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14. ABSTRACT

The primary objective of BBRAIN is to establish a retrospective and prospective biorepository network for GWI research by data mining from existing BBRAIN collaborator specimens and for recruiting 500 additional repository samples. The four prospective recruitment resource sites include Boston, Miami, Bronx and San Francisco. The BBRAIN structure provides centralized cataloguing and coordination of retrospective biorepository samples from 10 collaborating institutions who are sharing existing blood plasma, sera, PBMCs, cerebrospinal fluid, human-induced pluripotent stem cells (hiPSCs), DNA and saliva samples. Corresponding cognitive outcomes, brain imaging, demographics and health symptom surveys are included in the BBRAIN network datasets to allow for the comparison of biomarkers with behavioral outcomes. To date, data usage and material transfer agreements have been put in place with all sites and sharing has begun with retrospective data and outcomes.

15. SUBJECT TERMS

Gulf War Illness, Biorepository, consortium, CNS, innate immunity, cytokines, MRI neuroimaging, pesticides, DFP, sarin

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

The primary objective of the Boston Biorepository and Integrative Network for Gulf War Illness (BBRAIN) is to establish a retrospective and prospective biorepository network for Gulf War Illness (GWI) research by data mining from existing BBRAIN collaborator specimens and by recruiting 500 additional participants' repository samples. The four prospective recruitment resource sites include Boston University, Miami VA, Bronx VA and San Francisco VA. The BBRAIN structure currently provides centralized cataloguing and coordination of retrospective biorepository samples from 10 collaborating institutions who will share existing blood plasma, sera, PBMCs, cerebrospinal fluid, human-induced pluripotent stem cells (hiPSCs), DNA and saliva samples from participants previously consented to share their samples for future research. Corresponding cognitive outcomes, brain imaging, demographics and health symptom surveys will be included in BBRAIN network datasets to allow for the comparison of biomarkers with behavioral outcomes.

2. **KEYWORDS:**

Gulf War Illness, Biorepository Network, GW veterans, biomarkers

3. **ACCOMPLISHMENTS:**

Major goals of the project.

The approved statement of work lists the major goals of the project and the timeline for achieving each goal:

STATEMENT OF WORK

Table 1. Brain-Immune Interactions as the Basis of Gulf War Illness: Gulf War Illness Consortium

Tasks	Timeline
Major Task 1: Obtain IRB/HRPO approval	**Months**
1a. Obtain necessary IRB approvals or Exempt status	1-3
1b. Obtain DOD Human Research Protections Office (HRPO) approvals or Exempt Status for use of de-identified samples	4-6
Milestone(s) Achieved: Regulatory reviews completed, final approvals obtained	6
Major Task 2: Obtain Biorepository Data for Analysis and Catalogue Available Biospecimens for sharing at Repository Resource Sites	**Months**
2a. Obtain MRI, MRS, DTI, PET imaging data from retrospective resource (RR) sites and send to BUMC for cataloguing, post-processing and machine learning analyses	6-12
2b. Obtain demographic, health symptom and cognitive outcome data from RR Sites and send to BUMC for cataloguing, post-processing and analysis	6-12
2c. Catalogue and track available tissue, blood, saliva and CSF samples from RR sites	6-12
Milestone(s) Achieved: Biorepository data mining/cataloguing complete for 10 sites	12

Major Task 3: Perform Post-Processing of Imaging Data and Machine Learning Analysis with Combined Common Data Elements	**Months**
3a: Perform Brain image post-processing and cataloguing of images for repository.	1-24
3b: Perform data analysis of brain imaging and machine-learning analyses including cognitive data and health symptom data in cases and controls.	1-24
Milestone(s) Achieved: Brain imaging data mining analysis studies complete and imaging, demographic, cognitive outcomes repository created.	24
Major Task 4: Preparation and Training for Clinical Study Procedures	Months
4a. BUSPH Data Coordinating Center (DCC) will create website, data collection forms, specimen tracking system and databases for the entire repository network	1-6
4b. Develop manuals for the neuropsychological testing protocol, specimen collection protocols and recruitment screening procedures	1-9
4c. Train researchers and staff on protocols and quality control measures for the clinical study and repository collection	1-9
Milestone(s) Achieved: Staff trained and all databases and websites ready for subject recruitment and specimen tracking.	9
Major Task 5: Screening, Recruit and assessment of GW Veterans From Four Resource Sites	**Months**
5a: Obtain informed consent from potentially eligible GW veterans	9-36
5b: Assess subjects by obtaining demographics, medical history, self-report questionnaires, neuropsychological testing, Fitbit tracker, blood draw and saliva samples from 500 study participants.	9-36
5c. Obtain participants urine and stool sample kits back by mail to BUSPH for biorepository storage.	9-36
5d. Upload Fitbit sleep, heart rate variability and blood pressure data to BUSPH DCC to merge with other datasets.	9-36
5e. Score neuropsychological tests and upload summary data to DCC for entry, cleaning and analyses.	9-36
5f. Send blood and saliva samples to Nova University for analysis of cytokine and chemokine panels and cortisol measurements and biorepository banking.	9-36
Milestone(s) Achieved: Obtained blood, saliva, urine, stool, autonomic, demographic and cognitive data from 500 participants for biorepository and analysis.	36
Major Task 6: Process, Store and Manage samples for a total of 500 new participants.	**Months**
6a. Process and store blood, saliva, urine and stool samples received from 4 recruitment sites at two biorepository sites	6-33
6b. Perform local laboratory analyses (CBC) for 500 participants	6-33
6c. Extract DNA and RNA from 500 saliva samples and store in repository	6-33
6d. Run batched assays for cortisol and cytokine results (18 plex cytokine assay)	6-33
6e. Provide Sample request forms and track information regarding the use of samples	6-36+
6f. Ship samples to requesting investigators	6-36+
Milestone(s) Achieved: Processed all newly collected samples into biorepository storage, ran cytokine and cortisol measurements, extracted DNA/RNA for repository.	36
Major Task 7: Merge Data and Perform interim Data Analyses	**Months**

