, MSC-EVs from the bone marrow of a human donor (or PBS control solution) were administered 1 h after injury (or sham control). Among mice exposed to TBI, EV therapy was associated with reduced neuroinflammation when assessed 12-h post-injury, in a dose-dependent manner. This was evidenced by progressively lower levels of interleukin (IL)-1β in brain tissue with increased dose of MSC-EVs [19]. Moreover, EV therapy improved cognitive function (e.g., spatial learning and pattern separation) after TBI, compared to the control solution [19]. This study addressed limitations of previous studies including the development of novel protocols that facilitated the production and isolation of high volumes of EVs from bone marrow and evaluation of dose-response patterns [19].

Exosomes also hold promise for individuals with multiple sub-concussive hits, and the subsequent risk of chronic traumatic encephalopathy (CTE). This is a timely application for exosomes, since CTE has become an area of increased research emphasis due to its link with repeated head traumas in athletes [94]. In the context of National Football League players with CTE (vs. healthy controls), elevated levels of tau-positive, exosomal concentrations, suggest that exosomal tau in peripheral blood samples may serve as a clinically available, diagnostic biomarker for CTE [95].

Exosomes in Spinal Cord Injuries

Only a single published study was identified that examined exosomes in the context of SCI. This study examined exosomes isolated from the CSF of human SCI patients as well as exosomes in rats exposed to SCI. Notably, the sample used to address the clinical aim also included a small number of individuals with TBI, as well as uninjured controls [16]. Thus, this study also makes some contribution to the TBI knowledge base, though it was not summarized above. Additional pre-clinical and clinical studies are needed to garner further evidence of the potential for exosomes to guide care and subsequently improve outcomes of SCI.

The single published SCI study examined the clinical occurrence of inflammasomes in SCI/TBI patients, followed by a pre-clinical examination of the effects of therapeutic exosomes targeted against inflammasomes in a rat SCI model [16]. First, in the clinical portion of the study, post-injury spinal cord motor and cortical neurons from nine banked human tissue samples were demonstrated to have elevated levels of nucleotide-binding and oligomerization domain (NOD)-like receptor protein-1 (NLRP1) inflammasome (which regulates caspase 1 activation and processing of IL-1β and IL-18), caspase 1, and a caspase recruitment domain (ASC) as well as the presence of NLRP1 within human CSF exosomes versus uninjured controls. Thus, the clinical portion of the study demonstrated the elevation of inflammasomes within human CSF exosomes following CNS injury. Second, in the pre-clinical portion of the study, a rat model of moderate contusive SCI using adult female Fischer rats evaluated the use of exosomes to target this CNS inflammasome activation as compared to sham control rats. The exosomes were isolated from cultured rat embryonic cortical neurons. Two types of exosomes were

compared: therapeutic exosomes were siRNA labeled using green fluorescent protein against ASC, versus unmodified exosomes, which had scrambled siRNA [16]. In vitro, therapeutic exosomes were found to successfully deliver their cargo, resulting in blocked activation of inflammasome signaling. In vivo, exosomes loaded with siRNA against ASC protein resulted in lower ASC expression (76%), in addition to significantly lower caspase 1 activation and IL-1β processing, when compared to SCI rats treated with unmodified exosomes [16].

Exosomes in Stroke

A total of five studies were identified that examined exosomes in the context of ischemic stroke; no published studies examined exosomes in hemorrhagic stroke. Of these, one used clinical data, while four used pre-clinical models. Among the pre-clinical studies, the models and methods varied and included but were not limited to middle cerebral artery occlusion [20], carotid artery occlusion [17], and umbilical cord occlusion for in utero modeling of stroke [21].

One study used in vitro and pre-clinical methods to study stroke [23]. Wistar rats were exposed to a focal cerebral ischemia model that used intraluminal occlusions, either transiently or permanently, to the middle cerebral artery [23]. In this study, cultured human brain endothelial cells were also used to isolate exosomes. In culture, oxygen-glucose deprivation resulted in lower exosomal miR-126 levels [23]. In the rat model, the results suggested that exosomal miR-126 obtained from peripheral blood was more sensitive to the effects of cerebral ischemia, responding to both mild and severe ischemic episodes. However, total serum miR-126 may be a more specific indicator of the severity of ischemia [23]. Taken together, the study suggests that while both blood and exosomal miR-126 levels are informative for detecting cerebral ischemia, serum levels increased sensitivity to qualifying the severity of ischemia [23]. Future directions include exploring central and peripheral miRNA signaling, determining the source of miR-126 which may be vascular or non-vascular, and extending this work to more diverse samples [23].

Another study examined induced stroke in C57BL/6 mice using a model of hypoxic ischemic brain injury via cerebral artery occlusion [20]. This study examined the therapeutic effects of EVs derived from human bone marrow MSCs and found their therapeutic effect to be comparable to MSCs alone [20]. Only MSC-EVs were found to attenuate post-ischemic peripheral immune responses (B and T cell activity); however, infiltration of immune cells into the cerebral tissue was not modulated by MSC-EVs [20]. The finding that MSCs and MSC-EVs comparably promoted neurogenesis and angiogenesis post-stroke might suggest that the active component of MSC therapy is due in part to the administration of exosomes, though this remains to be empirically established [20].

A third study tested the therapeutic effects of exosomes in the context of hypoxic-ischemic injury in pre-term ovine brains modeled via umbilical occlusion [21]. In this study, EVs were derived from human bone marrow MSCs and administered on the day of umbilical cord occlusion (day 0) and again on day 4 [21]. In this study of pre-term brains, the therapeutic administration of MSC-EVs reduced the number and duration of seizures; MSC-EVs also preserved the sensitivity of the baroreceptor reflex, which was associated with an observed tendency to prevent hypo-methylation. There was no effect of MSC-EV therapy on apoptosis or neuroinflammation [21]. Future directions to build on this work include evaluation of the temporal effects of MSC-EV therapy by including additional endpoints and comparing administration of MSC-EVs to MSC alone, given the results of the abovementioned study [21].

The fourth study tested the therapeutic effects of MSC-derived exosomes obtained from stromal cells in the bone marrow on stroke outcomes modeled using both an endothelial cell culture model and a bilateral carotid artery ligation model of ischemic-reperfusion injury in adult Sprague-Dawley rats [17]. In this study, two types of MSC-derived exosomes were tested for their therapeutic potential: exosomes treated with 500 μL/mL Buyang Huanwu decoction (BYHWD) versus untreated exosomes [17]. A commercially available kit was used to isolate exosomes and exosomal markers CD9 and CD81 via western blot analysis; exosomes were visualized using electron microscopy. A key finding of this study is that BYHWD-treated exosomes resulted in higher expression of angiogenic miRNA in cell culture; in the rat model, expression of vascular endothelial growth factor (VEGF) and Ki-67 (also known as MKI67) was increased, which was associated with augmented vascular density after stroke [17].

The fifth and final study examined exosomes using 65 acute ischemic stroke patients and 66 healthy volunteers who did not have a history of stroke [18]. Patients provided serum samples which were used to isolate exosomes, and western blot analysis was used to assess levels of established exosomal markers (CD9, CD63, and CD81) [18]. When compared to controls, individuals with stroke had significantly higher concentrations of exosomes in serum, as well as significantly (all p's < 0.01) higher median levels of miR-9 and miR-124, two micro-RNAs implicated in regulation of gene expression [18]. A second key finding was that exosomal levels of both miR-9 and miR-124 were positively correlated with total score on the National Institutes of Health Stroke Scale and were also correlated with the overall volume of the infarct as well as the concentration of the inflammatory biomarker interleukin (IL)-6 in serum [18]. Overall, this study suggested that exosomes obtained from serum samples are helpful in identifying patients with acute ischemic stroke and can be used to gain insights into the likely extent of damage [18].

Pre-clinical models suggest that exosomes may have applicability as indicators of ischemic stroke injury severity [23] as well as delivery of potential therapeutics [17, 21] such as mitigation of the immune response [20]. Similarly, the clinical study suggests clinical utility of CNS-derived exosomes as markers of acute ischemic stroke, including injury severity [18]. Future studies should enrich for exosomes of central or at least nerve-cell origin to enhance the quality of the evidence. Continued exploration of the therapeutic effects of exosomes in the context of pre-clinical stroke models is needed, and, if warranted, translation of exosomal therapies to clinical trials should be pursued.

Discussion

Exosomes As Clinically Relevant Biomarkers

Compared to traditional biomarkers, the ability to localize the cell type of exosome origin enhances their diagnostic, prognostic, and pharmacodynamic utility. Exosomes are derived from a variety of tissues; thus, their cargo represents the microenvironment of the cell type from which they originated. Within the context of acquired neurological disorders, peripheral markers are needed that are indicative of central changes. By tailoring the isolation and enrichment methods, exosomes offer information on the nature and degree of CNS damage and the sites or cell types affected. In this way, exosomes provide a critical advantage over traditional systemic, peripheral biomarkers (e.g., levels of protein in serum or plasma). There are also several practical issues of peripheral biomarkers that can be mitigated by using peripherally obtained, but centrally derived, exosomes. For example, proteins and nucleic acids in the peripheral circulation are relatively unstable due to the abundance of proteinases and nucleases in plasma, whereas exosomes have known stability, due in part to their structure which protects their cargo from degradation and preserves their biological activity [96].

Some potential directions for studies of exosomal biomarkers include those involved in inflammation, neurodegeneration, and other pathological cascades activated in acquired neurological disorders. Past studies have implicated inflammatory biomarkers that feed into apoptotic pathways such as TNFα, IL-6, and IL-10 using peripheral samples, and ASC, NALP-1 using CSF samples to study the pathology associated with TBI [97, 98], stroke [99–104], and SCI [105, 106]. Alternatively, proteins traditionally used as markers of neurodegenerative diseases including those related to amyloid plaques and neurofibrillary tangles, such as Aβ-40, Aβ-42, and tau, which have been implicated in TBI [107, 108], stroke [109–111], and SCI [112].

Exosomes as Therapy

The therapeutic applications of exosomes are of great interest with many efforts underway. Three features of exosomes make them an excellent therapeutic agent, namely, they can effectively deliver functional molecules (e.g., siRNA, MSCs, miRNA) to target cells [113–116], their ability to rapidly pass through the BBB [117], and their known low immunogenicity [118]. Sources of exosomes administered therapeutically to date include MSCs [119] and induced pluripotent stem cells [120], though the therapeutic effects remain to be clarified. In these studies, the ultimate goal is to modulate intercellular communication networks and improve outcomes for patients with acquired neurological disorders [121]. Efforts to engineer the cargo are underway with publications to date exploring let-7 [122], miR-9 [123], miR-124a [124], and miR-204-5p [98]. Likewise, efforts to engineer targets are also underway, with published literature exploring connexin 26 [125], EGFR [126], notch [127], and tenasin [128]. Several delivery mechanisms of therapeutic exosomes have been explored including both intranasal [129, 130] and systemic routes [131–133]. In addition to being used as a therapy, studying sequential samples of exosomes may prove useful for monitoring the effects of therapies on pathophysiological processes. It may also be the case that therapies can alter endogenous exosomes, leading to subsequent improvements in downstream activities. One study found that microenvironmental enrichment was associated with generation of miR-219-containing exosomes which were associated with increased CNS myelination, and reduced oxidative stress [134].

Remaining Gaps in Knowledge and Future Directions

Reliance on pre-clinical methods is a limitation of most of the studies examining exosomes in the context of acquired neurological disorders. There remains a substantial gap in the clinical knowledge base surrounding the role of exosomes in clinical cases of TBI, SCI, and stroke. Many studies are also limited by small, homogenous samples, requiring validation in larger cohorts. For example, females are underrepresented in many of the pre-clinical and clinical studies, which limit the generalizability of the findings [14, 15, 23]. Further pre-clinical and clinical research will be required to supplement the current state-of-the-science. Ensuring that the exosomes/EVs examined are derived from the desired population of EVs is important. A small proportion of non-target EVs have been reported in some studies [19]. Future clinical studies are needed to fully understand how exosomal biomarkers can be used for diagnostic, prognostic, and pharmacodynamic purposes.

For studies exploring therapeutic effects of exosomes, dose-response considerations should be explored, as should the distribution of therapeutic exosomes, their cargo, and how to increase the specificity to target cells in the CNS

[14]. Moreover, the specific mechanism by which exosomes pass through the BBB should be further examined to increase the efficacy of key therapies. Some future directions include further exploration of exosomal miRNAs and growth factors and their effects on recovery [14].

Conclusion

Exosomal release is highly specific to the microenvironment from which it originates. For these reasons, exosomal cargo is an ideal biomarker to better understand the mechanisms underlying TBI, SCI, and stroke pathology. The stability of exomes in peripheral circulation suggests that they could be used both acutely and chronically and may be useful indicators of recovery. Exosomes can also transfer their contents to recipient cells, making them candidates for the therapeutic administration of key proteins or drugs. The methodological isolation and profiling of cargo in circulating exosomes can provide novel, objective diagnostic biomarkers for acquired neurological disorders. This field of research, especially within the context of acquired neurological disorders such as those described in this review, remains in the early stages. Further research is required to optimize and improve isolation techniques for greater CNS specificity and to understand fundamental exosome biology, in relation to these disorders, prior to larger clinical studies. Altogether, recent studies investigating the multiple roles of exosomes shed light on an opportunity to improve diagnostic and prognostic methods, and ultimately patient outcomes, in the clinical setting following a TBI, SCI, or stroke.

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Appendix 39

The Role of Pain Catastrophizing in Cognitive Functioning Among Veterans with History of Mild Traumatic Brain Injury

PAPER OR POSTER ABSTRACT SUBMISSION DETAILS:

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ABSTRACT PROOF--PLEASE REVIEW CAREFULLY:

TITLE: The Role of Pain Catastrophizing in Cognitive Functioning Among Veterans with History of Mild Traumatic Brain Injury
AUTHOR(S): S. N. Hoffman[1], M. S. Herbert[1], L. D. Crocker[1], N. E. DeFord[1], A. V. Keller[1], S. M. Jurick[1], M. Sanderson-Cimino[1], M. Lee[1], R. S. Vasudevan[1], A. J. Jak[1]
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ABSTRACT BODY:
Objective : Cognitive difficulties and chronic pain are highly prevalent among Veterans with a history of mild traumatic brain injury (mTBI). Moreover, those with mTBI history report chronic pain as a significant problem at a higher rate than those with moderate or severe TBIs. Pain catastrophizing, the exaggerated appraisal of the negative components of an actual or anticipated pain experience, has been associated with several adverse clinical outcomes, including cognitive deficits. However, relationships between pain catastrophizing and cognitive functioning in Iraq/Afghanistan Veterans with a history of mTBI has not been well characterized thus far.
Participants and Methods: 35 Iraq/Afghanistan Veterans in the post-acute phase following mTBI with valid neuropsychological testing completed questionnaires assessing TBI injury variables, pain catastrophizing, quality and intensity of pain, depression, and PTSD symptoms. Executive functioning, processing speed, learning/memory, and attention composites were created and entered as dependent variables into separate linear regressions to examine relationships with pain catastrophizing.
Results : Pain catastrophizing was a significant predictor of executive functioning, even when controlling for TBI injury variables, gender, pain intensity, depression, and PTSD symptom severity ($\beta = -.020$; $p = .037$). Pain catastrophizing was not a significant predictor of processing speed, learning/memory, or attention.
Conclusions : Pain catastrophizing is associated with worse executive functioning in Veterans with mTBI, even after controlling for TBI injury variables, gender, pain intensity, and psychiatric symptoms. This finding suggests that understanding not just severity of pain but one's interpretation of pain has implications for cognitive functioning. Treatments designed to alter how individuals cope with pain may also improve executive functioning.

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Appendix 40

Risk of Dementia Outcomes Associated With Traumatic Brain Injury During Military Service

EDITORIAL

Risk of Dementia Outcomes Associated With Traumatic Brain Injury During Military Service

Kimbra Kenney, MD; Ramon Diaz-Arrastia, MD, PhD

The chronic effects of traumatic brain injury (TBI), particularly dementia and related neurodegenerative disorders in military veterans, have become an intense research focus. It has long been recognized that moderate to severe TBI in early life or midlife is associated with increased risk of late-life dementia.[1] The association between severe TBI and dementia in civilians has relied on epidemiology of patients with remote TBI and late-onset Alzheimer disease (AD) (usually after age 65 years) and other dementias. Epidemiologic studies have had mixed results of risk of developing dementia after mild TBI (mTBI).[2-6] Earlier community-based and population-based studies found no increased association between mTBI with loss of consciousness (LOC) and late-onset dementia or AD.[5,6] More recent studies have shown an association between TBI and earlier-onset dementia, suggesting an association between number and severity of head injuries and increasing dementia risk.[3,4] Discordance across epidemiologic studies likely results from methodological differences as well as diagnostic uncertainty of both TBI and dementia, compounded by the current absence of validated clinical criteria for TBI-associated dementia.

Related article

Military veterans are at high risk of experiencing moderate and severe TBI compared with civilians, a risk not limited to combat-exposed veterans.[7] Additionally, veterans, particularly ones who served in combat, have a much higher rate of mTBI, which has not always been recognized as injuries at the time of occurrence, particularly before 2008. Careful studies from the Operation Enduring Freedom–Operation Iraqi Freedom era indicate 15% to 20% of deployed service members have had 1 or more mTBIs[8]; multiple mTBIs are common.[9] Although mTBIs were not considered clinically significant injuries and were not monitored by the military medical system before the Iraq conflict, studies from the Vietnam era show that mTBI exposure was comparable with levels reported in Iraq and Afghanistan.[10] With recent reports of chronic traumatic encephalopathy in active-duty service members,[11] it is urgent to understand long-term effects of mTBI among veterans, in hopes of developing preventative strategies. However, few studies have focused on the association between mTBI and dementia among active-duty personnel and veterans, despite their higher TBI exposure compared with civilians. In this issue of *JAMA Neurology*, Barnes et al[2] performed a cohort analysis and found a 2-fold increase in dementia diagnosis risk among veterans with a prior diagnosis of mTBI without LOC.

Barnes et al[2] studied a cohort of patients who had received a TBI diagnosis in the Veterans Administration (VA) system between 2001 and 2014.[2] They identified participants with and without TBI through 2 VA databases, the National Patient Care Database (n = 328 192; 91.7% of the total), and the Comprehensive TBI Evaluation database (CTBIE) (n = 12 714; 3.6%); 16 652 participants (4.7%) were in both databases. They classified the most severe TBI as the index TBI, classified as none, mild without LOC, mild with LOC or LOC status unknown, or moderate or severe. They classified dementia per a comprehensive list of *International Classification of Diseases, Ninth Revision (ICD-9)* codes. They accounted for medical and psychiatric comorbidities, and models were adjusted sequentially for demographics and medical and psychiatric comorbidities, along with sensitivity analyses stratified by the TBI data source. They found 4698 cases of incident dementia in veterans without TBI and 10 835 cases in veterans with TBI; the adjusted hazard ratios (HR) for dementia was 2.36 for patients with mTBI without LOC, 3.19 for those with mTBI with LOC or LOC status unknown, and 3.77 for those with moderate to severe TBI. Although the participants in the CTBIE database were significantly younger than those in the National Patient Care Database, the HR for each TBI group were similar. Both showed an association with increasing TBI severity.

Not only is this the first epidemiological study among a military cohort receiving care through the VA health care system (to our knowledge), it is among the largest epidemiological studies to date, and it confirms earlier findings of an association between TBI and dementia. One of the strengths of this study is the large sample size. Another is the reliance on clinical evaluations rather than self-report for TBI diagnoses and severity among participants in the CTBIE database. Also, a careful sensitivity analysis was performed before combining results from 2 demographically disparate databases, and similar HRs were found in both. Finally, the HRs found show a dose effect of TBI severity, which enhances confidence in the robustness of the findings.