7a. Merge Clinical datasets data from prior studies for brain imaging, cognitive, demographic and health symptom report data	6-18
7b. Perform machine learning and/or meta-analytic techniques on common data elements from prior study epidemiological, cognitive and brain imaging data	6-18
7c. Discussion of results and preparation of abstracts for meeting presentations and initial manuscript for publication	18-24
7d. Annual reports of progress will be written	12-24
Milestone(s) Achieved: Preliminary analysis of results and presentation of initial results at scientific meetings and potential publication. Possible diagnostic markers from machine learning and meta-analyses.	6-24
Major Task 8. Perform Final Analysis, Prepare Manuscripts for Preparation and Finalize Biorepository for Sharing of Samples	**Months**
8a. Merge clinical datasets for prospective and retrospective data sets for GWI cases and GW controls and other symptomatic controls (fibromyalgia, IBS, CFS)	24-30
8b. Perform data analysis comparing cytokine, cortisol, cognitive outcomes, Fitbit and self-reported health symptom outcomes within GWI cases and controls from prospective data collection	25-26
8c. Coordinate interim and final collaborative publications and/or meta-analyses and Final Study Report	24-36
8d. Finalize websites for BBRAIN biorepository with data dictionaries and a searchable indexed site	24-36
Milestone(s) Achieved: Final analyses performed, publications prepared and biorepository dataset and indexed repository website prepared	24-36

The statement of work for year 2 is inclusive of Tasks 1-7 above. The statement of work for year 2 primarily describes the completion of the start-up phase of the biorepository network including obtaining local and funder institutional review approvals for clinical studies as well as establishing protocols for sharing samples with retrospective clinical sites and finalizing clinical protocols for neuropsychological assessments, blood, saliva and Fitbit sleep and other metrics. In addition, in year 2, the plan was to recruit 400 study participants for the study protocol including cognitive evaluations and specimen collection. Progress toward completing each task is listed below.

Summary of Clinical Assessments and Tests Collected from 4 Clinical Study Sites

	Year 1				Year 2				Year 3			
Target Enrollment (per quarter)	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Boston University			20	20	30	30	30	30	20	10	10	
San Francisco VAMC			10	10	15	15	15	15	10	5	5	
Bronx VAMC			10	10	15	15	15	15	10	5	5	
Miami VAMC			10	10	15	15	15	15	10	5	5	
Target Enrollment (cumulative)			50	100	175	250	325	400	450	475	500	

Accomplishment under these goals.

TASK 1. OBTAIN IRB & HRPO APPROVAL (MONTHS 1-6)

Task 1a. Obtain necessary IRB approvals or Exempt status

Institutional Review Board (IRB) approvals for the prospective sites have been obtained at Boston University, Miami VA, NOVA Southeastern University, Bronx VA, and the San Francisco VA/UCSF.

The DUA and MTA documents have been finalized and approved between BU and SF VAMC, NOVA Southeastern University, Bronx VA, Mass General Hospital, Georgetown University and University of Alabama.

All retrospective sites/samples have received IRB approvals (this includes, BUSPH, SF VAMC, NOVA Southeastern University, Drexel University, Beth Israel/Deaconess/Harvard, Mass General Hospital, Georgetown University, and the University of Alabama).

Task 1b. Obtain final DOD Human subjects Research Protections Office (HRPO) approvals or Exempt Status for Use of de-identified samples.

All participating sites (BUSPH, SF VAMC, NOVA Southeastern University, Miami VA, and the Bronx VA) have received HRPO approvals.

TASK 2. OBTAIN BIOREPOSITORY DATA FOR ANALYSIS AND CATALOG AVAILABLE BIOSPECIMENS FOR SHARING AT REPOSITORY RESOURCE SITES (MONTHS 6-12)

The consortium coordinating center and Administrative Core at Boston University has led many monthly web and in-person meetings to prepare for the clinical studies kick-off once all institutional approvals were obtained. A significant amount of time and effort was devoted to obtaining all required study materials and to developing centralized web-based data collection forms for the consortium studies. Smaller working group meetings were held during the past year to plan for the study and to deal with the recruitment stopping due to COVID-19. Table 3 lists these planning meetings and Table 4 lists the working groups. Several planning meetings were held with the Data Management Service Group to develop the data sharing web software for potential collaborating investigators to request for samples and also obtain additional information on the study. Variable names of specimens from retrospective resource (RR) sites were obtained and a common variable names and data dictionary for catalogued samples have been created. We now have HRPO approval, and we are in the process of obtaining and cataloging samples to be shared with the consortium for analysis and catalog. To date, two requests have been approved for sharing of imaging data and CSF samples through our online request forms. The consortium website and sample/data request form are now online at the links below:

https://sites.bu.edu/bbrain and https://wwwapp.bumc.bu.edu/BEDAC_BBrainRetro

Table 3. BBRAIN Monthly Planning and EAB Meetings

Date	Type of Meeting	Discussion Items
11-20-2019	Monthly Web-meeting	Prospective and Retrospective site updates
12-18-2019	Monthly Web-meeting	Prospective and Retrospective site updates
01-29-2020	Monthly Web-meeting	Prospective and Retrospective site updates
03-25-2020	Monthly Web-meeting	Prospective and Retrospective site updates
04-29-2020	Monthly Web-meeting	Prospective and Retrospective site updates
05-27-2020	Monthly Web-meeting	Prospective and Retrospective site updates
06-24-2020	Monthly Web-meeting	Prospective and Retrospective site updates
07-29-2020	Monthly Web-meeting	Prospective and Retrospective site updates
08-26-2020	Monthly Web-meeting	Prospective and Retrospective site updates
09-30-2020	Monthly Web-meeting	Prospective and Retrospective site updates
10-28-2020	Monthly Web-meeting	Prospective and Retrospective site updates

Table 4. BBRAIN Network Working Groups

Working Group	Tasks	Members
Data Management Service Group	Assist with QC issues, data cleaning, data management and sharing, website management.	Joe Palmisano, DCC Consortium PI, co-PIs
Statistics Service Group	Perform analyses and provides statistical planning and advice for study investigators and research site PIs.	Timothy Heeren, Joe Palmisano, Consortium PI/co-PIs
Translational Working Group	Forum for Intellectual property and material (IP) issues, translation of results into papers, abstracts, new grant submissions and how clinical results can inform each other.	Michael Pratt – BU Tech Transfer office Consortium PI, co-PIs Research site PIs
Behavioral Studies Working Group	Plan imaging protocols and provide quality control for multiple imaging sites. Plan behavioral testing protocols and coordinate clinical studies for comparability.	Drs. Sullivan, Killiany, Koo Krengel, Toomey, Golier, Chao, Klimas
Immune Genetics Working Group	Plan and implement studies assessing brain-immune interactions involving glia and proinflammatory cytokines/chemokines through genetic SNPs and mRNA and miRNA protein studies.	Drs. Klimas, Sullivan
Gulf War Veterans Advisory working Group	Update fellow GW veterans about GWIC research efforts and results, assist with recruitment efforts by making fellow vets aware of GWIC studies.	Denise Nichols, Frances Perez Wilhite, Lynn Santosuosso, Tim Demers, Christine Tron, Jim Arrocho

Task 2a. Obtain MRI, MRS, DTI, PET Imaging data from retrospective resource (RR) sites and send to BUMC for cataloguing, post processing and machine learning analyses

Imaging data obtained from retrospective sites including the San Francisco VA and Mass General Hospital were sent to Drs. Killiany and Koo at Boston University for cataloguing, post-processing and analysis. The MRI scans were transferred electronically in either extended DICOM or par/rec format to the Center for Biomedical Imaging at Boston University School of Medicine.

The San Francisco VA site has contributed the following de-identified neuroimaging data types to the BBRAIN Imaging repository from prior studies on GW veterans: 1.5T data (T1, T2, and proton density scans) from 257 GW veterans, 4T data (T1, T2, and FLAIR scans) from 207 GW veterans, and 3T data (T1, T2 and FLAIR scans) from 230 GW veterans. These images will be categorized and stored for query for researchers interested in using them for analyses.

Data from the Harvard University/Mass General Hospital PET and diffusion tensor imaging studies were also shared from 40 scans with Dr. Koo at Boston University as part of the planned BBRAIN imaging studies. These machine learning and multi-modal analyses are currently being conducted. Imaging data from Georgetown University and University of Alabama will also be shared shortly now that the DUA has been approved for these sites. This data will also be added to the imaging post-processing pipeline and machine learning analyses.

Additional hard drives have been purchased to store the vast amount of imaging data that will be shared. As the images were obtained, each scan underwent quality checking that consisted of a visual inspection for the presence of noise or artifact as well as a review of scan parameters to ensure that the appropriate ones were used in the acquisition. Scans that failed the quality check were rejected by the study and remediation discussed with the appropriate retrospective site investigator. Scans that passed the quality check will be entered the post-processing pipeline for data mining and sharing.