There are limitations to this study, which the authors largely addressed. Most are inherent to a database analysis, which has the advantage of large sample size that strengthens statistical correlations but makes the investigators rely on clinical diagnoses and data obtained by others in a potentially nonuniform manner. The largest limitations are reliance on *ICD-9* coding for clinical diagnoses and the completeness of the databases. Also, some TBI *ICD-9* codes are not easily categorized into the TBI severity groupings used (eg, participants with TBI coded for postconcussion syndrome were clas-

sified as mTBI with LOC status unknown; clinical parameters of the TBI were unspecified). The coding limitations of the *ICD-9* are more problematic in the National Patient Care Database, the source of most participants with TBI (85%) and 98.9% of the 178 799 participants without TBI. The investigators included participants in their analysis from 2001 to 2014 from the National Patient Care Database database but only from 2007 to 2014 in the CTBIE database, which launched in 2007. The diagnoses and criteria in the Department of Defense and VA health care systems evolved during this period, as show by the considerably higher numbers of TBI diagnoses in the Defense and Veterans Brain Injury Center database after 2007 compared with 7 years prior. This likely resulted in underrepresentation of mTBI without LOC during the earlier years compared with TBI diagnoses with greater severity. Further, the databases could not differentiate single TBIs from multiple TBIs in their analysis and could not analyze effects of repetitive TBI on later development of dementia. The high prevalence of exposure to multiple mTBI in veterans is 1 factor that distinguishes them from civilians with TBI. Another differentiator is mechanism of injury. The authors describe the high numbers of blast-related mTBI among military personnel but were unable to capture the mechanisms by which TBIs were acquired. They assert that TBIs in this study were likely combat related because the index TBI occurred during the years of the Iraq-Afghanistan conflicts, but Department of Defense data suggest that more than 75% of TBIs among their personnel occur in garrison or training.[12] Finally, the authors note that they only included participants with a new diagnosis of dementia more than 2 years after the index TBI, but with *ICD-9* coding limitations, they could not reliably differentiate incident dementia developing at some latent period after recovery from a TBI-associated static encephalopathy miscoded as neurodegenerative dementia.

The mechanism by which TBI leads to dementia is unknown. It is asserted that TBI-associated dementia is similar to AD,[13] the most common dementia in the general population. However, prior studies on causative mechanisms of dementia associated with TBI have relied on medical records or clinical interviews, which have a low specificity. More recent studies using pathological cohorts have failed to find an association between a history of TBI and AD pathology but did detect an association between synuclein pathology, vascular disease, and TBI exposure.[14] A recent report of Vietnam-era veterans with moderate to severe TBI failed to detect increased rates of amyloid deposits on florbetapir positron emission tomography scans in TBI-exposed veterans.[15] Precise information on how TBI exposure increases risk of dementia in midlife and late life is crucial to developing preventative strategies.

This study[2] provides the best information to date that military veterans are at risk for dementia as a consequence of injuries sustained during their service to the United States. The young mean age of veterans in this study (50 years) raises concerns that this problem will increase as TBI-exposed veterans age. The implications for the military health system, VA health care, and society are profound. Substantial investments in clinical care and neuroscience research will be needed in the next decades to fulfill society's obligations to those who have served our country.

ARTICLE INFORMATION

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Appendix 41

The Role of Pain Catastrophizing in Cognitive Functioning Among Veterans with 1 History of Mild Traumatic Brain Injury

The Role of Pain Catastrophizing in Cognitive Functioning Among Veterans with History of Mild Traumatic Brain Injury

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Conflict of Interest

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Abstract

Objective: To determine the role of pain catastrophizing (PC) in neuropsychological functioning in Veterans with a history of mild traumatic brain injury (mTBI).

Participants: Thirty-nine Iraq and Afghanistan combat Veterans evaluated in the post-acute phase following mTBI.

Methods: Participants underwent psychiatric and TBI clinical interviews, neuropsychological tests, and self-report assessments of PC, pain intensity, depression, and posttraumatic stress disorder (PTSD) symptoms. Cognitive functioning composite scores of executive functioning, processing speed, and learning and memory were created. Composites were entered as dependent variables into separate linear regressions to examine relations with PC.

Results: Greater PC was associated with worse executive functioning and processing speed, even when controlling for confounding variables.

Conclusions: One's interpretation of pain, in addition to pain intensity, has implications for cognitive functioning. Future research is encouraged to determine if adaptive pain coping mechanisms improve cognitive functioning or alternatively, if cognitive rehabilitation strategies reduce PC.

Keywords: Pain catastrophizing, neuropsychological functioning, posttraumatic stress disorder, mild traumatic brain injury, combat, Iraq war

Introduction

Relative to the general population, veterans of Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn (OEF/OIF/OND) are at an increased risk for sustaining a mild traumatic brain injury (mTBI), developing posttraumatic stress disorder (PTSD), and experiencing chronic pain.[1,2] It is estimated that 15% of OEF/OIF/OND Veterans have sustained an mTBI, and the majority of these Veterans have co-occurring PTSD and/or chronic pain.[1,3] While individuals who sustain an mTBI typically return to pre-injury functioning within three months , there have been self-reports of persistent cognitive complaints and cognitive difficulties well past the acute phase.[4] In one sample of OEF/OIF/OND veterans, 67% reported three or more persistent cognitive difficulties for more than three months after an mTBI.[4] However, a growing body of literature supports a mental health etiology of persistent cognitive difficulties in those with a remote mTBI history.[5-7]

In Veterans returning from recent conflicts with mTBI history, research suggests that both PTSD and pain symptoms contribute to the prolongation of cognitive complaints and complicate overall recovery.[1,4] While previous literature has shown that PTSD is associated with impairments in memory, attention, processing speed, and executive functioning in OEF/OIF/OND Veterans with history of mTBI, [8,9] less attention has been given to the role that pain intensity and pain coping play in neuropsychological functioning. Interestingly, in individuals without history of mTBI, several studies demonstrate that pain coping, in addition to pain intensity, is related to cognitive dysfunction.[10,11] Pain catastrophizing (PC) is a coping style characterized by an exaggerated negative appraisal of actual or anticipated pain and feelings of helplessness

in the context of pain. PC is associated with several adverse outcomes, including greater psychological distress, poorer functioning, and deficits in learning and memory in both pain-free and chronic pain samples.[10-13] Given the high comorbidity of pain and positive mTBI screens, the associations between PC and poor outcomes, as well as the paucity of information about pain coping and its relation to cognition in Veterans with mTBI history, the current study examines the role of PC in neuropsychological functioning in a sample of combat Veterans with a remote history of mTBI. Research examining pain coping styles in Veterans who sustain mTBIs may elucidate the atypical protraction of cognitive complaints and difficulties. We hypothesized that higher levels of PC would be associated with worse cognitive functioning across domains, even when controlling for pain intensity.

Methods:

Participants

Participants included 42 OEF/OIF/OND combat Veterans in the post-acute phase following mTBI (M=6.32 years, SD=4.28, range 8 months-21 years since most recent mTBI). Lifetime history of mTBI was assessed and included events both within and outside of deployment and military settings. Participants were recruited as part of a larger neuroimaging study that included Veterans with and without a current diagnosis of PTSD, thus providing a range of PTSD symptoms in the present study. Exclusion criteria included a history of moderate or severe TBI, active substance use disorder, suicidal intent or attempt within the month prior to participation, current psychotic disorder, dementia, non-English speaking, or a history of bipolar disorder. The sample was predominantly male (92.3%), Caucasian (69.2%), and non-Hispanic (71.8%). Participants

had a mean age of 32.69 years (SD=5.80), a range of 12-18 years of education (M=14.72, SD=1.67), and sustained an average of 3.72 lifetime mTBIs (SD=3.40). A total of 69.2% of participants sustained an mTBI resulting in loss of consciousness (LOC; the rest had alteration of consciousness only) and 92.3% reported experiencing posttraumatic amnesia (PTA). In the total sample, 48.7% screened positive for a diagnosis of PTSD, and 28.2% screened positive for major depressive disorder (MDD). At the time of testing, 30.8% of the sample was seeking service connection or an increase in service connection. Because we were primarily interested in the appraisal of actual or anticipated pain as opposed to pain itself, a diagnosis of chronic pain was not a prerequisite for the current study.

Procedure

Participants were recruited from the Veterans Affairs San Diego Healthcare System and Veteran Centers within the local community. The local institutional review board approved the study, and all participants provided informed consent. Participants underwent clinical diagnostic interviews for mTBI and psychiatric disorders followed by a comprehensive neuropsychological assessment and administration of various self-report questionnaires.

Measures

Clinical Assessments

Lifetime history of mTBI (LOC ≤ 30 minutes, PTA ≤ 24 hours) was determined via the Virginia Commonwealth University Retrospective Concussion Diagnostic Interview.[14] Version 7 of the Mini-International Neuropsychiatric Interview (MINI), a structured clinical diagnostic interview, was used to screen for current and lifetime psychiatric disorders according to DSM-5 criteria.[15] The 20-item PTSD Checklist for

DSM-5 (PCL-5) was used to assess PTSD symptom severity.[16] The Patient Health Questionnaire-9 (PHQ-9) was used to measure depressive symptoms.[17] Participants' overall pain intensity was measured via an 11-point Likert scale on the Patient-Reported Outcomes Measurement Information System-Pain Interference questionnaire (PROMIS-PI), which asks participants to rate their pain from 0 (No Pain) to 10 (Most severe pain imaginable) over the past 4 weeks.[18] PC was measured via a 5-point Likert scale on the Pain Catastrophizing Scale, a validated 13-item self-report measure that asks participants to rate various thoughts and feelings experienced during pain ranging from 0 (Not at all) to 4 (All the time).[19] The Pain Catastrophizing Scale is a widely used instrument for measuring catastrophic tendencies related to pain and has been shown to have good to excellent internal consistency (α =.87-.93), high test-retest reliability, and evidence of concurrent, discriminant, and predictive validity.[19,20]

Neuropsychological Functioning

Participants were administered standardized neuropsychological tests of attention, processing speed, learning and memory, and executive function. Measures of processing speed included the WAIS-IV Symbol Search and Coding, and D-KEFS Trail Making Test Visual Scanning, Number Sequencing, and Letter Sequencing conditions.[21,22] The California Verbal Learning Test-Second Edition (CVLT-II) Learning Trials 1-5, Short Delay Free Recall, and Long Delay Free Recall conditions were used to measure learning and memory.[23] Measures of working memory/executive function included the total number correct on trials 1 through 3 of the Paced Auditory Serial Addition Test (PASAT), DKEFS Trail Making Test Number-Letter Switching condition, WAIS-IV

Digit Span Sequencing condition, and the Inhibition condition of the DKEFS Color Word Interference Test.[21,22,24]

Performance validity tests included the Test of Memory Malingering (TOMM) Trial 2 and Retention Trial and the CVLT-II Forced Choice trial, commonly used and well-validated indicators of performance validity.[23,25] A score of 44 or below on either Trial 2 or Retention of the TOMM or a score of 14 or below on CVLT-II Forced Choice indicated performance validity failure.

Data Analyses

The raw scores for the neuropsychological tests were converted into z-scores and averaged to create composite scores for the domains of executive functioning ($\alpha = .808$), processing speed ($\alpha = .848$), and learning and memory ($\alpha = .921$). Cronbach's alpha for each composite indicated good to excellent internal consistency. Higher scores indicated better performance. Correlations between the composite scores, PC, and pain intensity were calculated. In addition, the composite scores were entered as dependent variables into separate linear regression models to examine relations with PC when controlling for age, gender, years of education, overall pain intensity levels, PTSD symptoms, and total number of TBIs. Because depression is also a prominent concern in Veterans with pain, PTSD symptoms, and a history of mTBI (including in the present sample), analyses were repeated controlling for depression symptoms in place of PTSD symptoms. Depression was examined in separate regression models to avoid issues related to multicollinearity, as PTSD and depression were highly correlated ($r = .72$). All analyses were conducted using IBM SPSS, Version 24.

Results

Descriptive information for study variables is summarized in Table 1. <<Insert Table 1>> A total of 39 participants remained in analyses after three were excluded for failure on one or more performance validity test. Bivariate Pearson's correlations between key study variables were examined. There were no significant correlations between pain intensity and any of the neuropsychological functioning composite scores (*p's* > .368). PC was negatively correlated with executive functioning (r = -.39, p = .015) and processing speed (r = -.46, p = .004), but not significantly correlated with learning and memory (r = -.276, p = .093). In our regression models, greater PC remained significantly predictive of worse executive functioning and processing speed after adjusting for age, gender, years of education, pain intensity, PTSD symptoms, and total number of TBIs (see Table 2). <<Insert Table 2>> Moreover, results of regression analyses remained consistent when controlling for depression symptoms instead of PTSD symptoms (see Table 3). <<Insert Table 3>> Results also remained consistent in a follow-up analysis considering current dichotomous PTSD and MDD diagnoses from the MINI within the same model instead of symptom ratings; PC was still significantly associated with executive functioning (p = .015) and processing speed (p = .019), but not learning and memory (p = .075).

Discussion

The primary aim of the study was to better understand the role of pain and pain coping in neuropsychological functioning in OEF/OIF/OND combat Veterans with a history of mTBI. Our results showed that pain catastrophizing - but not pain intensity- was associated with worse executive functioning and processing speed, even when controlling for PTSD and depression symptoms, pain intensity, number of TBIs, and

demographic variables. These findings appear~~re~~ consistent with previous literature[5-7] suggesting that psychological factors are notable contributors ~~, rather than injury characteristics, contribute~~ to persistent cognitive dysfunction after mTBI and adds to the literature by suggesting PC is independently related to neuropsychological functioning in this population.

A recent study of Veterans by Legarreta et al.[11] found that PC was associated with learning and memory but not executive function or attention. However, the sample in Legarreta et al.[11] was atypical of the OEF/OIF/OND Veteran population and included mostly female participants with higher levels of education and no mTBI history. Both the present study and that of Legarreta et al., [11] reported a relation between cognitive functioning and PC, though specific cognitive domains affected may be differentially affected by methodology (e.g., use of effort measures, variation in neuropsychological tests utilized), gender, or other injury variables.

The current study offers PC as a possible risk factor for neuropsychological dysfunction in mTBI outcome. That is, how one interprets pain - as opposed to the pain intensity itself - was associated with greater executive and processing speed dysfunction. PC involves the appraisal of future pain as well as one's ability to manage said pain and is therefore inherently linked to executive function (planning, problem-solving, etc.). Although the idea is speculative, greater PC may drain cognitive resources, thus exacerbating the cognitive effects of mTBI and co-occurring psychiatric distress. Alternatively, cognitive dysfunction may interfere with a person's ability to cope with the adverse effects of co-occurring psychiatric and pain-related distress after mTBI and thus lead to greater levels of PC.

Clinically, PC has been linked to increased utilization of healthcare systems and prescription medications as well as increases in overall negative affect and non-adherence to pain-related treatments.[13,26] The results of this study hold important clinical implications for targeting catastrophic thinking in individuals who have sustained a mTBI and experience ongoing pain. The use of cognitive behavioral therapy (CBT) for chronic pain, which focuses on the reappraisal of pain-related cognitions, may serve as a compelling avenue for mitigating adverse outcomes in this population. Moreover, CBT has been shown to be effective for treating psychiatric disorders and chronic pain in individuals with a history of mTBI. Conversely, cognitive rehabilitation strategies targeting executive function and/or cognitive training for processing speed may improve neuropsychological functioning and in turn reduce PC in this population. Determining potential targets of treatment, such as PC or cognitive functioning, may improve cognitive performance or reduce PC, respectively, and therefore, enhance quality of life in returning Veterans experiencing PTSD, pain, and postconcussive symptoms.

To our knowledge, this is the first study to investigate the relation between PC and neuropsychological functioning in OEF/OIF/OND combat Veterans with a history of mTBI. A limitation of this study was the predominantly male and modest sample size. In addition, the sample consisted of individuals with and without a PTSD diagnosis. However, the high rate of comorbid PTSD (48.7%) in our sample is typical for OEF/OIF/OND Veterans with mTBI[27] and results remain consistent when controlling for PTSD symptomatology, as even subclinical PTSD symptoms may contribute to cognitive dysfunction. Strengths of the study include use of a structured TBI interview and a comprehensive battery of well-validated neuropsychological tests and effort measures.

However, given the myriad performance validity tools available, assessing the impact of use of other validity indices in pain catastrophizing samples would be a valuable future direction. Future studies would also benefit from longitudinal research examining the causal relations between PC and cognitive functioning as well as examining whether PC tendencies in the acute phase of mTBI are related to neuropsychological performance and contribute to poorer long-term recovery.

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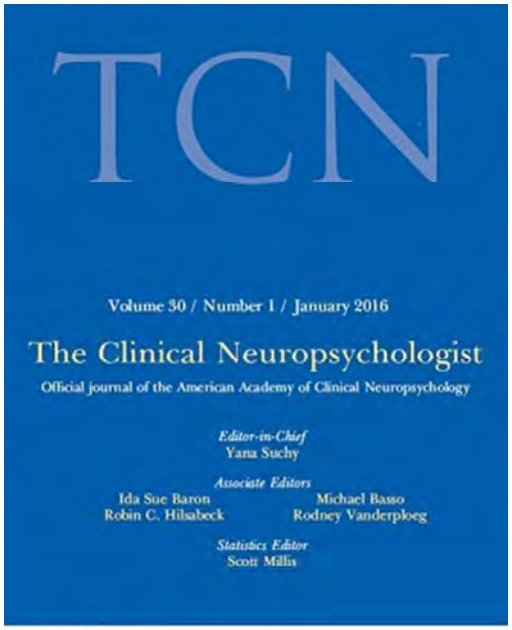
Appendix 42

A Systematic Review of Sex Differences in Concussion Outcome: What Do We Know?



A Systematic Review of Sex Differences in Concussion Outcome: What Do We Know?

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Keywords:	head injury, gender differences, post-concussion symptoms, neuropsychological outcomes, mild traumatic brain injury

RUNNING HEAD: SEX DIFFERENCES IN CONCUSSION OUTCOME

A Systematic Review of Sex Differences in Concussion Outcome: What Do We Know?

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Abstract

Objective: The purpose of this review was to examine sex differences in concussion, or mild traumatic brain injury (mTBI) outcome, updating previous critical reviews of the literature.

Method: Within adult human studies, we reviewed a wide range of concussion outcome variables: prevalence of concussion, injury characteristics, post-concussion symptom trajectories and psychiatric distress, neuropsychological performance, and neuroimaging findings. Sports-related concussion, civilian, and military samples were included in the review.

Results: Given the robust concussion literature, there is a relative paucity of research addressing sex differences following concussion. The majority of available studies focused on sports-related concussion, with fewer studies targeting other civilian causes of concussion or military-related concussion in females. Prevalence of concussion was generally reported to be higher in females than males. Although symptom reporting largely showed a pattern for females to report greater overall symptoms than males, examining individual symptoms or symptom clusters resulted in mixed findings between the sexes. Neuropsychological studies generally showed females performing more poorly than males on measures of visual memory following concussion, though this finding was not consistently reported.

Conclusions: Research examining sex differences in humans following concussion, in general, is in its infancy, and exploration of sex differences in studies outside of the sports concussion domain is particularly nascent. Given the increased prevalence of concussion and potential higher symptom reporting among women, ongoing research is necessary to better understand the role of biological sex on outcome following concussion. Understanding sex differences has important implications for assessment, management, and treatment of concussion.

Key Words: mild traumatic brain injury; head injury; gender differences; post-concussion symptoms; neuropsychological outcomes

Introduction

Interest in concussion, or mild traumatic brain injury (mTBI), has escalated in recent decades as a result of the increased awareness of the consequences of such injuries. While it is difficult to estimate the true prevalence of concussion, as many may go undetected or are not reported, estimates suggest that of the approximately 2.5 million brain injuries that occur annually (Taylor, Bell, Breiding, & Xu, 2017), around three-quarters are classified as mTBI or concussion (Boyle et al., 2014; Prevention, 2003; Prevention., 2015). Concussions affect individuals of all ages, and occur not only in sports and military-related settings, but also in civilians who have experienced motor vehicle accidents and falls, for example (Carroll et al., 2014; Taylor et al., 2017). Concussions are presently a major public health concern, and questions regarding proper assessment and management of mTBI have dominated the literature for years.