Task 2b. Obtain demographic, health symptom and cognitive outcome data from RR sites and send to BUMC for cataloguing, post-processing and analysis

HRPO approvals and DUAs have now been obtained from most study sites and the demographic, health symptom and cognitive outcome data have now been obtained from several RR sites. Data variables names, REDCap shells, and data dictionary were obtained from retrospective sites to create common variable names for specimens that are in the process of being catalogued for sharing.

To date, GWIC demographic, health symptom and cognitive data from 263 study participants has been added to the BBRAIN repository. In addition, the San Francisco VA has also shared demographic information, health symptom and cognitive outcomes from 224 GW veterans and the Roskamp Institute shared demographic information, health symptom and cognitive outcomes from 63 GW veterans.

Additional demographic, case status and health symptom data will be obtained from Georgetown University and the University of Alabama now that the DUAs have been approved for these study sites. Once the rest of these data are combined and common data elements (CDEs) are determined, analyses will begin on cognitive outcomes and health

symptom outcomes and submitted for publication.

Task 2c. Catalogue and track available tissue, blood, saliva and CSF samples from RR sites

We are currently in the process of obtaining and cataloguing specimen data information from the retrospective resource sites (RRS) to add to the list of available samples for sharing. This has included human induced pluripotent stem cell (hiPSC) lines, serum samples, plasma samples, DNA and RNA samples and cerebrospinal fluid.

Specifically for the BBRAIN repository of hiPSC cells, we have:

- Expanded capabilities to provide partially differentiated neurospheres
- Expanded technical knowhow into organoid technology
- Plans to provide Dr. James Cai of Texas A&M with hiPSC lines if his proposal is funded by the DOD. If funded, this study will use single-cell RNA sequencing (scRNAseq) to map transcriptomic landscapes in neurons derived from induced pluripotent stem cells (iPSCs) of symptomatic and nonsymptomatic Gulf War Veterans. We will use machine learning (ML) approaches to infer single-cell gene regulatory networks (scGRNs) from scRNAseq data for neuronal samples to identify genes implicated in neuropathological development associated with GWI and gene expression programs underlying GWI predisposition. A better understanding of these mechanisms will shed new light on evidence-based strategies of clinical intervention.
- Drs. Baas and Qiang have submitted DOD proposals using the hiPSC lines that would involve collaborations with Dr. James O'Callaghan of the CDC and Dr. Ashok Shetty of Texas A&M.

TASK 3. PERFORM POST-PROCESSING OF IMAGING DATA AND MACHINE LEARNING ANALYSIS WITH COMBINED COMMON DATA ELEMENTS (MONTHS 1 - 24)

Task 3a. Perform brain image post-processing and cataloguing of images for repository

Post-processing and cataloguing of images will has begun for sites that have already shared their imaging data and will continue when the rest of the sites share their data.

Task 3b. Perform data analysis of brain imaging and machine-learning analyses including cognitive data and health symptom data in cases and controls.

Machine learning multi-modal approach to brain connectomics analysis will to be conducted once brain scans are post-processed and added to the machine learning data analysis computational pipeline. This work will be used to validate Dr. Koo recent paper using GWIC data analyses (Cheng et al., 2020).

TASK 4. PREPARATION AND TRAINING FOR CLINICAL STUDY PROCEDURE (MONTHS 1 - 9)

As previously described, monthly web meeting and working group meetings were ongoing during the past year to prepare for the planned clinical studies. In addition, extensive training was conducted with the site research assistants as the cognitive battery and other parts of the protocol were updated due to COVID-19 safety issues.

Task 4a. BUSPH Data Coodinating Center (DCC) will create website, data collection forms, specimen tracking system and databases for the entire repository network

The Data Coordinating Center (DCC) now renamed 'BEDAC' at BUSPH has developed a website to assist in the management and conduct of the repository that will contain the following components: a data entry application, participant and data tracking applications, reports for investigators to monitor status and research staff to manage day to day operations; public-facing web application for repository information, data requests, and data access. The website now contains publicly available informational pages, including descriptions of RS, projects, investigator profiles, and publications with links to PubMed; as well as informational areas to be used for dissemination of project results. All project-specific applications (e.g., tracking, data entry and upload) is accessible via the website and restricted to project personnel through secure logins. The site also includes areas for NCC, RS and project level communications including news (announcements, meetings); manuals, forms and protocols; up-to-date personnel contact information; an area for secure transfer of data; reports for enrollment, follow up and data management. The sites are listed at the links below:

http://sites.bu.edu/bbrain/ and https://wwwapp.bumc.bu.edu/BEDAC_BBrainRetro

Progress to date includes that BEDAC staff have finalized the study participant telephone recruitment screening tool and constructed an electronic participant screening tool using REDCap software. BEDAC staff also finalized data collection forms for study personnel use and built an electronic data capture system using REDCap web-based software. A customized participant tracking and appointment log system was also constructed with separate secure login for each study site. BEDAC also worked with consortium research investigators to design a customized bar-coded bio-specimen tracking and inventory system, and conducted in-person trainings with all clinical research staff for web-based screening, tracking, and data collection tools. The cleaned data will be converted into analytic datasets for the centralized statistical programming and data analysis. The sample request electronic form and approval process has also now been created and is shown below:

Task 4b. Develop manuals for the neuropsychological testing protocol, specimen collection protocols and recruitment screening procedures

Manuals for the neuropsychological testing protocol, blood, saliva, urine and microbiome specimen collection and recruitment protocols have been compiled and finalized. The table below describes the full study protocol for the four study sites in Boston, Miami, Bronx and San Francisco.

Table 5. BBRAIN study protocol

Study Protocol	Boston		Miami		Bronx		San Francisco		Total
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	
Questionnaires (demographics, general health and symptoms, pain, fatigue, sleep, medical conditions, deployment and exposure history)	150*	50*	50	50	50	50	50	50	n = 500 (300 cases/200 controls)
Clinical evaluation and autonomic measures (medical history, height, weight, supine/standing BP and pulse; FitBit BP, HRV, sleep quality)	150	50	50	50	50	50	50	50	n = 500 (300 cases/200 controls)
Clinical lab tests (CBC, metabolic profile, lipid panel, TSH, ANA, RF)	150	50	50	50	50	50	50	50	n = 500 (300 cases/200 controls)
Biorepository Samples and Research assays (plasma cytokines /chemokines, salivary cortisol; plasma, serum, whole blood, DNA, RNA, Urine, fecal sample)	150	50	50	50	50	50	50	50	n = 500 (300 cases/200 controls)
Neuropsychological assessment (executive function, attention, memory, psychomotor function, motivation, mood)	150	50	50	50	50	50	50	50	n = 500 (300 cases/200 controls)
Longitudinal assessment (clinical evaluation, clinical lab tests, plasma cytokines, neuropsychological assessment; biorepository samples)	100	50	25	25	-	-	-	-	n = 125 (cases/ 75 controls)

*100 participants will be recruited on site and 100 participants remotely.

Task 4c. Train researchers and staff on protocols and quality control measures for the clinical study and repository collection

A detailed in-person training session was held in June 2019 at the Boston University Coordinating Center for all clinical research personnel who will be working directly with study participants to ensure adequate quality control of test administration and interview procedures among the study sites. All neuropsychological testing materials and survey instruments have been ordered purchased and were distributed among the four clinical study sites at this meeting. Three out of the four sites recently hired new RAs to replace the initially trained RAs. As a result, a new in person training was conducted in October 2019 for all four site RAs for adequate quality control of test administration among the study sites. Quality control measures will continue to be instituted and monitored by experienced Administrative Core investigators including Dr. Toomey as the clinical studies proceed to ensure good inter-rater reliability and to reduce tester drift among the study sites.

TASK 5. SCREENING, RECRUIT AND ASSESSMENT OF GW VETERANS FROM FOUR RESOURCE SITES (MONTHS 9 - 36)

Obtaining all necessary institutional approvals has taken longer than initially expected. However, to date, we have received approval to begin study recruitment at all study sites. We began recruitment in Boston in February and saw two study participants before being

shut down by COVID-19 in March. We had six additional participants scheduled who will now be rescheduled in this next quarter. However, the first two participants were a good test of the study protocols and all samples were obtained from these participants including blood, saliva, stool and urine in addition to surveys, demographic and health information and Fitbit data.

In total, 500 study participants (300 GWI cases, 200 controls) will be recruited from four RS sites; Boston, MA, Miami, FL, Bronx, NY and San Francisco, CA. At the Miami, Bronx and San Francisco sites, 100 study participants each will be recruited. At the Boston site, 100 study participants will be recruited to participate on site and an additional 100 participants not residing close to the any of the four recruitment sites will be given offered travel costs to participate at the Boston site. This will not occur until it is deemed safe to travel people after COVID-19 concerns are resolved.

To date, 76 participants have been screened. Of the 76, 41 are eligible (37 GWI Cases and 4 healthy controls). Please see recruitment data tables below.

BBRAIN: Screening and Enrollment Summary
October 29, 2020

	Total	Boston	Bronx	Miami	San Francisco
Number of Subjects Contacted	76	44	0	7	25
Number of Subjects Screened	73 (96.1%)	44 (100.0%)	0 (.%)	7 (100.0%)	22 (88.0%)
Number of Subjects Eligible	41 (56.2%)	32 (72.7%)	0 (.%)	2 (28.6%)	7 (31.8%)
Number of Subjects with Appointments Made	8 (19.5%)	8 (25.0%)	0 (.%)	0 (0.0%)	0 (0.0%)
Number of Subjects Assessed	2 (25.0%)	2 (25.0%)	0 (.%)	0 (.%)	0 (.%)

	Total		Boston		Bronx		Miami		San Francisco	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Number of Subjects Screened	67	5	42	2	0	0	6	0	19	3
Number of Subjects Eligible	37	4	30	2	0	0	2	0	5	2
Number of Subjects Assessed	2	0	2	0	0	0	0	0	0	0

Task 5a. Obtain informed consent from potentially eligible GW veterans

To date, we have received informed consent from two eligible GW veterans.