More recently, consensus statements and position papers concerning mTBI/concussion have been published highlighting the importance of considering individual differences, pre-injury characteristics, and injury-specific variables as possible modifiers of concussion outcome (Broglio et al., 2014; Giza et al., 2013; Harmon et al., 2013; McCrory et al., 2017). Biological sex is one such variable that has been considered, with emphasis placed on better understanding the extent to which sex modifies, or influences, the nature and course of recovery following mTBI/concussion. Although a growing number of animal studies have indicated that female sex relative to male sex may be protective, leading to reduced mortality and improved cognitive functioning following TBI (Kupina, Detloff, Bobrowski, Snyder, & Hall, 2003; Velosky, Tucker, Fu, Liu, & McCabe, 2017), findings regarding the influence of biological sex on recovery in the broader human concussion literature have been more heterogeneous. The relative importance of

this variable, therefore, remains unknown. Developing a better understanding of how sex influences recovery and outcome following mTBI is extremely valuable, though, as concussed individuals may benefit from a more individualized approach to care.

An earlier review of sex differences in TBI outcomes included all severity levels of TBI and only eight studies were available to be included at that time (Farace & Alves, 2000). The main findings from this original review indicated that women demonstrated worse outcome than men in 85% of the variables evaluated. However, authors cautioned that few studies at that time had characterized outcomes by sex, and that future studies would need to better address the extent to which sex impacts recovery and outcome following TBI. Since that time, there has been an increased number of studies evaluating sex differences, with many emphasizing sex differences in the context of sports-related concussion.

The current review aims to update previous critical reviews in the literature by providing a comprehensive summary of our current understanding regarding the influence of sex on mTBI/concussion outcome. We focus specifically on studies evaluating the mild end of the TBI spectrum, covering the following domains: the prevalence of concussion, injury-specific characteristics (such as mechanism of injury or location of injury), baseline and post-concussion symptom trajectories and psychiatric distress, neuropsychological performance, and neuroimaging variables. Given that the majority of available studies for review examined concussed athletes, the findings are largely based on the sports concussion literature, although non-sport civilian studies and military studies will be discussed as available.

Methods

Online databases, including PubMed, PsycINFO, and Google Scholar, were first used to identify relevant articles for the review. After locating articles of interest through online databases, a hand-searching approach of the cited references within each article was conducted to ensure completeness. Articles published from database inception through December 2017 were included in the review. The specific search terms were as follows: "concussion"; "mild traumatic brain injury"; "TBI"; "head injury"; "gender"; "gender differences"; "sex"; and "sex differences". Only articles published in English were retained. Additionally, we focused exclusively on studies pertaining to humans, and to limit the confound of neurodevelopmental issues, only studies pertaining to *adult* concussion/mTBI were reviewed. Oftentimes, articles evaluating sports-related concussion included both adolescent/youth and adult (≥18 years of age) participants in the same study; under these circumstances, the articles were retained. However, articles were excluded from this review if the study focused exclusively on adolescents/youths. Table 1 summarizes the included studies and highlights key findings from each.

Results

Prevalence of mTBI/Concussion

Several empirical studies have examined sex differences with regard to the prevalence or frequency of mTBI/concussion, with the majority of studies focused on athlete populations. Before exploring this literature, it is first relevant to understand that one issue that has complicated making a direct comparison of concussion prevalence between male and female athletes is the sheer number of male athletes relative to female athletes. Given the higher proportion of male sports that traditionally have been studied, it is perhaps not surprising that when examining concussions that occur within the context of athletics, a greater number of

concussions were sustained by males than females when all sports were considered together (Giza et al., 2013). However, more recently, investigators have been incorporating additional female sports teams into their analyses, thus causing a shift in the overall injury rates. Black, Sergio, and Macpherson (2017), for example, examined 20 varsity level sports at a Canadian university (with roughly equal representation of male and female sports teams) and reported that more female athletes sustained concussions relative to male athletes. Similar results were also noted in Zuckerman et al. (2015), who examined 25 National Collegiate Athletic Association (NCAA) sports.

Interestingly, when examining sports played by both males and females, there is mounting evidence to suggest that females may experience more concussions than males. Numerous studies evaluating soccer, basketball, and baseball/softball have generally reported higher concussion rates in female athletes relative to male athletes (Covassin, Moran, & Elbin, 2016; Covassin, Swanik, & Sachs, 2003; Delaney, Lacroix, Leclerc, & Johnston, 2002; Dick, Hootman, Agel, & Marshall, 2008; Fuller, Junge, & Dvorak, 2005; Gessel, Fields, Collins, Dick, & Comstock, 2007; Hootman, Dick, & Agel, 2007; Kerr et al., 2017; Roos et al., 2017; Tanveer, Zecavati, Delasobera, & Oyegbile, 2017; Zuckerman et al., 2015). However, two older studies, both evaluating the frequency of concussion in soccer players, found the opposite pattern—that is, men were more likely than women to have sustained concussions (Barnes et al., 1998; Boden, Kirkendall, & Garrett, 1998).

In sports beyond soccer, basketball, and baseball/softball, more equivocal findings have been reported. With regard to ice hockey, several studies showed no significant differences with respect to concussion prevalence between male and female athletes (Dick et al., 2008; Kerr et al., 2017; Schick & Meeuwisse, 2003), whereas one study documented more concussions in females

(Covassin et al., 2016) and another study documented fewer concussions in females (Zuckerman et al., 2015) relative to males. As for concussion rates in lacrosse, a similar pattern emerged, with some evidence to suggest no sex differences exist (Covassin et al., 2003; Kerr et al., 2017), one study showing females having higher rates of concussions than males (Zuckerman et al., 2015), and a final study demonstrating fewer concussions sustained by females relative to males (Covassin et al., 2016).

In studies examining the prevalence or incidence of TBI in other civilian samples (i.e., non-sports concussion studies), it was much more common for investigators to consider mild, moderate, and severe TBI samples altogether and report sex differences for overall injury prevalence. Given the focus of concussion/mTBI in the present review, we do not provide a comprehensive synopsis of these articles herein, as they are beyond the scope of the review. Instead, to briefly summarize, recent data from the Centers for Disease Control and Prevention (2016) indicate that rates of TBI were much greater for men than women between the years 2001-2010. Analogous findings were documented in a meta-analysis by Frost, Farrer, Primosch, and Hedges (2013) who examined prevalence rates of TBI in the general adult population. Their meta-analysis revealed that men were more than twice as likely to have experienced a TBI as women.

With regard to studies evaluating sex differences in the prevalence/incidence of military mTBI, there appear to be no studies examining this as a primary outcome. However, some researchers provided information pertaining to sex differences when describing the characteristics of the sample under investigation. For instance, Schneiderman et al. (2008), in their examination of military personnel following deployment to Operation Iraqi Freedom (OIF) and/or Operation Enduring Freedom (OEF), reported a similar rate of mTBIs sustained by males

and females. Specifically, among those deployed in both conflicts, 12% of males and 12% of females experienced mTBI. More recently, Hendricks et al. (2013) reported that the rate of having a positive TBI screen in OIF/OEF service members was about double for males (23.1%) than females (10.7%); however, this encompassed all TBI severity and did not include comprehensive TBI evaluation, only screening.

Injury Characteristics

In addition to evaluating concussion prevalence by sex, some investigators have examined injury characteristics such as the magnitude and location of head impacts as a function of sex. Brainard et al. (2012) studied collegiate ice hockey players and compared males and females on the frequency, magnitude, and location of head impacts. The authors showed that male hockey players experienced a greater number of impacts than female hockey players and were more likely than females to experience impacts of greater magnitude. With respect to injury location, Brainard and colleagues (2012) showed that although there were minor differences in injury location by sex (with females experiencing a greater number of left and right side-of-the-head impacts than males), the location of greatest-magnitude impacts was similar for both males and females—the back of the head.

As for injury mechanism, Barnes et al. (1998) examined elite soccer players and reported that the most common form of injury in their sample for both males and females was player-to-player contact. Fuller et al. (2005), who also evaluated elite soccer players, utilized a more fine-grained approach to examining mechanism of injury; their findings showed that the most common causes of concussion in males and females were use of the upper extremity and head-to-head contact, with males more often experiencing the former and females more often

experiencing the latter. In a study of lacrosse players, Lincoln and colleagues (2007) found that the most common injury mechanism for males was player-to-player contact, whereas the most common injury mechanism for females was contact with an object (i.e., stick, ball). Finally, Rosene et al. (2017) assessed male and female ice hockey players and reported that player-to-player contact was the most common mechanism of injury for both sexes, followed by surface contact. However, a greater proportion of males sustained their concussions by player contact whereas more females experienced concussions through surface contact.

Post-Concussion Symptoms & Psychiatric Distress

Among the variables receiving a substantial amount of research attention are post-concussion symptoms. Although the majority of published studies on this topic fall within the context of sports concussion, the civilian and military TBI literatures have also begun examining sex differences with respect to symptom reporting. In addition to post-concussion symptoms, assessment of psychiatric symptoms is also relevant, given the burgeoning literature establishing a connection between concussion/mTBI and mental health symptoms (for example, see Kerr et al., 2014; MacDonald et al., 2017; Morissette et al., 2011). Below, study results will be described according to the population of interest (i.e., sports concussion, other civilian studies, and military studies), as well as when symptoms were assessed relative to the concussive event. Broadly, studies evaluating symptoms at baseline (pre-concussion) will be discussed first, followed by studies examining symptoms in the acute and post-acute phases of injury.

Baseline Assessments:

To begin, within the sports concussion literature, there appears to be some evidence showing that female athletes may report higher "post-concussive" symptoms than male athletes

upon baseline testing. In a study of NCAA college athletes, Covassin et al. (2006) found that females overall reported more "post-concussion" symptoms at baseline than males. When evaluating individual symptoms, females were significantly more likely than males to endorse 14 of the 22 individual symptoms evaluated on the Post-Concussion Symptom Scale (PCSS). In another study of male and female college athletes, Shehata et al. (2009) found similar results using the Sport Concussion Assessment Tool (SCAT). In addition to evaluating the mean total symptom score, they also evaluated other symptom indices such as the median total symptom score and the percent of males and females having a total symptom score of "0." They demonstrated that females had greater mean and median total symptom scores, and that a greater proportion of males exhibited total symptom scores of "0" (47.4% of males had a total symptom score of "0" compared to 24.3% of females). Additionally, Kontos et al. (2012) examined symptom clusters derived from the PCSS and established that females endorsed greater cognitive-sensory, sleep-arousal, vestibular-somatic, and affective symptoms than males at baseline.

Examining the sports-related concussion literature via meta-analysis, Brown, Elsass, Miller, Reed, and Reneker (2015) found that females were 43% more likely than males to report *any* symptom associated with concussion at baseline, and in particular, females were more likely to report pre-concussion symptoms of headache, poor concentration, vision/hearing concerns, and mood and sleep symptoms. Additionally, at baseline, females had significantly higher total symptom scores than males; however, Brown and colleagues concluded that this difference was not clinically significant.

Few studies within the sports-concussion literature have evaluated sex differences with respect to baseline (pre-morbid) psychiatric distress. Yang et al. (2007) was perhaps the first

group to examine whether sex differences are associated with baseline symptoms of depression in a sample of NCAA college athletes; they revealed that female athletes had a higher risk of experiencing depressive symptoms relative to male athletes. In contrast to these findings, Covassin, Elbin, Larson, and Kontos (2012), who examined high school and college athletes, showed that there were no significant differences between male and female reports of depressive symptoms at baseline. They also found no sex differences for overall post-concussion symptoms at baseline, but when examining symptom cluster scores, females endorsed greater cognitive, emotional, and sleep symptoms than males (with no significant differences found for the somatic/migraine symptom cluster).

Acute Concussion Assessments:

With regard to symptoms endorsed acutely after a concussive event, anywhere between 1-14 days post-injury, numerous studies within the sports-concussion literature have established that females endorse greater post-concussion symptoms than males (Broshek et al., 2005; Colvin et al., 2009; Covassin, Elbin, Bleecker, Lipchik, & Kontos, 2013; Covassin, Elbin, Harris, Parker, & Kontos, 2012; Mihalik et al., 2013). Additionally, in an examination of a civilian concussion sample who sustained injuries by a variety of mechanisms (including sports, motor vehicle accidents, and falls, etc.) and were evaluated in the acute period following concussion (most participants were tested within 48 hours of referral), females reported a higher number and severity of post-concussive symptoms than males (Benedict et al., 2015). Although individuals as young as 10 were included in the sample, the average age was 35 and so we have reported the results here.

Not all studies, though, have documented such clear sex differences in the acute phase following injury. The meta-analysis by Brown et al. (2015), referenced above, also evaluated post-concussion symptom reporting following concussion. Their findings revealed that only one individual symptom - confusion - differed between males and females post-injury, with females actually having lower odds than males of endorsing confusion. Furthermore, although the meta-analysis found that overall symptoms (total symptom score) were greater for females than males post-injury, they again concluded that the difference was not clinically meaningful (2015).

Next, Kontos et al. (2012) compared male and female symptom reports (gathered 1 to 7 days post-injury) across four post-concussion symptom clusters—cognitive-fatigue-migraine, affective, somatic, and sleep—and only found sex differences for the affective symptom cluster, with females endorsing greater symptoms than males. Another study by Kontos and colleagues (Kontos, Covassin, Elbin, & Parker, 2012) examined post-concussion symptoms and depressive symptoms at 2, 7, and 14 days following sports concussion, and found no sex differences for both total post-concussion symptoms and depression symptoms. Covassin, Schatz, and Swanik (2007) examined post-concussion symptom reporting in a sample of college athletes and also found no sex differences in total symptoms between males and females when evaluated at two time points post-injury—approximately 3 and 10 days post-concussion. However, the investigators documented that concussed males reported more vomiting and sadness than concussed females, with no other individual symptom differences reported between the sexes. Similar to Covassin et al. (2007), Tanveer et al. (2017) found that males were more likely than females to experience specific symptoms; these included loss of consciousness, retrograde and anterograde amnesia, and confusion. However, females experienced greater overall post-concussion symptoms (total symptom score) than males (Tanveer et al., 2017).

Post-Acute Concussion Assessments:

While the above studies documented acute sex differences in symptom reporting, other studies have examined whether males and females differ with regard to symptom reporting in the post-acute phase of injury. Among 1,425 individuals (of which almost half were female) who presented to an emergency department, females were more likely to have higher post-concussive symptom endorsement than males at three months post injury (Bazarian, Blyth, Mookerjee, He, & McDermott, 2010). However, other bodily injuries, in addition to concussion, notably contributed to higher post-concussive symptoms scores in this sample. Despite this higher symptom endorsement by females, return to work and other activities did not differ between females and males.

Age may also be a relevant variable when examining sex differences, as adult females with sports-related concussion had higher Rivermead Post Concussion Symptoms Questionnaire scores three months post-injury than adult males, though this difference was not present in children (Preiss-Farzanegan, Chapman, Wong, Wu, & Bazarian, 2009). Specific symptoms more highly endorsed by females included headache, dizziness, fatigue, irritability, and concentration difficulties. Sport specific variables or other demographics did not better account for any differences (Preiss-Farzanegan et al., 2009). Finally, a systematic review of prolonged post-concussive symptoms also found females at higher risk for elevated symptom reporting at 12-18 months post mild head injury, relative to males (King, 2014b). At 3-6 years post mTBI, only half (2 out of 4) of the correlational studies found that females were at higher risk for 'permanent' post-concussive symptoms (King, 2014a).

Investigators have also studied psychiatric distress in the post-acute phase of injury. Scott et al. (2015) examined psychosocial functioning, including rates of depression and anxiety, substance use disorders, and internalizing and externalizing problems/behaviors in male versus female adults with a history of childhood TBI. When examined as adults, females who had sustained childhood TBI of any severity had greater internalizing problems than males, while males had greater externalizing problems than females (Scott et al., 2015). Although an interesting finding, it is not fully understood whether these differences are uniquely related to the history of TBI, or whether there are baseline differences in internalizing and externalizing behaviors that may then be amplified or exacerbated following TBI.

Military Studies

Concussion has always been a prevalent issue in the military and attention to it heightened during the wars in Iraq and Afghanistan as blast and combat related concussions increased. Despite concussion being a signature injury of these wars, focus on mTBI in female military personnel and Veterans has been notably lacking. Given that females make up only approximately 15% of active duty military (Department of Defense, 2015), they have often been excluded from military TBI research. As a result, sex differences have often not been reported given the low frequency of women in this unique population. More recently, though, studies have begun addressing the role of sex on TBI outcomes, generally focusing on the presence of post-concussion symptoms and psychiatric distress.

Iverson et al. (2011) conducted one of the largest examinations of sex differences in military concussion. She and her colleagues examined sex differences in psychiatric diagnoses and neurobehavioral symptom reporting between males and females in a large, retrospective

study of over 12,000 Iraq and Afghanistan Veterans who underwent TBI assessment within the VA system. All severities of TBI were included, though statistically, mTBI makes up the vast majority of all TBIs reported. They found that females with a history of TBI were less likely to have PTSD or substance use diagnoses, relative to males, but were more likely to carry a diagnosis of depression, anxiety, or comorbid depression and PTSD. However, PTSD, anxiety, and substance use sex differences did not remain after controlling for blast exposure. Neurobehaviorally, females were more likely to report higher levels of somatosensory, vestibular, and cognitive (but not affective) symptoms than males on the Neurobehavioral Symptom Inventory (NSI).

In a more recent study of a matched sample of 86 female and 86 male service members with a history of mTBI who were evaluated within 2 years post-injury, females reported more neurobehavioral and PTSD symptoms than males (Brickell et al., 2017). Follow-up analyses revealed that sex differences were greatest for the neurobehavioral symptoms of sensitivity to light, change in taste/smell, change in appetite, nausea, poor sleep, and fatigue. As for PTSD symptoms, sex differences were most pronounced for poor concentration, trouble remembering a stressful event, and disturbing memories/thoughts/images. However, after controlling for PTSD symptoms, injury details, other bodily injuries, and symptom validity, post-concussion symptom reporting was much more equivalent between males and females (Lippa et al., 2017); female service members with both a history of TBI and PTSD reported only more somatosensory symptoms than males, with no other symptom reporting differences.

Neuropsychological Outcomes

The majority of literature relating to sex differences in neurocognitive function following mTBI/concussion has focused on sports-related concussion, and typically has utilized the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) computerized program, which measures neurocognitive performance across verbal memory, visual memory, reaction time, and processing speed domains, as well as post-concussion symptoms (discussed previously). As will be shown below, there are some findings that suggest there may be sex-related differences in specific domains, however there does not appear to be a consistent pattern of impairment between sexes.

The cognitive domain most frequently identified as being associated with sex-related differences is visual memory, with some evidence of greater impairment in females than males in the acute recovery period (Covassin et al., 2007; Kontos, Covassin, et al., 2012). In a further study, it was also reported that visual memory impairment was greater in females relative to males 8 days after injury, even after controlling for body-mass index (Covassin et al., 2013). Most recently, Tanveer et al. (2017) examined ImPACT performance and analogously reported worse visual memory scores in females compared to males when examined acutely following concussion. No sex differences were identified for the remainder of the ImPACT cognitive variables. Notably, the participants studied by Tanveer and colleagues were relatively younger than the studies reviewed above, ranging in age between 10-20; nevertheless, the study was included in the present review given that a subset of the sample comprised college athletes.

Interestingly, contradictory results were found when exploring the influence of multiple concussions. Covassin, Elbin, Kontos, and Larson (2010) found that males with a history of multiple concussions actually fared worse than females on some ImPACT cognitive tasks. Specifically, females with three or more concussions performed better than males with three or

more concussions on the visual memory composite. Additionally, females with two and three or more concussions performed better than males with similar concussion histories on the verbal memory composite. The authors suggest this may indicate that female sex hormones are protective in the event of sports-related concussion. However, given the differences in muscle mass and other sports-related factors such as acceleration and stabilization (Tierney et al., 2005), it is also possible that severity of concussion may differ between sexes and this effect becomes evident when concussions accumulate. Such a relationship could explain the contradictory results between the Covassin et al. (2010) study and other studies reviewed above. Finally, Colvin et al. (2009) studied male and female soccer players and found that females who had sustained a prior concussion had slower reaction times on ImPACT testing than males, and found a trend for females having poorer memory and processing speed scores relative to males.

Others have used computerized programs other than ImPACT to explore sex differences in sports-related concussion outcomes. Broshek et al. (2005), using a computerized package that predominantly measured reaction time and processing speed (the Concussion Resolution Index), compared baseline performance to post-concussion performance (approximately 3-4 days post-injury) using reliable change index scores. It was found that female athletes had greater reductions in neurocognitive function following concussion, and also were 1.5 times more likely than males to experience cognitive impairment. Accounting for helmet use did not notably impact results.