Task 5b. Assess subjects by obtaining demographics, medical history, self-report questionnaires, neuropsychological testing, Fitbit tracker, blood draw and saliva samples from 500 study participants.

Two study participants have been seen in-person to date, however all study protocols for the clinical studies have been finalized and are listed in the tables below and in Table 1 above. We have been greatly delayed in subject recruitment due to COVID-19, however we have gotten approval to resume recruitment in a limited capacity for all study sites. We have also submitted an IRB amendment to remove some of the cognitive tests that involved the most touching and sharing of materials back and forth and included a different executive function task to reduce COVID-19 risks. We also instituted plexiglass between the tester and the study participants as well as PPE including masks and gloves. All study protocols that can be done remotely will also be done that way including study surveys.

This will get us back to reaching our recruitment goals as soon as possible. We will begin by re-contacting participants from GWIC and other GW studies at the SF VAMC, Miami VAMC and Bronx VAMC who have agreed to be re-contacted for future studies. The tables below list the updated complete survey and cognitive data that will be collected at the prospective sites. To date, two participants have completed the study protocol.

Table 6. BBRAIN study surveys

Name	Description
Demographics	Subjects report information on age, education, gender, ethnicity, marital status, GW duty service (active vs. reserve/National Guard), military rank and military status.
SF36V	Veterans' version of the SF36 which assesses functional health-related quality of life in 8 domains and provides overall summary scores for physical and mental health status.
Kansas Gulf War and Health Questionnaire	Queries veterans about demographics, military and deployment history, and chronic symptoms and diagnoses required to ascertain Kansas GWI and CMI
Medical Conditions	A checklist with 21 medical conditions that the subject is asked to rate if they have ever had the condition, how it was diagnosed (self or doctor) and when it
Kansas Gulf War Experiences and Exposures Questionnaire	A questionnaire that assesses veteran-reported experiences and exposures during their deployment to the 1991 Gulf War
Structured Neurotoxicant Assessment Checklist (SNAC)	The SNAC assesses the degree of past and current exposure to neurotoxicants during civilian and military occupations and includes questions pertaining to recent occupational and environmental exposures.
Pittsburg Sleep Quality Index (PSQI)	PSQI assesses sleep quality during the past month. It covers domains of sleep quality, latency, duration, efficiency, disturbances, medications and daytime dysfunction. Total global scores range from 0-21.
Multidimensional Fatigue Inventory Questionnaire (MFI-20)	20 item self-report fatigue instrument that covers general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity.
McGill Pain Questionnaire	A pain questionnaire that includes 3 sections including what the pain feels like, change over time and strength of pain. Scores range from 0-78.

Table 7. BBRAIN Neuropsychological Test Battery

Test Name	Description	Outcome Measure
I. Executive System Functioning		
Controlled Oral Word Association Test (COWAT)	Spontaneous generation of words from letters F, A and S and animals category.	Total correct words generated
D-KEFS Category switching	Number of correct words generated switching between two categories	Total number of words Total number of correct category switches
D-KEFS Color-Word Interference Test (Stroop)	The Stroop is a test that measures the ability to inhibit competing responses in the presence of salient conflicting information. This ability can be called response inhibition, or behavioral inhibition. Secondarily, the test also measures processing speed of verbal (words) and nonverbal (colors) stimuli.	Total Errors Self-corrected errors Uncorrected errors
D-KEFS Category switching	Number of correct words generated switching between two categories	Total number of words Total number of correct category switches
II. Tests of Attention, Vigilance and Tracking		

Trail-making Test (Reitan &Wolfson, 1985)	Timed connect-a-dot task to assess attention and motor control requiring sequencing (A).	Time to Completion Self-Corrected errors Uncorrected errors
Continuous Performance Test (Connors' CPT3)	Target letter embedded in series of distractors; to assess sustained attention and reaction time.	Reaction Time, Total Omission and Commission Errors
III. Tests of Motor Function		
Finger Tap Test	Continuous tapping of computer key with alternate hands; assesses simple motor speed.	Number of taps
IV. Tests of Visuospatial Function		
Rey-Osterrieth Complex Figure Test	Copy of a complex figure	Total correct out of 36
V. Tests of Memory		
California Verbal Learning Test (CVLT- II; Delis et al., 2000)	List of 16 nouns from 4 categories presented over multiple learning trials with recall after interference; assesses memory and learning strategies.	Total Trials 1-5 Long Delay
Rey-Osterrieth Complex Figure Test	Immediate and delayed recall of a complex figure	Total recall out of 36
VI. Tests of Motivation and General Intellectual Ability		
CVLT – Forced Choice Recognition	Forced choice of word pairs for each of the 16 target items.	Total correct
Wide-Range Achievement Test - Reading	Measures word reading skills and word decoding through letter identification and word recognition.	Total Correct Scaled Score

Task 5c. Obtain participants urine and stool sample kits back by mail to BUSPH for biorepository storage.

BUSPH serves as a biorepository storage (BS) site for urine and stool sample collection. Urine and stool sample collection kit will be handed to participants on the day of their in person appointment at the four prospective sites. Subjects will provide their first morning urine and ship it overnight to the BUSPH Exposure Assessment laboratory for analysis and storage. Subjects will also collect stool samples using detailed instructions provided on the day of appointment and will also ship it to BUSPH Exposure Assessment laboratory for analysis and storage. This procedure worked well for the first two study participants.

Task 5d. Upload Fitbit sleep, heart rate variability and blood pressure data to BUSPH DCC to merge with other datasets.

The BUSPH BEDAC will maintain the tracking database for the Fitbit sleep, heart rate variability and blood pressure data collection and transfer. The database will reside on a secure, password-protected SQL server at the Boston University Medical Campus (BUMC). Because the server is part of the BUMC network, only connections from users authenticated from the domain controller will be accepted, thus providing a secure environment for all project data. The database will be automatically backed up on a nightly basis. Fitbits capable of collecting heart rate variability and sleep metrics have been purchased and shared with the recruitment sites to administer to participants when

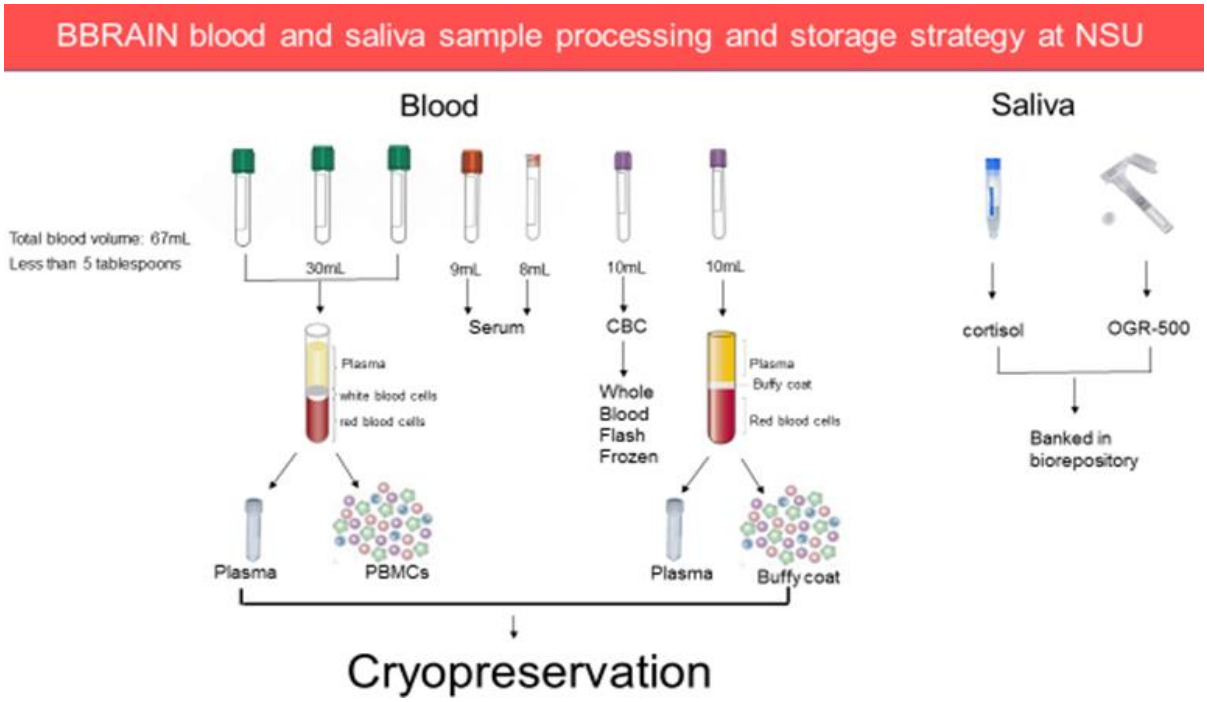
recruitment resumes.