In another study, Ellemberg, Leclerc, Couture, and Daigle (2007) examined female soccer players. At six to eight months after a single lifetime concussion, concussed females were compared to age-matched females who had never experienced a concussion. In this post-acute period, the concussed females had significantly slower processing speed than non-concussed

females. There were no significant differences in other cognitive domains (including memory, attention, and executive functioning). This sample was small, with only 10 concussed and 12 non-concussed female soccer players, but they utilized a more comprehensive neuropsychological battery, as opposed to brief computerized testing used by most other studies. Other strengths included assessment of number of 'headers' that did not result in concussion; these sub-concussive incidents were also found to be equivalent between concussed and non-concussed groups. These athletes did not, however, have baseline testing; while this avoids practice effects or motivations to do poorly on baseline testing to positively impact return to play decisions in the future, it limits interpretability of change post-concussion. Finally, this study did not compare male and female performance, thus, it is not possible to determine whether the deficits experienced by the concussed females were greater than would be expected in males.

A meta-analysis of the neurocognitive outcomes associated with sports-related concussion also explored the role of sex differences (Dougan, Horswill, & Geffen, 2014). The authors reported that females consistently experienced poorer neurocognitive outcomes during the initial recovery period (within 1-10 days post-injury), and this was particularly apparent when baseline measures had been obtained. Furthermore, deficits appeared to be more pronounced in adults. The authors noted that there was a lack of research exploring sex-differences in the post-acute recovery period, and therefore it was not possible to determine whether the observed sex differences in the acute recovery period extended to later recovery.

To date, few studies have explored the role of sex in post-mTBI neurocognitive function outside of the sports concussion literature. Moore, Ashman, Cantor, Krinick and Spielman (2010) compared performance of males and females with mTBI on tasks of processing speed, executive functioning, and visual memory using the Cambridge Neuropsychological Test

Automated Battery (CANTAB). All participants were evaluated at least one year post-injury. Differences between males and females were only found in visual memory, where females outperformed males. This finding aligns with the results of Covassin et al. (2010), who found similar deficits where multiple concussions had occurred, but contradicts a number of other findings (Covassin et al., 2013; Covassin, Elbin, et al., 2012; Covassin et al., 2007; Kontos, Covassin, et al., 2012), where males outperformed females in this domain during the initial recovery phase. In another study examining civilian adults approximately two years following mTBI, there were virtually no sex differences in neuropsychological functioning on the Halstead-Reitan neuropsychological battery (Tsushima, Lum, & Geling, 2009); however, females over 30 performed more poorly than males on the Category Test and Trails A.

Concussion Recovery

Concussion "recovery," has been conceptualized in numerous ways in the literature, but generally studies have associated recovery with time—that is, the number of days to return to regular activities or how long it took to become asymptomatic following concussion, for example. Black et al. (2017) evaluated symptom and cognitive recovery in collegiate athletes representing a wide range of sports. In their study, recovery was assessed using the SCAT (or SCAT2) and the ImPACT computerized battery. The main outcomes evaluated were (1) the number of days from the concussion to symptom resolution as per SCAT/SCAT2 and (2) the number of days from the concussion to cognitive recovery as per ImPACT test performance. When outcomes were compared by sex, Black et al. (2017) reported no sex-related differences with respect to both symptom and cognitive recovery. Similarly, Henry et al. (2015) also found no differences between males and females regarding cognitive recovery, but did find that at four

weeks post-injury, males were more likely than females to be asymptomatic. Lastly, Covassin et al. (2016) reported that females in some sports, but not all, had greater time loss from their sports as compared to males.

Neuroimaging

Very few sex-based differences in neuroimaging outcomes following concussion have been explored and represents an area in need of increased study. In a small study of 10 female athletes who had sustained a concussion compared to 10 non-concussed female athletes, the concussed athletes (at least 7 months post-injury) showed lower levels of myo-inositol in the hippocampi and primary motor cortices and higher white matter mean diffusivity and lower fractional anisotropy (FA) in the corpus callosum as compared to the non-concussed athletes (Chamard et al., 2013). Another study by the same group (Chamard, Lefebvre, Lassonde, & Theoret, 2016) compared 10 female concussed athletes (evaluated 6 months post-injury) to 8 non-concussed female athletes and similarly found that the concussed females showed lower mean diffusivity and radial diffusivity in the corpus callosum compared to the non-concussed females. In a final study that evaluated both sexes, females showed relative sparing of the uncinate fasciculus following mTBI as compared to males; males had significantly lower FA bilaterally in the uncinate fasciculus than concussed females or non-concussed controls (Fakhran, Yaeger, Collins, & Alhilali, 2014). Male sex and uncinate fasciculus FA also predicted persistent post-concussive symptoms and time to symptom resolution. Given the extremely limited work in this area, definitive or even preliminary conclusions about any sex-specific differences in neuroimaging markers after concussion cannot be reached.

Discussion

The present review evaluated what we currently know about sex differences following concussion, or mTBI, with a focus on the following domains: prevalence of concussion, injury characteristics, post-concussion symptoms and psychiatric distress, neuropsychological outcomes, and neuroimaging. The majority of the available studies for review pertained to sports-related concussion, with fewer studies examining sex differences in mTBI/concussion outcome in other civilian and military populations. Thus, any conclusions that can be made regarding sex differences is largely based on findings from within the sports-concussion literature.

Overall, the current evidence suggests that females may be more vulnerable to concussion than males in a sports setting, but that males encounter a greater number of TBIs than females in the general adult population (i.e., non-sports concussion setting). Soccer, basketball, and baseball/softball—specific sports played by both males and females—had the most consistent findings regarding rates of concussion, with females experiencing proportionally more concussions than males. However, other sports, including ice hockey and lacrosse, showed more equivocal findings regarding concussion prevalence. As for non-sport populations, there was limited data on the prevalence of mTBI/concussion specifically. Instead, concussion rates were generally reported as a function of all TBI severities, with findings supporting the opposite pattern as what was observed in the sports-concussion literature—more TBIs are sustained by males than females. Additional research is needed to better understand the factors that increase females' vulnerability to concussion in sports, and future studies should specifically examine whether sex differences exist regarding the prevalence of mTBI/concussion in civilian and military populations. Although females make up a small component of active duty military

forces, they are the fastest growing segment seeking VA care (Frayne et al., 2014); nonetheless, examination of sex differences following concussion in military or Veteran samples remains notably limited in the existing research literature, and represents an area of much needed research.

As for injury characteristics, there appears to be insufficient data to support any clear sex differences regarding head impact data and mechanism of injury. Only one study evaluated head impacts, and although findings support a greater number and magnitude of impacts in males than females, it is important to recognize that findings were based on a specific sport (ice hockey) and therefore may not generalize to other sports or civilian and military populations. Regarding mechanism of injury, within the sports-concussion literature, player-to-player contact and object/surface contact appear to be the most common forms of injury experienced by both males and females; although minor differences may exist between the sexes with regard to the proportion of males and females experiencing each mechanism, taken together, there do not appear to be substantial sex differences in this domain. Additionally, findings pertaining to recovery rates were also rather ambiguous, though the available data do not suggest any overt sex differences with regard to concussion recovery. Given the limited data available for review, future studies should more specifically address whether males and females differ with respect to recovery and functional outcomes, such as days of school or work missed following concussion, or length of time to return to play.

The domains receiving the greatest research attention to date regarding sex differences were post-concussion symptoms and neuropsychological outcomes. Regarding symptom reporting, although not definitive, the data suggest a stronger likelihood for females to endorse greater symptomatology than males. Interestingly, this finding was reported across concussed

athletes, civilians, and military personnel, as well as across time (i.e., baseline assessment and post-injury assessment). It is possible that sex differences in response styles may account for the apparent greater symptom reporting in females. That is, perhaps males are underreporting symptoms and females are accurately reporting symptoms, or it may be that females are more willing to report post-concussive symptoms than males. The influence of environmental or cultural norms, or more simply *gender* differences, on male and female symptom reporting patterns has long been referenced as a possible explanation or cause of differing symptoms between the sexes (Granito Jr, 2002; Lovell et al., 2002). Given this possibility, the data reviewed above raises the question as to the extent to which biological sex differences versus gender differences contributes to post-injury outcomes. Furthermore, with regard to symptom reporting, more thought needs to be given as to whether or when sex-based norms should be used for post-concussion symptom interpretation, and if implemented, how this would impact clinical outcome.

Related to this is other work demonstrating the non-specificity of post-concussion symptoms; specifically, there is a burgeoning literature establishing that traditional "post-concussion symptoms" are commonly endorsed by non-concussed populations including college students and community volunteers, as well as patients with pre-existing medical or psychiatric conditions (Asken et al., 2017; Garden & Sullivan, 2010; G. L. Iverson & Lange, 2003; Smith-Seemiller, Fow, Kant, & Franzen, 2003; Wang, Chan, & Deng, 2006). This in itself is not surprising given the broad nature of post-concussion symptoms, but highlights the need to be cautious not to infer causation from reported post-concussion symptomatology.

Another interesting possibility for further consideration is how hormonal systems, neural architecture, and musculature/biomechanical systems differ between the sexes and may impact

response to concussion and/or contribute to the sex differences in outcomes (i.e., symptom reporting) following concussion. The Brown et al. (2015) meta-analysis hypothesized that at least some difference in symptom reporting is a result of phase of menstrual cycle in which the injury was sustained and/or when symptoms were reported, but animal studies have documented overall sex differences as opposed to just hormonal cycle based ones (Velosky et al., 2017). Interestingly, in a study evaluating *healthy* participants, Hu and colleagues (2013) examined sex differences in the context of brain metabolic networks and showed that female brains, compared to male brains, have *higher* metabolic demands in posterior regions such as the occipital cortex and posterior parietal cortex, as well as the thalamus and hippocampus, whereas female brains have *lower* metabolic demands relative to male brains in anterior regions such as the frontal cortex and anterior parietal cortex (Hu et al., 2013). It is therefore possible that these metabolic differences at baseline may lead to differential symptom reporting between males and females, and that these differences are exacerbated post-injury. Furthermore, although our review found some evidence for post-injury sex differences with regard to neuroimaging findings, future studies will need to more comprehensively examine sex differences at baseline and post-concussion to understand whether the differences observed post-injury are a result of baseline sex differences or if these differences are exacerbated post-injury.

With regard to other pathophysiological and biological aspects of concussion, a very recent study of neural architecture of TBI revealed that female axons were smaller with fewer microtubules and were subsequently at higher risk to break and/or exhibit greater axonal pathology following injury than male axons following an equivalent force from simulated TBI (Dolle et al., 2018). Additionally, previous research has established that females have weaker neck muscles compared to males and consequently may experience greater angular acceleration

of the head/neck (Barnes et al., 1998; Tierney et al., 2008; Tierney et al., 2005). It is possible that these factors may result not only in a differential risk of concussion but also in the experience of post-concussion symptoms for males and females.

As for the neuropsychological findings, it appears that differences between neurocognitive function of males and females are mostly limited to increased deficits for females in visual memory in the acute recovery phase. However, given the limitations of the available findings, additional research is needed, especially for long-term recovery and non-sports concussion mTBIs. Further, recruiting participants who are in mid to late adulthood, and who are more sedentary, will clarify the relationship between sex and mTBI/concussion in terms of neurocognitive outcomes.

There are also a number of factors that should be considered when interpreting the literature regarding sex differences in cognitive functioning. First, the differences reported post-injury may reflect pre-existing individual differences. For example, Covassin and colleagues (2006) compared male and female athletes' baseline performance on the ImPACT battery, and found that females outperformed males on verbal memory, whereas males outperformed females on visual memory (T. Covassin et al., 2006). Similar findings have also been reported in healthy participants (Weiss, Kemmler, Deisenhammer, Fleischhacker, & Delazer, 2003). Thus, there is evidence that males and females may perform differently on cognitive tasks prior to injury. However, it must be noted that there were no differences in baseline ImPACT scores, stratified by sex, in the Covassin et al. (2007) study described above. Furthermore, Broshek et al. (2005) noted that in their sample, males had a higher frequency of learning disabilities (LD) and attention-deficit/ hyperactivity disorder (ADHD) (Broshek et al., 2005). While they excluded individuals who reported LD or ADHD, others have not reported the presence of LD or ADHD.

Given prevalence of LD and ADHD is known to be higher in males, and is known to impact neurocognitive function (Seidman, 2006), it may be advisable to report and control for these factors when exploring sex differences in this population.

Additionally, as stated previously, most of the research reported herein has recruited young athletes, which may reduce generalizability. For example, it is well established that neuroplasticity influences recovery after injury, and that neuroplasticity decreases with age, and there is emerging evidence that both exercise and sex-differences impact plastic processes (Voss, Thomas, Cisneros-Franco, & de Villers-Sidani, 2017). Expanding mTBI research to older adults and particularly older women is much needed. The aging of the population is contributing to the steady increase in TBI-related emergency room visits from older adults, with rates of emergency room visits following mTBI rising exponentially every decade after age 65 (Albrecht et al., 2016). In older adults, the incidence of mTBI in females was higher than that of males (Albrecht et al., 2016); these findings further highlight the need to study mTBI in older adults more broadly, but specifically in older women, as most work to date has been conducted on concussions sustained by younger cohorts. Caution must therefore be applied in extending the current findings to older and/or less active individuals, where neuroplasticity may be reduced.

Other areas in which concussion in females is notably underexamined is within the context of intimate partner violence (IPV). Although extremely limited data is available, one investigation found almost 68% of physically abused women had sustained an mTBI at the hands of their partner (E. M. Valera & Berenbaum, 2003), with a high likelihood of multiple mTBI incidents (Kwako et al., 2011). The TBIs sustained in the context of IPV lead to cognitive (E. M. Valera & Berenbaum, 2003) and altered brain functional connectivity (E. Valera & Kucyi, 2017). Female veterans also report higher rates of IPV than non-veterans (Dichter, Cerulli, &

Bossarte, 2011), demonstrating an intersection of two understudied populations in the concussion literature. Further study of concussion in women who have or are experiencing IPV is warranted, as impact of and recoveries from both physical and psychological trauma will be uniquely intertwined in females in this context.

A final area yet to be explored in relation to sex differences in mTBI is the potential for interaction with genes known to influence post-injury recovery. A number of genes have been identified as influencing recovery after TBI (Davidson, Cusimano, & Bendena, 2015; Weaver, Chau, Portelli, & Grafman, 2012), and there is evidence of sex-gene interactions in relation to neurobiological and general outcomes after injury (Lopez et al., 2016; Ost et al., 2008). However, there is limited evidence of sex × gene interactions in the context of cognitive function, with only one study in TBI to date. Myrga and colleagues (2016) found that a number of genes associated with dopamine pathways interacted with sex in relation to cognitive recovery at 6 and 12 months after severe TBI (Myrga et al., 2016). Thus, at present, there are no published findings in relation to mTBI, and only limited research in more severe TBI; as such, this represents another area in need of future research.

A number of methodological factors should also be taken into account when considering the extant findings related to sex differences in cognitive functioning following sports-related concussion. Firstly, as noted by Dougan et al., (2014), there is a lack of evidence relating to post-acute recovery. The majority of studies have focused on the first two weeks of recovery, and it appears from the limited evidence (Moore et al., 2010) that the effect of sex differences on outcome may differ during later phases of recovery. A further consideration is the use of ImPACT, which has both advantages and disadvantages. Consistent use of the same measures allows better comparison between studies, and the ImPACT program has been reported to be

valid and reliable by some studies (Nakayama, Covassin, Schatz, Nogle, & Kovan, 2014; Schatz, 2010; Schatz, Pardini, Lovell, Collins, & Podell, 2006). However, there is also evidence that the alternate forms used in ImPACT are not always equivalent (Resch, Macciocchi, & Ferrara, 2013), and that it may be less reliable than other neurocognitive tests (Broglio, Ferrara, Macciocchi, Baumgartner, & Elliott, 2007; Resch et al., 2013). Finally, almost no study utilized performance or symptom validity measures, and examining sex differences with regard to validity is an area of much needed research.

Summary and Conclusions

In conclusion, research examining sex differences in humans following concussion, in general, is in its infancy, and exploration of sex differences in studies outside of the sports concussion domain is particularly nascent. Thus, there is substantial need for additional research to be conducted in this area to better understand the influence of biological sex on concussion recovery and outcome. This review highlights what we currently know about sex differences following concussion, and provides avenues for future exploration.

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Declarations of Interest

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Table 1. Summary of studies included in review.

Author	N (M, F)	Study Type	Time Point(s)	Population	Measures	Key Findings
Barnes et al., 1998	M = 72, F = 65	Epidemiology		Sports-Related Concussion		Females were less likely than males to have sustained concussions
Bazarian et al., 2010	M = 782, F = 643	Cross-sectional	3 months	ED presentations	RPCQ, return to normal activities, missed work days	Females were more likely than males to report post-concussive symptoms (in association with greater orthopedic injury); No difference in return to work
Benedict et al., 2015	Not reported	Cross-sectional	Not reported	Sports and non-sports related concussion (multidisciplinary concussion center)	BESS, K-D, SAC, SCAT3	Females reported more frequent and more severe post-concussive symptoms
Black et al., 2017	Concussed: M = 33, F = 42	Epidemiology		Sports-Related Concussion	SCAT, ImPACT	Females were more likely to experience concussion than males, but no differences in symptom and cognitive outcome
Boden et el., 1998	M = 162, F = 188	Epidemiology		Sports-Related Concussion		Overall concussion incidence was less in females relative to males
Brainard et al., 2012	M = xx F = xx	Epidemiology		Sports-Related Concussion		Females experienced fewer impacts than males; females also experienced impacts of lesser magnitude relative to males; location of greatest-magnitude impacts was similar for females and males—back of head
Brickell et al., 2017	M = 86, F = 86	Cross-sectional	< 30 months	Military mTBI	NSI and PCL-C	Females reported more frequent PTSD and neurobehavioral

Author	N (M, F)	Study Type	Time Point(s)	Population	Measures	Key Findings
						symptoms relative to males
Broshek et al., 2005	M = 94, F = 37	Repeated Measures	Baseline and 1-2 days	Sports-Related Concussion	CRI	Females experienced reduced neurocognitive function and greater cognitive impairment relative to males
Brown et al., 2015		Meta-analysis				Females were more likely to report symptoms at baseline
Chamard et al., 2013	F = 20 (concussion = 10, no concussion = 10)	Cross-sectional	18.9 months (mean)	Sports-Related Concussion	Neurometabolic and microstructural alterations	Concussed females had lower hippocampal and primary motor myo-inositol; Concussed females had greater white matter diffusivity and reduced fractional anisotropy in corpus callosum
Chamard et al., 2016	M = 57 (mTBI = 47, control = 10), F = 33 (mTBI = 22, control = 11)	Cross-sectional	6 months	Sports-Related Concussion	White matter in corpus callosum and corticospinal tract	Concussed females had reduced mean diffusivity and radial diffusivity in the corpus callosum, as compared to non-concussed females
Colvin et al., 2009	M = 93, F = 141	Cross-sectional	9 days (median)	Sports-Related Concussion	ImPACT	Female soccer players with concussion history had slower reaction times than males
Covassin et al., 2003	See article	Cohort		Sports-Related Concussion		Overall, females sustained a higher percentage of concussions during games than males; highest concussion injury rate was in women's soccer and men's lacrosse

Author	N (M, F)	Study Type	Time Point(s)	Population	Measures	Key Findings
Covassin et al., 2006	M = 651, F = 558	Cross-sectional	Baseline	Sports-Related Concussion	ImPACT	Females more likely to report symptoms at baseline than males
Covassin et al., 2007	M = 41, F = 38	Repeated Measures	Baseline, approx. 2 and 8 days	Sports-Related Concussion	ImPACT	No differences between males and females on post-concussive symptoms
Covassin et al., 2010	M = 100, F = 88	Retrospective	Baseline with prior concussion (grouped by number of previous concussions)	Sports-Related Concussion	ImPACT	Females performed better than males on visual memory after multiple concussions
Covassin et al., 2012a	M = 203, F = 93	Repeated Measures	Baseline, 2, 7, 14 days	Sports-Related Concussion	ImPACT and BESS	No differences between males and females on individual symptoms, but females reported greater cognitive, emotional, and sleep symptoms when clustered
Covassin et al., 2012b	M = 1104, F = 512	Cross-sectional	Baseline	Sports-Related Concussion	ImPACT, BDI-II	Females performed better on the verbal memory composite than males; females endorsed greater cognitive, emotional, and sleep symptom clusters compared with males
Covassin et al., 2013	M = 39, F = 56	Repeated Measures	Baseline and 8 days	Sports-Related Concussion	ImPACT	Females experienced greater visual impairment than males post-concussion
Covassin et al., 2016	M = 779, F = 903	Epidemiology		Sports-Related Concussion		Females had higher rates of concussion in specific sports (baseball/softball, basketball, ice hockey, and soccer) compared to males; females took longer to recovery than males in all sports except lacrosse
Dougan et al., 2014	Meta-analysis			Sports-Related		Females had poorer

Author	N (M, F)	Study Type	Time Point(s)	Population	Measures	Key Findings
				Concussion		neurocognitive outcomes initially
Ellemberg et al., 2007	F = 22 (concussion = 10 no concussion = 12)	Cross-sectional	6-8 months	Sports-Related Concussion	CVLT, Ruff selective attention, BTA, SDMT, SCWT	Concussed females had slower processing speed than non-concussed females
Fakhran et al., 2014	F = 18 (concussion = 10, no concussion = 8)	Cross-sectional	Not reported	General population	White matter abnormalities and ImPACT	Compared to females and non-concussed males, concussed males had significantly lower fractional anisotropy bilaterally in the uncinate fasciculus
Henry et al., 2015	M = 42, F = 24	Repeated Measures	Initial assessment within 7 days of injury, then 3 and 4 weeks post injury	Sports-Related Concussion	ImPACT, PCSS, DHI	No difference in recovery, although at 4 weeks post injury, males were more likely to *not* report symptoms
Iverson et al., 2011		Epidemiology		Military mTBI	NSI and neuropsychiatric diagnosis (using ICD-10)	After controlling for blast exposure, females were more likely to report higher levels of somatosensory, vestibular, and cognitive symptoms than males with TBI
King, 2014a		Review				Approximately half of the studies reviewed found females had greater risk of chronic post-concussive symptoms (measured 3-6 years post mTBI)
King, 2014b		Review				Females were more likely to report post-concussive symptoms at 12-18 months post mTBI relative to males
Kontos, Covassin, et al., 2012	M = 51, F = 24	Repeated Measures	Baseline, 2, 7, and 14 days	Sports-Related Concussion	ImPACT, PCSS, BDI	No sex differences in PCSS total score or

Author	N (M, F)	Study Type	Time Point(s)	Population	Measures	Key Findings
						depression levels; females performed more poorly than males on ImPACT visual memory, otherwise no sex differences on ImPACT cognitive composites
Kontos, Elbin, et al., 2012	Concussed: M = 961, F = 477	Case Series	1-7 days	Sports-Related Concussion	PCSS	Females reported higher levels of the affective symptom cluster than males
Lippa et al., 2017	M = 79, F = 79	Cross-sectional	< 30 months	Military mTBI	NSI, PCL-C, Abbreviated Injury Scale	Females with TBI reported greater somatosensory symptoms, but only when PTSD was also present
Mihalik et al., 2013	M = 241, F = 55	Repeated Measures	Baseline, time of injury, days 1, 2, 3, 5, 7, and 90	Sports-Related Concussion	BESS, SAC, GSC	Concussed females experienced greater post-concussive symptoms than males during acute recovery
Moore et al., 2010	M = 83, F = 75	Cross-sectional	> 1 year	General population	CANTAB	Females performed better than males on visual memory 12 months after concussion; no other differences
Preiss-Farzanegan et al., 2009	M = 144, F = 71	Cross-sectional	3 months	Sports-Related Concussion	RPCQ	Adult, but not pediatric, females with concussion reported greater post-concussive symptoms
Scott et al., 2015	M = 94, F = 75	Cross-sectional	11.1 years (mean)	ED presentations	Self-reported anxiety or major depressive disorder (internalizing), offending behavior or substance abuse dependence (externalizing)	Females who reported childhood TBI had greater internalizing problems than males, while males had greater externalizing problems than females
Shehata et al., 2009	M = 190 (non-	Cross-	Baseline	Sports-Related	SCAT and PCSS	Females reported more

Author	N (M, F)	Study Type	Time Point(s)	Population	Measures	Key Findings
	concussed = 116, concussed = 74), F = 70 (non-concussed = 51, concussed = 19)	sectional		Concussion		symptoms at baseline than males
Tanveer et al., 2017	M = 362, F = 333	Cross-sectional	1 day-4 weeks	Sports-Related Concussion	ImPACT and PCSS	Concussed males reported greater loss of consciousness, amnesia, and confusion, whereas females reported greater overall post-concussive symptoms
Tsushima et al., 2009	M = 62, F = 40	Retrospective; Cross-sectional	2 years	General population	Halstead-Reitan Neuropsychological Battery	No significant differences in neuropsychological performance at 2 years post mTBI, although females over 30 years old performed worse than males on two measures—Category Test and Trails A

Note: M= Male, F = Female; ***Abbreviations:*** BDI = Beck Depression Inventory; BESS = Balance Error Scoring System; BTA = Brief Test of Attention; CANTAB = Cambridge Neuropsychological Test Automated Battery; CRI = Concussion Resolution Index; CVLT = California Verbal Learning Test; DHI = Dizziness Handicap Inventory; GSC = Graded Symptom Checklist; ImPACT = Immediate Post-Concussion Assessment and Cognitive Testing; K-D = King-Devick; NSI = Neurobehavioral Symptom Inventory; PCL-C = Posttraumatic Stress Disorder Checklist – Civilian Version; PCSS = Post-Concussion Symptom Scale; RPCQ = Rivermead Post Concussion Symptoms Questionnaire; SAC = Standardized Assessment of Concussion; SCAT = Sport Concussion Assessment Tool; SCAT3 = Sport Concussion Assessment Tool, 3rd Edition; SDMT = Symbol Digits Modalities Test; SCWT = Stroop Color Word Test.

Appendix 43

Hippocampal and entorhinal cortex Alzheimer's disease-like pathology in human chronic traumatic encephalopathy: a chronic effects of neurotrauma consortium study

Hippocampal and entorhinal cortex Alzheimer's disease-like pathology in human chronic traumatic encephalopathy: a chronic effects of neurotrauma consortium study

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Chronic traumatic encephalopathy (CTE) is a progressive neurodegenerative condition resulting from repetitive mild head trauma, prevalent in contact-sport athletes and military personnel. Although the regional spread of tau pathology in the CTE brain marks disease stage and severity (McKee et al., 2013), very little is known about the distribution and morphology of tau and amyloid positive profiles within the hippocampal complex. Eighteen male Caucasian and African-American former professional contact-sport athletes from Stage II (n = 6, age at symptom onset 20–65 y; age at death 25–70 y), Stage III (n = 6, age at symptom onset 24–40 y; age at death 45–67 y), and Stage IV (n = 6, age at symptom onset 30–68 y; age at death 62–80 y) were obtained from Boston University School of Medicine. Paraffin blocks containing the hippocampus and entorhinal cortex (EC) were sectioned at 8 μm and mounted on slides, treated with citric acid and immunolabeled with AT8 (an early tau marker). In addition, amyloid pathology was evaluated with antibodies against the amyloid precursor protein and Aβ (6E10), Aβ1–40 and Aβ1–42. AT8 positive profile number and size were analyzed using a 60X oil-immersion lens controlled by a MicorBrightField software suite; presence of various Aβ species was examined with a Nikon Eclipse 80 microscope. Quantitative analysis

revealed significantly more AT8-positive neurons in the CA1 and CA3 hippocampal subfields and the EC in Stage IV compared to Stage II (CA1, 12.6-fold; CA3, 11.5-fold; EC, 11.0-fold; Mann-Whitney U, $p < 0.01$). The EC and hippocampal subfields also displayed significantly smaller AT8-positive neuronal area in Stage IV compared to Stage II by an average of 37.8 % (EC, 26.5 %; CA1, 35.1 %; CA3, 51.7 %; Mann-Whitney U, $p < 0.01$). Stage III displayed intermediate values for both AT8-positive neuron count and size, suggesting a transitional pathological stage. In contrast, minimal Aβ profiles were mainly seen in the hippocampal-EC complex in Stage IV suggesting that amyloid is not a necessary recondition for the initiation of tau pathology in CTE. Data suggest that phosphorylated tau (AT8) protein levels may provide a biomarker and a drug target to slow the progression of CTE.

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Appendix 44

A living phantom study to evaluate the echo planar imaging (EPI) distortion correction effects in reducing inter-site variability

A living phantom study to evaluate the echo planar imaging (EPI) distortion correction effects in reducing inter-site variability

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Synopsis

In this study we evaluate the effect of echo planar imaging (EPI) distortion artifact as a contributing factor in inter-site variability. With living phantom data acquired with opposite phase encoding direction protocol (blipup-blipdown), we show the effectiveness of a robust EPI distortion correct method in reducing inter-site variability.

Introduction

Diffusion Tensor Imaging (DTI) multicenter studies are becoming increasingly popular for their ability to improve statistical power by utilizing a larger number of subjects. [1,2] However, processing and analyzing data originating from various centers presents unique challenges due to the intrinsic higher heterogeneity of experimental procedures compared to a single center study. DTI data acquired with echo planar imaging (EPI) sequences are usually affected by geometrical distortions resulting from susceptibility artifacts and other field inhomogeneities, primarily affecting the tissue air interface in the brain. Measures have been taken to reduce the intra- and inter-site variability arising from noise in data, motion artifacts, scanners used in acquiring data, [3,4] but uncorrected EPI distortions have not been considered as a potential contributor to increased variability of DTI metrics in population studies. Here, we evaluate the potential contribution of EPI distortion to the observed inter-site variability in DTI metrics. This assessment is timely because methods exist that correct EPI distortions effectively from data acquired with reversed polarity of phase encoding (blip up and down).[5,6,7] Such correction methods could be used in multicenter studies.

Methods

Experimental Design

To address this issue, we need an appropriate experimental design. First, we need data from the same healthy subject at various sites, so that we can assume that all the measured variability across different scans is of experimental origin only, without contributions from biological variability. Second, we need data that is acquired with both blip-up and blip-down so that an effective distortion correction is possible. Third, by using only the blip-up or down acquisition, we can simulate what is typically done in multicenter DTI studies in which reverse phase encoding is generally not used. Finally, by comparing the voxel-wise variance for data processed with EPI distortion correction and without EPI distortion correction, we can evaluate the contribution of EPI distortions to the variability because the other sources of variability are the same for the two sets of data. Therefore, we used data from a healthy living phantom, scanned at 5 sites as part of Chronic effects of Neurotrauma Consortium (CENC) [8] with opposite phase encoding direction schemes [AP, PA].

Image Processing

Step1: Each AP and PA dataset from all sites underwent DTI data processing to remove eddy, motion distortion artifacts; Step2: EPI distortion correction was then performed on AP-PA data, using a fat suppressed T2W structural from one site that was used as an anatomical reference image[9,7]; Step3: Diffusion tensors (DT)s were computed for each output from step1 and step2 processing [9]. FA maps were derived from the computed DTs.

Analysis

Three groups were created comprising of data from each site, based on the EPI correction method used, namely: Group1- AP $_{\text{(distortion uncorrected)}}$, Group2- PA $_{\text{(distortion uncorrected)}}$ and Group3- AP-PA $_{\text{(distortion corrected)}}$. Standard deviation maps were created for each of the three groups. In addition to looking at the differences visually, we generated whole brain voxel-wise histograms to visualize the differences between the uncorrected and corrected data.

Results

The standard deviation maps for AP (distortion uncorrected) and PA (distortion uncorrected) show increased inter-site variability in fractional anisotropy (FA), in the following regions: brainstem, corpus callosum (CC) and at apex of the brain, as seen in figs 1, 2, and 3, respectively. These regions of increased variability are in line with the regions of maximal EPI distortion artifacts generally seen in DTI data. The figures also show the standard deviation maps computed for AP-PA (distortion corrected), where these inter site variability due

to EPI distortions have been eliminated. Whole brain histograms in fig 4 for the three groups show the positive effect of EPI distortion correction at a voxel level, compared to the uncorrected data.

Discussion

EPI distortion is one of the most prevalent artifacts in DTI acquisition and has generally been overlooked as a contributor towards inter-site variability. Moreover, DTI with reverse phase encoding is typically not collected in multicenter DTI studies, precluding the positive effects of robust EPI distortion correction on the data. In this analysis, we have demonstrated the importance of EPI correction in reducing inter-site variability using a living phantom. We showed reduced variability in FA between sites after EPI correction, even though the data were acquired with different scanner models from the same manufacturer and had slight differences in acquisition protocol. EPI correction is especially important for studies that focus on regions that can be especially corrupted by the distortions (e.g. mild TBI). It is therefore essential that multicenter studies consider the potential effects of EPI distortions when collecting DTI data and employ an effective means of EPI correction.

Acknowledgements

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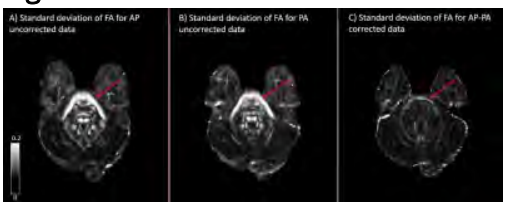
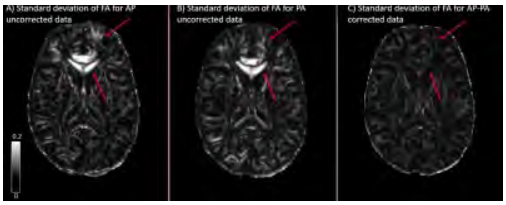
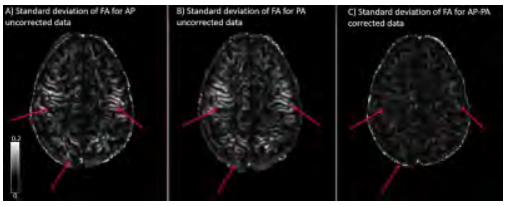
Figures



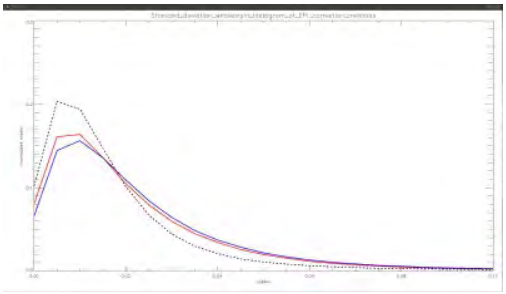
Standard deviation maps of FA that shows the intersite variability at the level of the brainstem. (A) and (B) show higher variability in uncorrected AP and PA FA maps respectively and (C) shows the removal of variability in FA maps after EPI correction with blip up- down correction is performed using information from AP-PA scans.



Standard deviation maps of FA that shows the intersite variability at the level of the Corpus Callosum (CC). (A) and (B) show higher variability in uncorrected AP and PA FA maps respectively and (C) shows the removal of variability in FA maps after EPI correction with blip up- down correction is performed using information from AP-PA scans.



Standard deviation maps of FA that shows the intersite variability at the level of the apex of the brain. (A) and (B) show higher variability in uncorrected AP and PA FA maps respectively and (C) shows the removal of variability in FA maps after EPI correction with blip up- down correction is performed using information from AP-PA scans.



Whole brain voxelwise histogram plotted for the three standard deviation of FA. Dotted line: Standard deviation of FA for AP-PA data after EPI correction, Red line: Standard deviation of FA for EPI uncorrected AP data, Blue line: Standard deviation of FA for EPI uncorrected PA data.

Appendix 45

Spatial normalization of individual fractional anisotropy (FA) maps to widely used population templates for analysis can increase variability and create spurious differences in the measured FA values

Spatial normalization of individual fractional anisotropy (FA) maps to widely used population templates for analysis can increase variability and create spurious differences in the measured FA values

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Synopsis

In this study we evaluate the effects of spatial normalization of individual fractional anisotropy (FA) maps to widely used population templates for analysis and its introduction of variability, creating spurious differences in the measured FA values.

Introduction

Multicenter studies such as Chronic Effects of Neurotrauma Consortium (CENC) [1] acquire both healthy and mild traumatic brain injury (mTBI) patient population data across various sites. In such large studies, group analysis is often performed by registering individual data to a pre-existing template, using regions of interest (ROIs) defined in that template space. [2,3] These methods have been used by several Diffusion Tensor Imaging (DTI) studies to analyze data. The advantage of analysis in a template space is the convenience of using pre-defined ROIs that can be mapped onto the study population data, either by bringing individual subject data into the template space or transforming the ROIs back onto the subject native space. The success of a template based ROI analysis relies on the accurate registration of individual data to the template. While there are proposed methods to harmonize multicenter data [4,5] to reduce inter-site variability, the implications of added heterogeneity from registration misalignments in template-based group analysis have not been fully considered. Since effects in mTBI can be potentially widespread and affect cortical and subcortical structures, any additional heterogeneity due to misalignment may obscure the interpretation of results. To investigate the potential misalignment effects of registering individual FA scans to a template, we will register living phantom DTI data from CENC, scanned at multiple sites to two commonly used templates in DTI analysis: JHU ICBM and ENIGMA. [6,7]

Method

We used DTI data of a living phantom, from CENC that were acquired on Siemens scanners at five different sites. The datasets were acquired with opposite phase encoding direction scheme [AP, PA]. The scans were corrected for eddy, motion and EPI distortion artifacts. Diffusion Tensor (DT)s were computed and Fractional Anisotropy (FA) maps were derived from the DTs using TORTOISE. [8,9] These FA maps derived from the DTs were used as the starting point for each of the following analyses. To address the potential inconsistencies in FA measurements between post processed scans from the same subject, we performed a rigid body alignment of the FA scans to a single scan using MIPAV [10] and computed a standard deviation map, $FA_{\text{rigid SD}}$. To address the accuracy of the registration software used in performing the alignment, we registered FA scans, to a mean FA from the group using ANTS SyN, [11,12] to create a standard deviation map out of the aligned outputs, named here as $FA_{\text{scalar SD}}$. To address the potential misalignments arising from registering to a template individual FA maps were ANTS SyN registered to the JHU ICBM FA and ENIGMA FA map. Standard deviation maps, $FA_{\text{scalar JHU SD}}$ and $FA_{\text{scalar ENIGMA SD}}$ were computed using the outputs from the two tests respectively. The standard deviation maps were inspected visually to identify variability between FA scans arising from each of the registrations.

Result

$FA_{\text{rigid SD}}$ and FA_{scalar} have almost no variability in the measured FA values, as expected within repeated scans on a healthy subject (fig 1-3). This supports that there is almost no variability between post processed scans and the registration algorithm performs satisfactorily when subjects are registered to a subject specific template. However, $FA_{\text{scalar JHU SD}}$ and $FA_{\text{scalar ENIGMA SD}}$, show regions of high variability such as in the apex of the brain, cingulum and deep brain structures such as cerebral peduncles. This indicates that registering individual FA images to a non-subject specific template, can introduce potential misalignments.

Conclusion

In DTI studies, careful measures are taken to design experiments and correct for potential DTI artifacts, to measure small changes in brain anatomy of patients with respect to controls. With our living phantom data analysis, we show the risk of additional sources of variability being introduced in regions that were not present prior to registering to a common template. Since the injury effects of mTBI are not limited to white matter structures and can be present in the cortical regions of the brain, the misalignments introduced along the brain periphery cannot be ignored. The reduction of variability in FA measurements when individual data is registered to a subject specific template can be particularly appreciated in longitudinal studies.

Acknowledgements

This material is based upon work supported by the U.S. Army Medical Research and Material Command and from the U.S. Department of Veterans Affairs Chronic Effects of Neurotrauma Consortium under Award No. W81XWH-13-2-0095. The U.S. Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick MD 21702-5014 is the awarding and administering acquisition office. Any opinions, findings, conclusions or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the views of the U.S. Government, or the U.S. Department of Veterans Affairs, and no official endorsement should be inferred.

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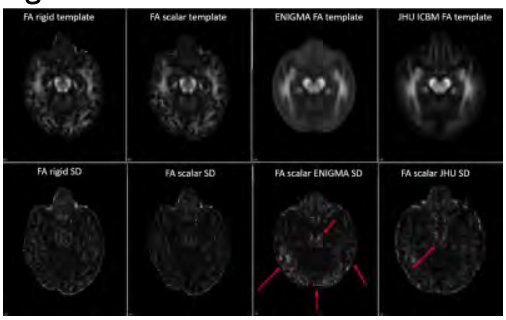
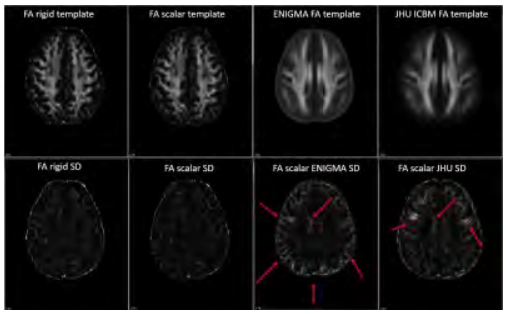
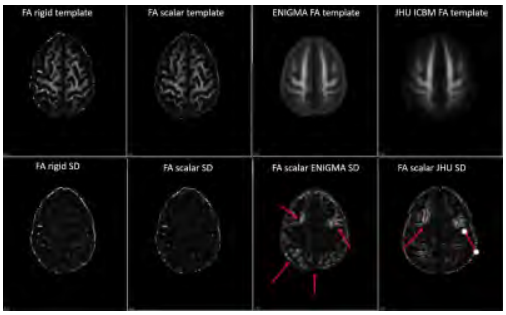
Figures



Top row shows the templates each of the FA map was registered to in the four tests. The bottom row shows the standard deviation (SD) maps of FA created for the four test, show at the level of brainstem, the introduction of variability (shown with red arrows) in FA scalar ENIGMA SD and FA scalar JHU SD ,when FA maps are individually registered to blurrier template.



Top row shows the templates each of the FA map was registered to in he four registration groups. The bottom row shows the standard deviation (SD) maps of FA created from the FA maps generated after the registrations. The SD maps show there is an introduction of variability (shown with red arrows) in the cingulum and in the periphery of the brain in $FA_{\text{scalar ENIGMA SD}}$ and $FA_{\text{scalar JHU SD}}$ maps.



Top row shows the templates each of the FA map was registered to in he four registration groups. The bottom row shows the standard deviation (SD) maps of FA created from the FA maps generated after the registrations. The SD maps show there is an introduction of variability (shown with red arrows) at the apex and in the periphery of the brain in $FA_{\text{scalar ENIGMA SD}}$ and $FA_{\text{scalar JHU SD}}$

Appendix 46

Comorbidity Phenotypes in Afghanistan and Iraq War Veterans with mild and no TBI:

A Chronic Effects of NeurotraumaConsortium Study

Comorbidity Phenotypes in Afghanistan and Iraq War Veterans with mild and no TBI: A Chronic Effects of Neurotrauma Consortium Study

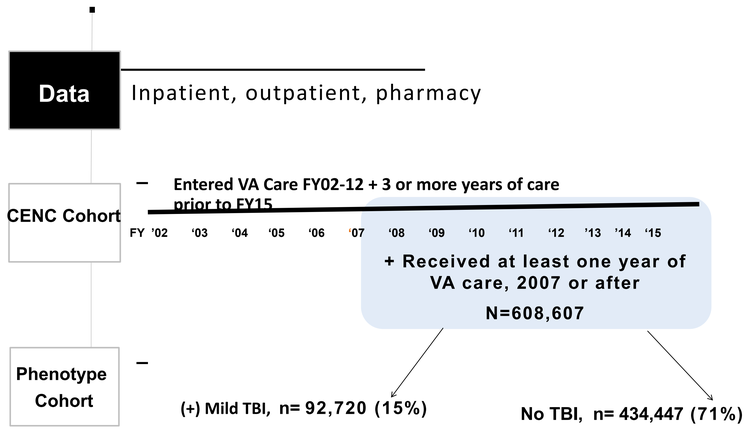
Mary Jo Pugh PhD, RN[1], Alicia Swan PhD[2], Roxana Delgado, PhD[2] Megan Amuan MPH[3] David Tate PhD[4]
Kristine Yaffe MD[5] Chen-Pin Wang PhD[6]

[1]Department of Internal Medicine, University of Utah and VA Salt Lake City; [2]South Texas Veterans Healthcare System and Department of Medicine UT Health San Antonio; [3]Bedford VA Medical Center; [4]Department of Psychology University of Missouri Saint Louis; [5]Department of Psychiatry University of California San Francisco and San Francisco VA Medical Center; [6]Department of Epidemiology & Biostatistics UT Health San Antonio

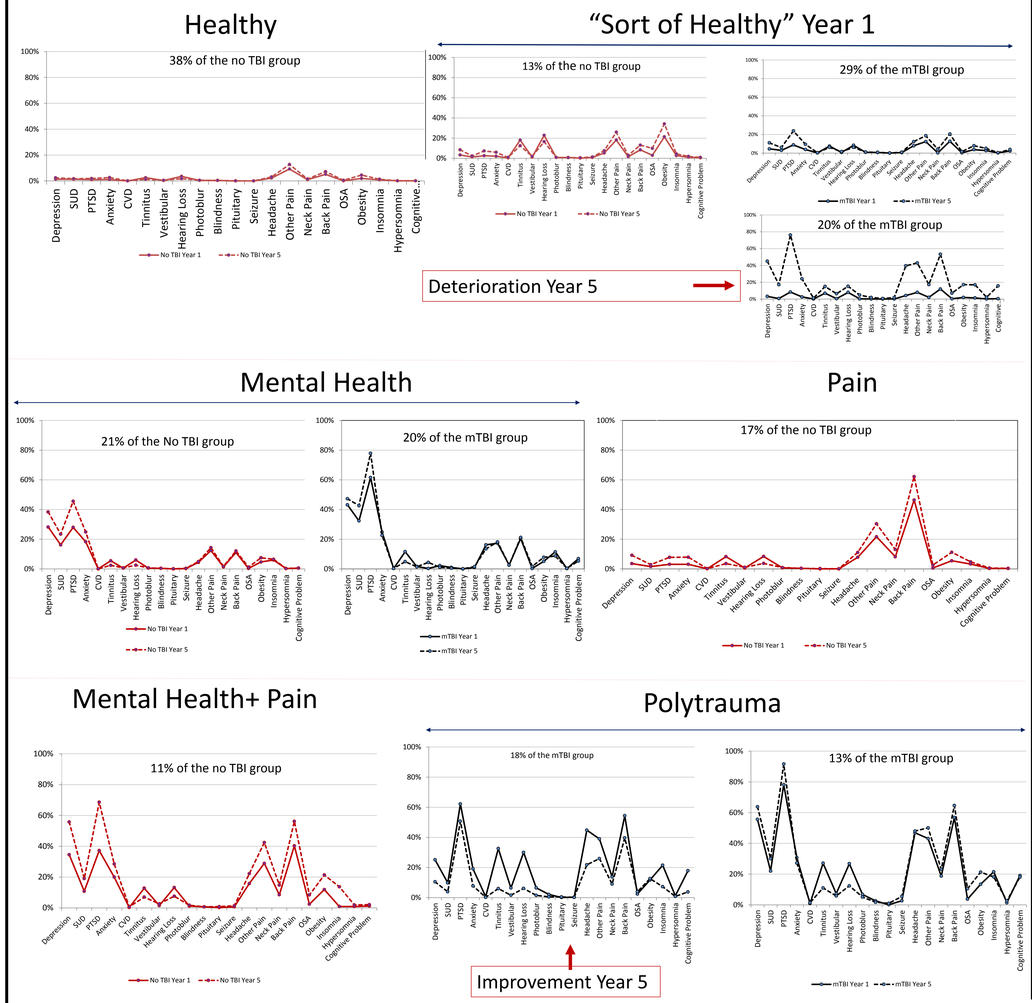
INTRODUCTION

- There is an established association between traumatic brain injury (TBI), pain, and posttraumatic stress disorder (PTSD) (i.e., Polytrauma Clinical Triad [PCT]) among both civilian and Veteran patients.
- More recent work has examined the possibility of different patterns of comorbidity beyond the PCT.
- Lippa et al. used factor analysis of a limited number of conditions identified by self-reported symptoms and found four factors in deployed Post-9/11 Veterans:
  1. Deployment Trauma Factor: Depression, PTSD, mTBI
  2. Somatic Factor: Pain and Sleep
  3. Anxiety Factor: Non-PTSD Anxiety Disorders
  4. Substance Use Factor: Substance Use/Dependence
- Studies of the population Post-9/11 Veterans using latent class analyis (LCA) with a broader array of comorbidity and longitudinal data found a latent class or **comorbidity phenotype** that reflected a combination of the PCT and Deployment Trauma Factor in both men and women.
- While individuals with TBI were primarily included in this PCT-like comorbidity phenotype, some were included in other phenotypes including: *Healthy, Chronic Disease, Mental Health, and Pain*.
- In order to better understand this heterogeneity, we now examine comorbidity phenotypes among more homogeneous groups: mild TBI and no TBI
- We hypothesized that there would be some overlap of comorbidity phenotypes between the mTBI and no TBI strata, but that there would be significant variation.
- Based on our prior LCA studies we also hypothesized that longitudinal patterns would reflect stability or deterioration, where individuals within a class were more likely to receive care for mental health, pain, and conditions that are potentially related to sequelae of mTBI (e.g., cognitive complaints, tinnitus, vestibular)

METHODS



PHENOTYPE RESULTS



CONCLUSIONS

- **Significant differences between mTBI and no TBI**
  - **In mTBI only: Polytrauma Phenotypes,**
  - **In No TBI only: Healthy**
    Pain only
    Mental Health + Pain
- **Patterns of progressive decline were evident in all.**
- **Patterns of dramatic decline was evident in one "Relatively Healthy" mTBI group.**
- **Patterns of improvement were evident for one Polytrauma phenotype.**
- **Additional data from DoD are required to understand baseline characteristics for these groups, particularly the mTBI groups that showed dramatic decline, and improvement over time.**
- **Linking these patterns to treatments received may also provide insight into treatments that are associated with better and worse outcomes.**
- **Examining health outcomes (e.g., suicide, overdose, homelessness, mortality) will provide insight into "So What" related to comorbidity phenotypes.**

ACKNOWLEDGEMENTS

This work was funded by the Chronic Effects of Neurotrauma Consortium, (CENC) by joint U.S. Department of Defense or the U.S. Department of Veterans Affairs funds, W81XWH-13-2-0095-04 and I01 CX001246.
The content of this poster is solely the responsibility of the authors and does not necessarily reflect the official views of the Veterans' Health Administration

Appendix 47

Age-Dependent Effects in Response to Repetitive Mild TBI in hTau Transgenic Mice at Latent Time Points

Age-Dependent Effects in Response to Repetitive Mild TBI in hTau Transgenic Mice at Latent Time Points

Scott Ferguson, Benoit Mouzon, Coral Hahn-Townsend, Carlyn Lungmus, Michael Mullan, Fiona Crawford

Introduction

Traumatic brain injury (TBI) is a serious illness which on average strikes one person every 15 seconds in the US. Even mild TBI, which comprise as many as 75% of all TBI cases, carries long term consequences. We have investigated the effects of repetitive mild TBI in young and aged hTau transgenic mice. Previous published research by our group revealed age-dependent gender differences in the response to TBI, within the current study we have also found chronic changes in the gender-dependent responses at late time points after TBI in animals that were injured at 1 year of age.

Methods and Materials

Male and female hTau transgenic mice at either 4 months or 1 year of age received 5 hits with an inter-mTBI injury interval of 48 hours. Briefly, an electromagnetic impactor generated a midline mTBI on the mouse scalp with a 5.0mm diameter flat face tip, at a 5m/s strike velocity, with a 1.0mm strike depth, and a 200msec dwell time. Anesthesia controls were matched for time spent under anesthesia. At 3, 6, or 12 months after the final injury or sham procedure, mice were assessed for motor performance using the Rotarod. Spatial learning and memory were assessed using the Barnes maze.

Results

Whereas young hTau mice show improvement to sham levels of performance after repetitive TBI, aged hTau mice showed significant TBI effects on their memory at chronic post injury time points. Gender differences continued to show significant effects on the TBI response of the aged mice at chronic time points, but further studies are needed to determine the pathological correlates of these differences.

Appendix 48

Altered White Matter Organization after Military Brain Injury: Preliminary Results from the ENIGMA Military Brain Injury Group

Altered White Matter Organization after Military Brain Injury: Preliminary Results from the ENIGMA Military Brain Injury Group

Emily L. Dennis[1,2], Elisabeth A. Wilde[3-5,11], Randall S. Scheibel[3,4], Maya Troyanskaya[3-4], Carmen Velez[6], Benjamin S.C. Wade[6,7] Ann Marie Drennon[8], Gerald E. York[9], Erin D. Bigler[10], Tracy J. Abildskov[10], Brian A. Taylor [3,4,11]; Carlos A. Jaramillo[12], Blessen Eapen[12], Heather Belanger[13,14], Rajendra Morey[15], Courtney Haswell[15], Mary R. Newsome[3,4], Harvey S. Levin[3,4], Sidney R. Hinds II[16]; William C. Walker[8,17,18], Paul M. Thompson[1,2,19], David F. Tate[6]

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Traumatic brain injury (TBI) in the military has a significant impact on troop readiness, and can lead to long-term physical, psychological, and cognitive difficulties. Most of these injuries are considered "mild", but can still have negative consequences. Detecting mild injuries can be more difficult than moderate or severe injuries, as the effects are more subtle and there is heterogeneity inherent in injury variables. Diffusion MRI (dMRI) is more sensitive to disruptions post-injury than traditional imaging modalities, but there have only been a few studies examining dMRI in military brain injury, with mixed results. Using the methods and approach of the ENIGMA consortium, we examined the effect of brain injury on dMRI metrics in the military. Participants were scanned and assessed via 5 different projects, for a total of 461 participants who reported history of at least one event consistent with TBI or concussion (TBI group) and 336 comparison participants who have never been diagnosed with TBI. All cohorts included participants who were either Veterans or Active Duty Service Members (ADSM) of the United States military. One study included Vietnam-era Veterans, and the other four included Veterans or ADSM of the American military operations in Iraq or Afghanistan (Operation Iraqi Freedom/Operation Enduring Freedom/Operation New Dawn). All sites processed dMRI brain scans locally with a standard protocol based on TBSS (tract-based spatial statistics) (http://enigma.usc.edu). FA and mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) were calculated and FA images were used to register data to the ENIGMA-DTI FA template. Each subject's FA values were then projected onto the ENIGMA-DTI FA skeleton; corresponding voxels from diffusion scans were also extracted. Measures were averaged across the entire skeleton, and within each of 5 midline, and 19 bilaterally averaged white matter (WM) regions of interest (ROIs) from the Johns Hopkins University (JHU) atlas, some of which partially overlap. Preprocessing included automated and visual quality control of the data, and exclusion of outliers. TBI/control effect sizes were calculated within each site, and statistical results were pooled across sites to conduct a meta-analysis on the individual regression parameters, testing for group differences across the WM ROIs. Our primary model included age, sex, and educational level. As educational level was not available for all participants, the final sample included 437 TBI participants and 268 comparison participants. Results were corrected for multiple comparisons using a Bonferroni correction ($p<0.05/25 = 0.002$). We found significantly higher FA in the right superior longitudinal fasciculus (SLF) in participants with a history of TBI (Cohen's

D=0.28, p=0.0013), with borderline results in the left SLF and left/right average. Examining males and females separately, the effect remained in the males, but not in females. This is likely in part due to the much smaller female sample size (53 TBI/74 control). Higher FA after brain injury is an unexpected result, and could indicate on-going recovery, or could be due to gliosis or other pathology. Future work will further examine whether this increased FA appears to have a beneficial or deleterious effect on brain function.

Appendix 49

Meta-Analysis of Diffusion MRI in the ENIGMA Military Brain Injury Group: Preliminary Results

Meta-Analysis of Diffusion MRI in the ENIGMA Military Brain Injury Group: Preliminary Results

Emily L. Dennis[1,2], Elisabeth A. Wilde[3-5,11], Mary R. Newsome[3,4], Randall S. Scheibel[3,4], Maya Troyanskaya[3-4], Carmen Velez[6], Benjamin S.C. Wade[6,7] Ann Marie Drennon[8], Gerald E. York[9], Erin D. Bigler[10], Tracy J. Abildskov[10], Brian A. Taylor [3,4,11]; Carlos A. Jaramillo[12], Blessen Eapen[12], Heather Belanger[13,14], Rajendra Morey[15], Courtney Haswell[15], Harvey S. Levin[3,4], Sidney R. Hinds II[16]; William C. Walker[8,17,18], Paul M. Thompson[1,2,19], David F. Tate[6]

[1]Imaging Genetics Center, Keck School of Medicine of USC, Marina del Rey, CA, USA; [2]Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior, UCLA, Los Angeles, CA, USA; [3]Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX, USA; [4]Department of Physical Medicine and Rehabilitation, Baylor College of Medicine, Houston, TX, USA; [5]Department of Neurology, University of Utah, Salt Lake City, UT, USA; [6]University of Missouri-St. Louis, St. Louis, MO, USA; [7]Ahmanson-Lovelace Brain Mapping Center, Department of Neurology, UCLA, Los Angeles, CA, USA; [8]Defense and Veterans Brain Injury Center, San Antonio, TX, USA; [9]Alaska Radiology Associates, Anchorage, AK, USA [10]Department of Psychology and Neuroscience, Brigham Young University, Provo, UT, USA; [11]Department of Radiology, Baylor College of Medicine, Houston, TX, USA; [12]Polytrauma Rehabilitation Center, South Texas Veterans Health Care System, San Antonio, TX; [13]James A. Haley Veterans Hospital, Tampa, FL, USA; [14]University of South Florida, Tampa, FL, USA; [15]Psychiatry, Duke University, Durham, NC; [16]Department of Defense/United States Army Medical Research and Materiel Command; [17]Department of Physical Medicine & Rehabilitation, Virginia Commonwealth University, Richmond VA; [18]Hunter Holmes McGuire VAMC, Richmond VA; [19]Departments of Neurology, Pediatrics, Psychiatry, Radiology, Engineering, and Ophthalmology, USC, Los Angeles, CA

Introduction

Traumatic brain injury (TBI) in the military has a significant impact on troop readiness, and can lead to long-term physical, psychological, and cognitive difficulties. It is one of the most common injuries affecting members of the United States military. Most of these injuries are considered "mild", but can still have negative consequences for an extended period post-injury. Detecting mild injuries can be more difficult than moderate or severe injuries, as the effects are more subtle and there is heterogeneity inherent in injury variables. Diffusion MRI (dMRI) is more sensitive to disruptions post-injury than traditional imaging modalities, but there have only been a few studies examining dMRI in military brain injury, with mixed results [1-5]. Our study included both Veterans and Active Duty Service Members (ADSM) of the United States military, across 5 cohorts. Using the methods and approach of the ENIGMA consortium [6], we examined the effect of brain injury on dMRI metrics in the military.

Methods

Participants were scanned and assessed via 5 different projects, for a total of 461 participants who reported history of at least one event consistent with TBI or concussion (TBI group) and 336 comparison participants who have never been diagnosed with TBI. All cohorts included participants who were either Veterans or ADSM of the United States military. One study included Vietnam-era Veterans, and the other four included Veterans or ADSM of the American military operations in Iraq or Afghanistan (Operation Iraqi Freedom/Operation Enduring Freedom/Operation New Dawn). All sites processed dMRI brain scans locally with a standard protocol based on TBSS (tract-based spatial statistics) [7] (http://enigma.usc.edu). FA and mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) were calculated and FA images were used to register data to the ENIGMA-DTI FA template [8]. Each subject's FA values were then projected onto the ENIGMA-DTI FA skeleton; corresponding voxels from diffusion scans were also extracted. Measures were averaged across the entire skeleton, and within each of 5 midline, and 19 bilaterally averaged white matter (WM) regions of interest (ROIs) from the Johns Hopkins University (JHU) atlas, some of which partially overlap. Preprocessing included automated and visual quality control of the data, and exclusion of outliers.

TBI/control effect sizes were calculated within each site, and statistical results were pooled across sites to conduct a meta-analysis on the individual regression parameters, testing for group differences in the 4 dMRI

measures averaged within each of the WM ROIs. Our primary model included age, sex, and educational level. As educational level was not available for all participants, the final sample included 437 participants with a history of TBI and 268 comparison participants. Our primary analyses were conducted on FA measures, with MD, RD, and AD serving as *post hoc* tests. Results were corrected for multiple comparisons using a Bonferroni correction ($p<0.05/25 = 0.002$).

Results

We found significantly higher FA in the right superior longitudinal fasciculus (SLF) in participants with a history of TBI (Cohen's D=0.28, $p=0.0013$), with borderline results in the left SLF and left/right average. We additionally found borderline results of higher FA in TBI in the posterior *corona radiata* and external capsule. Examining males and females separately, the effect remained in the males, but not in females. This is likely in part due to the much smaller female sample size (53 TBI/74 control).

Conclusions

Here we present preliminary analyses from the ENIGMA Military Brain Injury working group on dMRI markers of traumatic brain injury. Higher FA after brain injury is an unexpected result, and could indicate on-going recovery, or could be due to gliosis or other pathology. Future work will further examine whether this increased FA appears to have a beneficial or deleterious effect on brain function.

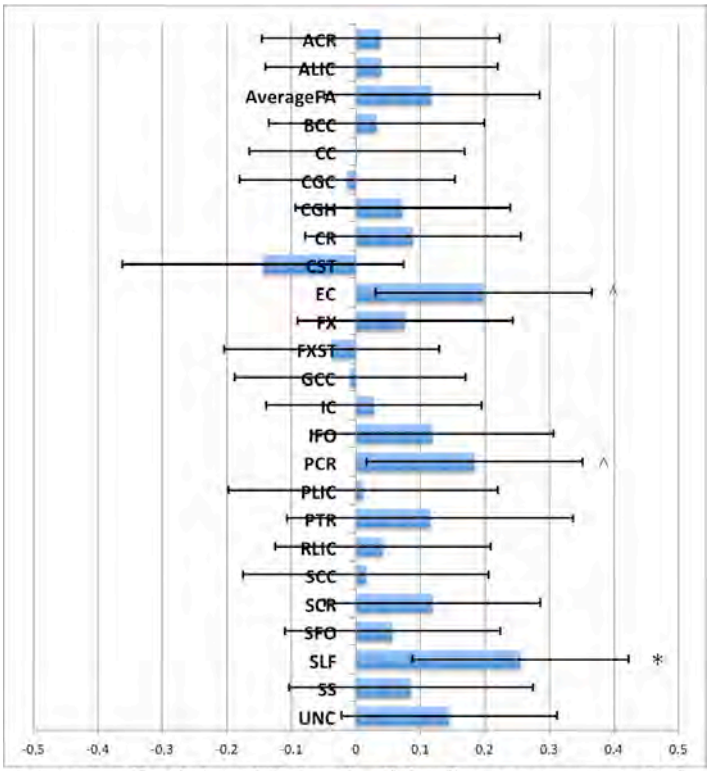

Figure 1. Effect sizes (Cohen's d) for the case vs. control meta-analysis in all sites across ROIs. Bars show 95% CI. * indicates significant at Bonferroni threshold ($p=0.002$), ^ indicates significant at $p<0.05$.

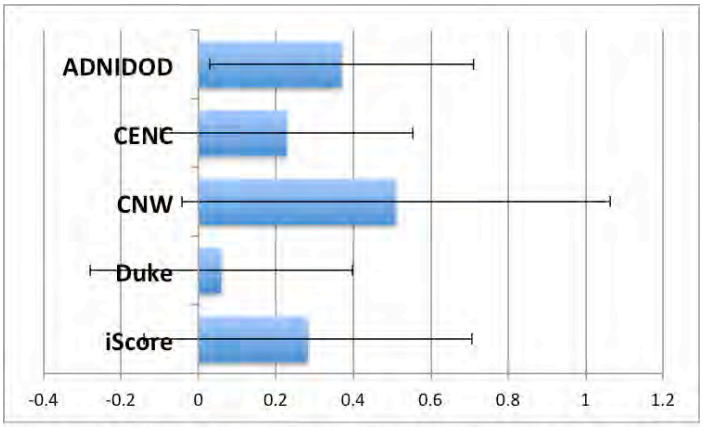

Figure 2. Effect sizes (Cohen's d) for each site for the SLF result from the meta-analysis.

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Appendix 50

Association of Clinically Diagnosed Depression With Total, Inpatient, Outpatient and Pharmacy VA Costs in Veterans Diagnosed with Traumatic Brain Injury

Association of Clinically Diagnosed Depression With Total, Inpatient, Outpatient and Pharmacy VA Costs in Veterans Diagnosed with Traumatic Brain Injury

Dismuke-Greer CE, Gebregziabher M, Hunt K, Taber D, Axon N, Egede LE.

BACKGROUND: In an Institute of Medicine (IOM) report, the IOM reviewed existing literature and concluded that there is sufficient evidence of an association between Traumatic Brain Injury (TBI) and depression. Based on this finding, the VA established depression as a secondary service connection condition if manifest within 3 years of the incurrence of moderate or severe TBI and within 12 months of mild TBI. Depression has been shown to be a major cause of disability and poor prognosis after TBI. Despite its demonstrated high prevalence in individuals diagnosed with TBI, currently the association of comorbid depression with Veterans Administration (VA) health care costs of Veterans diagnosed with TBI is unknown. The objective of this study was to examine the association of a clinical diagnosis of depression based on ICD9-CM codes with total, inpatient, outpatient and pharmaceutical costs in VA, for all Veterans and a subset of Operation Enduring Freedom (OEF)/Operation Iraqi Freedom (OIF) Veterans. The cohort consisted of all Veterans with TBI identified in VHA databases between 2000 and 2010, whose VHA costs were followed through FY 2014.

METHODS: TBI as well as its severity was identified using the ICD9-CM code algorithm developed for surveillance by the Defense and Veterans Brain Injury Center (DVBIC), the Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury, the US Army Public Health Command, the Armed Forces Health Surveillance Center and the Centers for Disease Control and Prevention. These ICD9-CM codes were provided to the Veterans Informatic and Computing Infrastructure (VINCI) who provided a cohort based on all Veterans diagnosed with these codes between 2000 and 2010. VINCI also provided all inpatient, and outpatient VHA claims and cost data for these Veterans. The validated algorithm for Elixhauser comorbidities which includes depression was used to identify depression and provide a count of other comorbidities. We examined differences in Veteran demographics, TBI severity, survival and other Elixhauser comorbidities by depression status using chi-square for categorical variables and t-tests for continuous variables. We examined unadjusted differences in VA total, inpatient, outpatient, and pharmacy costs by depression status using student t tests. We estimated adjusted total, inpatient, outpatient, and pharmacy VA costs associated with depression among Veterans diagnosed with TBI for all Veterans and a subset of OEF/OIF Veterans, using generalized linear models for total costs and seemingly unrelated (SURE) regression models for the separate inpatient, outpatient and pharmacy cost categories. SURE models are preferred as they allow for simultaneous estimation of the separate cost categories, recognizing the interdependence between clinical decision making and utilization of inpatient, outpatient and pharmaceutical services. We used box plots to examine visually the association of a depression diagnosis with total, inpatient, outpatient, and pharmaceutical VA costs for all Veterans diagnosed with TBI and a subset of OEF/OIF Veterans diagnosed with TBI. We used the Consumer Price Index (CPI) from the U.S. Department of Labor to adjust all VA costs to 2017 values. The CPI index was used to apply an inflation weight, which allows for all cost values to be valued in the same time period.

RESULTS: Of 113,339 all era Veterans diagnosed with TBI between 2000 and 2010, 72.91% were found to have a diagnosis of depression. Of 34,391 OEF/OIF Veterans diagnosed with TBI between 2000 and 2010, a higher percentage, 87.46%, were found to have a diagnosis of depression. For all era Veterans, those diagnosed with depression had significantly higher

($p<0.05$) unadjusted mean total VA costs per year ($13,908) relative to Veterans without a depression diagnosis ($9,988). For the subset of OEF/OIF Veterans diagnosed with TBI between 2000 and 2010, those diagnosed with depression also had significantly higher unadjusted total VHA costs per year ($8,550) relative to OEF/OIF Veterans without a depression diagnosis ($4,658). After adjustment for demographic, TBI severity, survival and Elixhauser comorbidities, depression was significantly associated with an additional $1,783 in total costs, $1,592 in outpatient costs, and $273 in pharmaceutical costs per year for all era Veterans and $1,237 in total costs, $1,683 in outpatient costs and $191 in pharmacy costs in OEF/OIF Veterans, relative to Veterans without a depression diagnosis. Interestingly, for OEF/OIF Veterans, depression was significantly associated with lower inpatient ($637) costs while depression was not significantly associated with inpatient costs for all era Veterans. Based on the estimated number of Veterans diagnosed with TBI and depression and the adjusted estimated cost per year, we estimated that the total VA cost burden of TBI and depression has been $1,101,577,870. For OEF/OIF Veterans we estimated that the total VA cost burden of TBI and depression has been $247,167,360 per year.

CONCLUSIONS: Depression has been established as a secondary service connection condition in Veterans diagnosed with TBI. We estimated that about 73% of all era Veterans and 87% of OEF/OIF Veterans who use VA facilities for care and diagnosed with TBI, have also been clinically diagnosed with depression in VA. We estimated the total VA burden of all era Veterans diagnosed with TBI and depression to exceed $1 billion per year, and a quarter $billion in OEF/OIF Veterans. The VA has evidence based treatment for depression, so future research needs to be conducted to examine whether Veterans diagnosed with TBI and depression are receiving appropriate mental health services.

ACKNOWLEDGEMENT: This work was supported by grant funding from: Department of Defense, Chronic Effects of Neurotrauma Consortium (CENC) Award W81XWH-13-2-0095 and Department of Veterans Affairs CENC Award I01 CX001135. The authors report no conflicts of interest. The views, opinions and/or findings contained in this article are those of the authors and should not be construed as an official Veterans Affairs or Department of Defense position, policy or decision, unless so designated by other official documentation.

Appendix 51

Examination of Symptom Over-Reporting and Self-Reported Pain and Depression in Iraq and Afghanistan Veterans with Mild Traumatic Brain Injury

Abstract for poster presented at the 46th annual International Neuropsychological Society Conference in Washington, D.C.

TITLE: Examination of Symptom Over-Reporting and Self-Reported Pain and Depression in Iraq and Afghanistan Veterans with Mild Traumatic Brain Injury

AUTHOR(S): R. S. Vasudevan[1], M. S. Herbert[2], S. M. Jurick[1], N. E. DeFord[2], A. V. Keller[2], S. N. Hoffman[2], M. Lee[2], M. Sanderson-Cimino[2], A. J. Jak[2]

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M.S. Herbert, N.E. DeFord, A.V. Keller, S.N. Hoffman, M. Lee, M. Sanderson-Cimino, A.J. Jak, Research, VA San Diego Healthcare System, La Jolla, California, UNITED STATES;

ABSTRACT BODY:

Objective : Pain, depression, and mTBI are highly prevalent and comorbid in Veterans. The relationship between these conditions is unclear; TBI may be directly associated with pain or only when mental health conditions are present. Persistent symptoms following mTBI and chronic pain are associated with elevated somatic focus and symptom over-reporting, so it is important to understand how symptom over-reporting impacts the relationship between pain, mood, and mTBI.

Participants and Methods: 42 OEF/OIF Veterans with history of mTBI completed self-report measures of post-concussive symptoms, depression, and pain. Veterans were separated into possible symptom over-reporting (SE; n=14) or non-over-reporting (NE; n=28) groups using a cutoff score of 13 on the Validity-10 (V-10), an embedded measure of symptom over-reporting in the Neurobehavioral Symptom Inventory. Group differences in pain and depression were examined via t-tests and linear regression.

Results : The SE group reported significantly greater depression symptoms, pain severity, pain catastrophizing, and pain interference (all $p's<0.05$) than the NE group despite no group differences on TBI injury variables. The relationship between depression and pain catastrophizing differed by group in a model containing pain severity. This relationship became non-significant in the NE group after controlling for pain severity ($r=0.219; p=0.292$), but remained significant in the SE group ($r=0.778; p=0.002$).

Conclusions : History of mTBI and elevated V-10 scores were associated with higher pain and depression symptoms, but in the SE group, the relationship between pain catastrophizing and depression was independent of pain intensity. Data suggest a general pattern of elevated symptom reporting in those with a history of mTBI and high V-10 scores where interpretation of symptoms may play a larger role in presentation and outcomes than objective markers of TBI or pain. Treatments for pain may need to be augmented to address pain catastrophizing in those with symptom over-reporting.

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Appendix 52

Phenotypes of Comorbidity among Women Veterans and Service Members after Mild Traumatic Brain Injury

Abstract ID: 420346

Abstract Title: ***Phenotypes of Comorbidity among Women Veterans and Service Members after Mild Traumatic Brain Injury***

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Mary Jo Pugh, PhD, RN - Professor, University of Utah Health Sciences Center, Division of Epidemiology (Role: Author)

Did you receive FEDERAL FUNDING for this work?

- Yes

If you received FEDERAL FUNDING, please provide your agency or grant number. Type NO, if you did not receive FEDERAL FUNDING for this work.
Chronic Effects of Neurotrauma Consortium: Department of Defense W81XWH-13-2-0095-04 and Department of Veterans Affairs I01 CX001246

Learning Objectives

1. Upon completion, participants will be able to names 4 common co-morbid conditions among post 9-11 veterans and service members.
2. Upon completion, participants will be able to identify 4 comorbidity phenotypes among post 9-11 veterans and service members.
3. Upon completion, participants will be able to state why it is important to understand comorbidity phenotypes in women and men with mTBI.
4.
5.

Objectives
To identify variation in longitudinal comorbidity phenotypes for men and women with mild traumatic injury (mTBI).

Design
Longitudinal study of post-911 veterans during the first five years of care in the Veterans Health Administration (VHA)

Setting
National VA outpatient and inpatient care data.

Participants
Women (n=5998) and men (n=87,122) with mTBI who entered VA care between FY2002-2012 and had three years of care at least one of which was after FY2007.

Interventions
N/A

Main Outcome Measure(s)
We conducted latent class analysis (LCA) stratified by sex, to develop comorbidity phenotypes using dichotomous indicators for TBI sequelae. TBI sequelae were identified using validated algorithms for use with ICD-9-CM codes each year of care.

Results
The LCA identified five trajectories for men and women during the first five years of VA care. Four latent classes were consistent across sexes (Healthy, Healthy with Deterioration, Mental Health+Pain, Polytrauma Clinical Triad (PCT; mental health, pain, and TBI). Women also had a Mood+Pain phenotype and men had a PCT phenotype that improved overtime. A higher proportion of women were classified as Healthy compared to men and a higher proportion of men were classified as Healthy with Deterioration.

Conclusions
Ensuring that Veterans healthcare needs are identified and met is a high priority. Women and men Veterans with TBI may have unique treatment needs. Findings from this study will help determine whether we need to tailor care for optimal outcomes. Understanding the complex comorbidity clusters between women and men may lead to gender specific interventions.

Content Topics
Life Stages
Young adult - 19 years to 29 years of age, Adult - 30 years to 66 years of age
Theme 1
Blast injury
Theme 2
Comorbid conditions
Theme 3
TBI as a chronic condition

Quad Charts for 2018

Chronic Effects of Neurotrauma Consortium: Longitudinal Cohort Study

PT120517-1/W81XWH-13-2-0095 (DoD); I01 CX001135(VA)

PI: Dr. David Cifu **Org:** Virginia Commonwealth University; Richmond VA

Award Amount: $5,663,894 (DoD) $7,058,370(VA)

Study/Product Aim(s)

Aim 1: Establish a longitudinal cohort of 1,100 OEF-OIF Veterans with and without mTBIs.

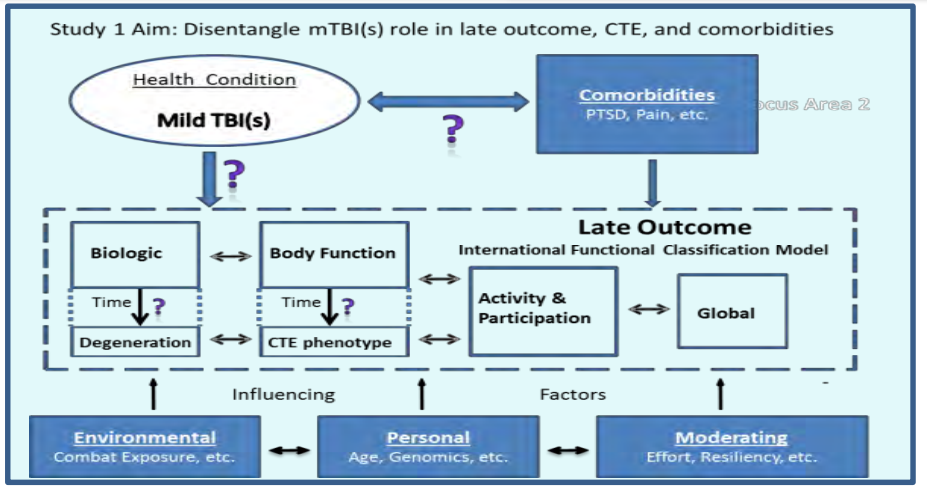
Aim 2: Determine the effects of mTBI and the effects of single versus multiple mTBIs on cognition and other key outcomes.

Aim 3: Identify mTBI subgroups with different levels or patterns of decline over time indicative of neurodegeneration.

Aim 4: Identify biologic variables associated with neurodegenerative behavioral patterns found.

Approach

A case-control study will comprehensively evaluate for late effects and comorbidities of combat-related mTBI while adjusting for all potential moderators of outcome.



100% of target recruitment to date and follow up visits ongoing at 8 sites: Richmond VA, Houston VA, San Antonio VA, Tampa VA, Ft. Belvoir, Boston VA, Portland VA, Minneapolis VA

Timeline and Cost

Activities FY	14	15	16	17	18
Planning and regulatory approval					
Enrollment and Initial Evaluations					
Follow-Up Assessments					
Data Analysis and Publications					
Estimated Budget (***$M***)	$1.7	$1.5	$2.7	$2.8	$3.3

Updated: (10/01/2018)

Budget Expenditure to Date (with key milestones & goals)

CY14 Milestones –Study initiated
✓ Summary: regulatory approvals, staff hiring/training, began enrolling
CY15 Milestones
✓ Summary: Baseline Assessments fully underway at all 4 initial sites
CY16 Milestones
✓ Ramped up # enrolled & ratio unexposed to align with target rate
✓ Implemented data quality procedures & site performance metrics
✓ Initiated enrollment at new DoD site
✓ Initiated mid-enrollment scientific data analyses
CY17 Key Goals
✓ Initiate enrollment at new VA sites
✓ Maximize retention for annual and in-person f/u assessments
✓ Prepare multiple scientific analyses with manuscripts based on baseline data from mid-way Data Snap-Shot
Projected Expenditure: $11,450,038 (DoD & VA)
Actual Expenditure: $12,050,422 (DoD & VA)

Chronic Effects of Neurotrauma Consortium: Epidemiology of mTBI and Neurosensory Outcomes

PT120517-4/W81XWH-13-2-0095 (DoD); I01 CX001246 (VA)

PI: Kristine Yaffe **Org:** Northern California Institute of Research and Education

Award Amount: $2,012,453(DoD) $1,067,675 (VA)

Study/Product Aim(s)

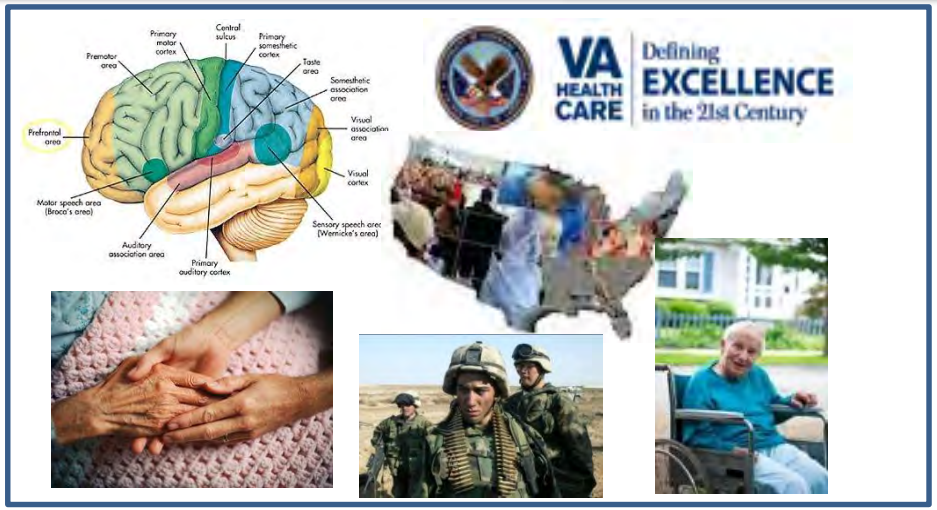
Aim 1: Among OEF/OIF/OND Veterans, to determine the association of mTBI and mental health disorders with adverse clinical outcomes with the goal of understanding why some Veterans with mTBI are more resilient than others

Aim 2: Among Veterans from any era, to determine whether mTBI is independently associated with adverse neurosensory outcomes and mortality across the life course and whether treatment of comorbid conditions reduces risk**.**

Aim 3: Among OEF/OIF/OND Veterans with mTBI who received five or more years of VA care, we will identify trajectories of neurosensory, psychiatric, and pain comorbidity.

Approach

We propose a series of related specific aims that capitalize on existing national databases to further our understanding of the association between mild TBI (mTBI), comorbidities, and adverse outcomes



Accomplishments: Creation of multiple databases for future mTBI research. One manuscript published, another in press, one submitted, several more in preparation.

Timeline and Cost

Activities	Year 1	Year 2	Year 3	Year 4 (NCE)
Planning and regulatory approval				
Conduct Analyses				
Manuscript Prep & Submission				
Dissemination				
Estimated Budget ($K)	$814	$814	$814	--

Updated: (10/01/2018)

Budget Expenditure to Date (with key milestones & goals)

Year 1 Goal

☑ Obtain all necessary regulatory approvals

Year 2 Goals

☑ Conduct Analyses for Aims 1-3

Year 3 Goal –

☑ Write Manuscripts

☑ Dissemination and Publication

Comments/Challenges/Issues/Concerns

- All sites have received IRB and HRPO approval
- All sites encountered budgetary delays due to a slower start-up than anticipated and plan to use the unspent funds for the same purpose as proposed and awarded

Budget Expenditure to Date

Projected Expenditure: $2,440,653

Actual Expenditure: $1,608,737

Chronic Effects of Neurotrauma Consortium: Tau Conformation and Modification in mTBI

PT120517-5/W81XWH-13-2-0095 (DoD); I01 RX001774 (VA)

PI: E. Mufson & F. Crawford **Org:** Barrows Neurological Institute, Roskamp Institute,

Award Amount: $3,587,062 (DoD) $1,596,031 (VA)

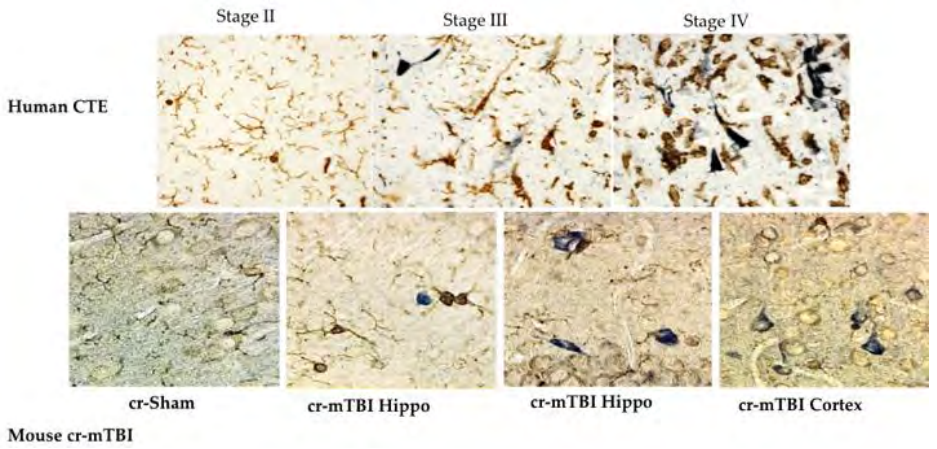
Study/Product Aims

- Characterization of tau and other pathological markers at a range of time-points following 5 repetitive mTBI or chronic r-mTBI in hTau mice.
- Perform genetic signatures studies from cortical and hippocampal tau positive neurons and correlate with neurobehavioral performance in a mouse model of mTBI.
- Characterize human hippocampal tau pathology in brains from soldiers and athletes who died with a pathological diagnosis or mTBI or CTE from the BU Neuropathology Core, correlate data with cases demographics.
- Perform single cell genetic array analysis of hippocampal tau positive neurons obtained postmortem form the brain of veteran and athletes who suffered from mTBI and CTE.

Approach

We will use single cell RNA profiling to assess gene expression alterations accompanying evolutionary time points in development of the tau pathology. We will use tau specific antibodies to evaluate NFT formation in human TBI.

Immunohistochemical demonstration of the similarity between Tau and glial pathology in the human CTE brain and mouse model of TBI



Timeline and Total Cost

Activities FY->	13	14	15	16	17
Breed, train test mTBI mice					
Brain removal and tissue staining					
Genetic assessments					
Data analyses and publication preparation					
Estimated Total Budget ($M)	1.2	1.2	1.2	1.2	1.2

Updated: 10/01/18

Goals/Milestones

CY15 Goal

✓Begin brain removal, continue breeding mice, start human brain studies

CY16 Goal

✓Continue breeding of colony
✓Conduct data analysis
✓Prepare publications

CY17 Goal

✓ Data analysis and publications

Budget Expenditure to Date

Projected Expenditure: $5,183,093 (DoD/VA)
Actual Expenditure: $5,082,616 (DOD/VA-Estimate)

Novel White Matter Imaging to Improve Diagnosis of Mild TBI

W81xWh-13-3-0095-20RX-002076-01

PI: Amy Jak, Ph.D. **Org:** VA San Diego Healthcare Systems, San Diego, CA **Award Amount:** $613,102

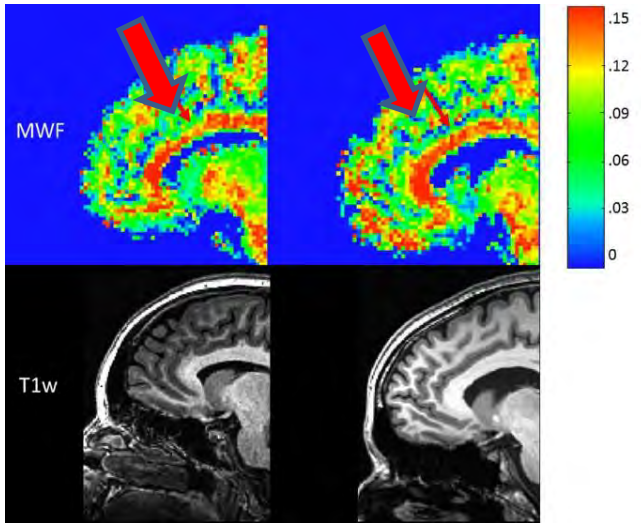
Study/Product Aim(s)

• Key Research Aims: Investigate utility of mcDESPOT to calculate myelin volume in vivo in a sample of 82 OEF/OIF Veterans with mild TBI, PTSD, or both, and controls, to improve differentiation of TBI from mental health etiologies for persistent post-concussive symptoms, improve understanding of the pathophysiology of mTBI, and enhance treatment planning.

- Aim 1: Determine if mcDESPOT myelin indices will significantly improve prediction of diagnostic group membership (normal, mTBI, PTSD, comorbid TBI/PTSD) relative to conventional neuroimaging markers used to assess mTBI (structural volume, DTI FA).
- Aim 2: Determine if cognitive functioning will correspond more strongly with mcDESPOT indices than with DTI in those with a history of mTBI.

Approach

The study will use a prospective design to examine the utility of the mcDESPOT sequence to identify white matter micro-structural damage in otherwise normal appearing white matter in OEF/OIF/OND Veterans with a history of mild TBI and/or PTSD.



Myelin water fraction (MWF) maps from combat-exposed Veteran with (top left) and without (top right) mTBI history. The red arrow highlights an area in which the MWF is visibly reduced in the subject with mTBI history

Timeline and Cost

Task	2015 (3 mo)	2016	2017	2018
Study Start Up				
Recruitment, enrollment, assessment, imaging				
Ongoing recruitment, assessment, data entry				
Data Analysis, dissemination of results				
Estimated Budget ($K)	**$37**	**$169**	**$220**	**$187**

Updated: (10/01/2018)

Goals/Milestones

FY16 Goal – Study Start Up

☑ Regulatory approvals obtained
☑ Study staff hired/trained
☑ Begin Recruitment/enrollment
☑ Begin Assessment/Imaging protocol

FY17 Goals – Recruitment, Enrollment, Assessment, Imaging, Data management

☑ Ongoing recruitment/enrollment/assessment & imaging protocol
☑ Data entry

FY18 Goals –Ongoing recruitment, assessment/imaging, data entry
Data Analysis, Presentation, Publication

☑ Ongoing recruitment/enrollment/assessment & imaging protocol
☑ Data Analysis
☐Dissemination of Results

Comments/Challenges/Issues/Concerns

Slow enrollment in some cells

Budget Expenditure to date – as of 08/31/18: $578,000 (estimate)

Chronic Effects of Neurotrauma Consortium: Structural & Functional Neurobiology of Veterans Exposed to Primary Blast Forces

PT120517-34 /W81XWH-13-2-0095 (DoD); I01 RX002172 (VA)

PI: Katherine H. Taber **Org:** W.G. (Bill) Hefner VA Medical Center

Award Amount: $1,528,934(VA only)

Study/Product Aim(s)

Specific Aim 1: We will characterize white matter abnormalities present in Veterans exposed to primary blast using multimodal neuroimaging.

Specific Aim 2: We will investigate how history of primary blast exposure and mild TBI are related to the presence of white matter abnormalities.

Specific Aim 3: We will characterize the sequelae of white matter abnormalities present in Veterans exposed to primary blast, including effects on brain function, cognitive function, and symptom presentation.

Approach

The goal of this project is to more fully characterize the neurobiological sequelae of exposure to primary blast forces. This is a cross-sectional prospective investigation of postdeployment Veterans exposed only to primary blast forces (with and without acute symptoms of TBI), Veterans with TBI due to blunt forces, and non-exposed Veteran controls using advanced multimodal neuroimaging, structured interviews, cognitive testing, and questionnaires.

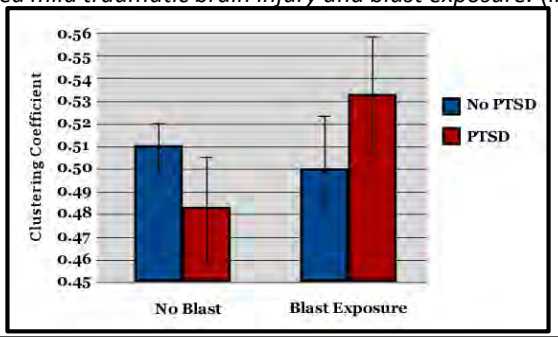
Timeline and Cost

Activities CY	15	16	17	18
Complete all preparatory to research tasks				
Participant recruitment & data acquisition				
Data entry, cleaning, initial processing				
Final data analyses, dissemination				
Estimated Budget ($K)	**$280**	**$510**	**$510**	**$229**

Updated: 10/01/2018

Rowland JA, Simpson SL, Godwin DW, Taber KH. *Functional brain network differences in Veterans developing PTSD following deployment-acquired mild traumatic brain injury and blast exposure.* (in preparation)

Blast exposure and PTSD interact to alter topology of functional brain networks (resting state fMRI) across many metrics. TBI was not associated with alterations in these same metrics.



Accomplishments: Full screening on 663 identified, 356 eligible for Visit 1, 354 willing to participate, 328 scheduled & **280 completed Visit 1**, 199 eligible for study Visit 2, 190 willing to participate, 188 scheduled & **164 completed Visit 2**. All neuroimaging datasets transferred to CENC. Three papers accepted for publication, two under review, seven in preparation. One pilot study approved for funding. **Grants**: Preparing three VA RR&D Merit Review resubmissions as well as one new K01 and one CDA-2 resubmission. Processing of MRI & MEG datasets & initial assessment data analytics ongoing.

Goals/Milestones

CY15 Goal Complete all preparatory to research tasks

- ☑ Obtain all required regulatory approvals
- ☑ Acquire/train new study staff
- ☑ Complete all required initial neuroimaging QA activities
- ☑ Acquire/install new equipment
- ☑ Complete data acquisition on first subject

CY16 Goals

- ☑ Complete data acquisition on 79 subjects
- ☑ Complete data cleaning on 40 subjects & begin analytics

CY17 Goal

- ☑ Complete data acquisition on 100 subjects
- ☑ Complete data cleaning on 80 subjects, initial analytics, disseminate

CY18 Goal

- ☑ Complete data acquisition on 21 subjects
- ☐ Complete data cleaning on 80 subjects, finalize analytics, disseminate

Budget Expenditure to Date

Projected Expenditure: $1,528,934

Actual Expenditure: $1,195,520

Chronic Effects of Neurotrauma Consortium: Clinical and Neuroimaging Correlates of Neurodegeneration in Military mTBI

PT120517-49/W81XWH-13-2-0095-49 (DoD); I01 RX 002171 (VA)

PI: Dr. Nicholas Davenport **Org:** Minneapolis VAHCS/Univ. Minnesota

Award Amount: $669,980 (DoD) $ 708,649 (VA)

Study Aims

Aim 1: To determine whether mTBI is associated with worsening symptoms and/or progressive neuropathology

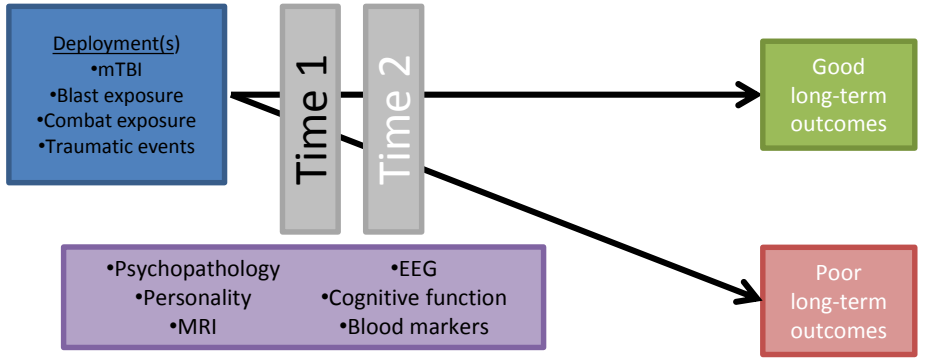
Aim 2: To identify clinical, self-report, neuroimaging, and biological measures that appear in the early chronic phase of mTBI and predict poor long-term prognosis

Aim 3: Identify changes in phenotypic measures that correspond to underlying evidence of progressive neuropathology

Aim 4: Address issues of sensitivity, specificity, and reliability in self-report and neuroimaging measures of mTBI-related outcomes

Approach

Longitudinal follow-up (3-6 year interval) of an existing cohort of 327 OEF/OIF military service members. Measures of TBI and mental health history, personality, cognitive function, structural brain connectivity, and functional brain coherence will be collected in a manner that allows direct comparison with existing data.



By collecting measures of biological and psychological health (purple box) at multiple time points along the putative course of post-concussive neuropathology, we can directly assess within-person changes associated with various experiences.

Accomplishment: We presented a poster at the Annual Meeting of the Society for Neuroscience (Nov 2017) demonstrating that mTBI is associated with an absence of normal age-related ventricular expansion.

Timeline and Cost

Activities	CY 15	16	17	18
Coordinate Resources				
Data Acquisition: Cohort 1				
Data Acquisition: Cohort 2				
Statistical Analysis				
Estimated Budget ($K)	**$134**	**$529**	**$508**	**$381**

Updated: 10/01/2018

Goals/Milestones

CY15 Goal – Coordination of resources

☑ All protocols established and tested

CY16 Goals – Data Acquisition: Cohort 1

☑ Enroll 70 veterans from SATURN

CY17 Goal – Data Acquisition: Cohort 2

☑ Enroll 10 veterans from SATURN

☑ Enroll 70 veterans from DEFEND

CY18 Goal – Dissemination of results

☑ Enroll 20 veterans from DEFEND

☐ At least 6 manuscripts in press by end of award

Budget Expenditure to Date

Projected Expenditure: $1,550,000

Actual Expenditure: $1,400,000 (Estimate)

Chronic Effects of Neurotrauma Consortium: Visual Sensory Impairments and Progression Following mTBI

PT120517-56/W81XWH-13-2-0095 (DoD); I01 RX002173 (VA)

PI: Randy Kardon MD, Kelvin Lim MD, **Org:** Iowa City, Palo Alto and Minneapolis VAHCS

Award Amount: $2,243,667 (VA only)

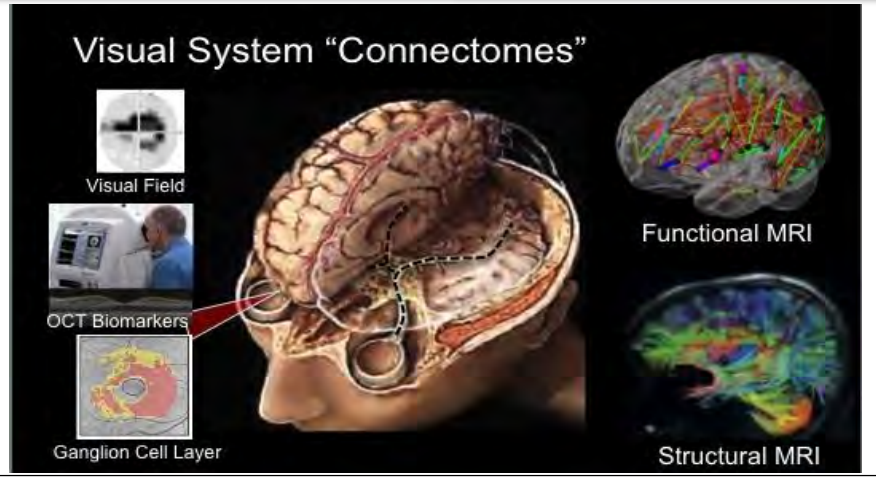
Study/Product Aims

Aim 1: Determine whether ocular functional and structural biomarkers correlate with corresponding CNS biomarkers after mild TBI

Aim 2: Determine whether ocular and CNS biomarkers deteriorate over time after mild TBI

Approach

These 2 aims will be accomplished by enrolling veterans with and without TBI and evaluating them at follow up intervals, using optical coherence tomography of the retinal layers, visual function testing, and structural and functional brain MRI to model progression.



The visual pathways in the eye and their connections within the brain are extremely well-characterized, allowing structure and function relationships to be precisely quantified using visual field, OCT, MRI and visual-cognitive tests in the eye and brain over time.

Timeline and Cost

Activities **CY**	2016	2017	2018
Recruitment/Screening Clinical/Cognitive Assessments (completed this quarter)			
Ocular / fMRI baseline (completed this quarter)			
Ocular / fMRI and Clinical/Cognitive Assessment follow-up			
Publications			
Estimated Budget ($K)	$ 904	$ 786	$ 788

Updated: 10/01/2018

Goals/Milestones

2017 Goals –

☑Subject screening and recruitment; baseline clinical & cognitive assessments; baseline (for new subjects) and follow-up (for returning subjects) Ocular and fMRI scanning and assessment; Data quality control and analysis. Milestones met.

☑Minneapolis VA – 136 subjects enrolled as of June 2017 (68 mild TBI and 68 control non-TBI veterans

❑Palo Alto VA – ended participation October 1, 2017.

2018 Goals –

☑Follow-up ocular and fMRI scanning and clinical & cognitive assessment; Data analysis; Publications on baseline data, now that recruiting has been completed.

- **Budget Expenditure to Date**
- Projected Expenditure: $1,956,660
- Actual Expenditure: $1,871,341 (Estimate)