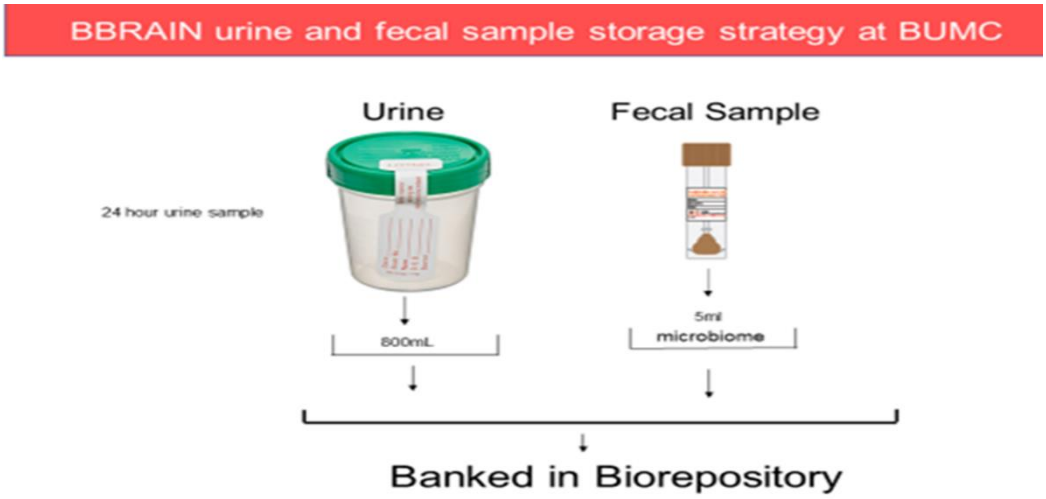
Task 5e. Score neuropsychological tests and upload summary data to DCC for entry, cleaning and analyses.

Neuropsychological protocols have been collected for two study participants to date and study staff at all sites have been trained for all test administration and standardized scoring procedures at the Boston Administrative Core now that slight modifications have been made to increase the safety of the cognitive assessments. As study protocols are obtained and data is collected, quality control procedures will remain in place including double entry of data collection forms in the REDCap data collection website, built in range checks and quality control audits of all data collection by the Data Coordinating Center staff and the local BU Administrative Core neuropsychologists.

Task 5f. Send blood and saliva samples to Nova University for analysis of cytokine and chemokine panels and cortisol measurements and biorepository banking.

Two blood and saliva samples have been sent to NOVA Southeastern University for this study. The analysis of cytokine, chemokine and cortisol measurements will include testing for neuroendocrine and immune alterations and for hypothalamic pituitary adrenal axis abnormalities. Specifically, blood samples will be sent to NOVA Southeastern University for analysis of proinflammatory cytokine and chemokines and RNA analysis. Multiplex Quansys ELISA system will be used with an existing cytokine platform created by Dr. Klimas' research laboratory. Dr. Klimas will measure 16 cytokines in plasma. Saliva samples will analyzed for DNA and cortisol measurements. See figure below for aliquotting and storage scheme for BBRAIN.





Task 6. Process, Store and Manage samples for a total of 500 new participants (Months 6-33)

As previously mentioned, we started subject recruitment in February and early March and completed two study participants before our sites were closed for COVID-19 concerns. These two samples were sent to the NOVA (NSU) and BUMC laboratories for processing and storage and this was a good trial to ensure that our study protocols would run smoothly. The INIM NSU lab is the biorepository site for all blood and saliva samples collected throughout the study. We have obtained all the required approvals from IRB and the exempt status for HRPO.

Dr. Abreu worked closely with Dr. Sullivan on the logistics of this project in weekly meetings to initiate the project and ensure the best approach. Reagents needed, such as blood collection tubes, saliva kits, and shipping kits were purchased and distributed to each site. Dr. Abreu established a protocol for the various study sites. The study coordinators were trained on blood and saliva sample collection and the sample shipment process. Study coordinators were also trained on urine and stool sample collection to be shipped to Boston University. Sample accessioning, barcoding, and sample processing was reviewed with the laboratory technician at the INIM NSU lab. Blood and saliva samples are accessioned, processed, and aliquoted for storage. Saliva, plasma, and serum samples are stored at -80°C freezers. Flash-frozen whole blood, buffy coat, and isolated peripheral blood mononuclear cells (PBMCs) are stored in liquid nitrogen. Sample tracking is maintained in WebLDMS, a laboratory information management system (LIMS) for managing collections of biological specimens.

Due to the pandemic, many of the study sites were inactive but are just starting to resume study subject recruitment efforts and the NSU and BU labs are open to receive study samples.

Task 6a. Process and store blood, saliva, urine and stool samples received from 4 recruitment sites at two biorepository sites

We processed and stored the blood, saliva, urine and stool samples from our first two participants and will continue with our study protocols that have now been finalized.

Task 6b. Perform local laboratory analyses (CBC) for 500 participants

We have performed local laboratory analyses for our first two participants and will continue this protocol for the next 498 participants.

Task 6c. Extract DNA and RNA from 500 saliva samples and store in repository

We will extract DNA and RNA from saliva samples in batches as we have enough participant samples collected.

Task 6d. Run batched assays for cortisol and cytokine results (18 plex cytokine assay)

We will also run batched assays for cortisol and cytokine results as we have enough particpants samples collected.

Task 6e. Provide Sample request forms and track information regarding the use of samples

We have gotten to requests for samples/data to date that have been sent to our steering committee for approval. These two requests have been approved and we have shared brain imaging data and will soon share CSF samples with Boston University and Baylor Medical College investigators.

Task 6f. Ship samples to requesting investigators

We have shared brain imaging data and will ship CSF samples to the requesting investigators who have been approved to date through the online BBRAIN sample request form.

Major Task 7: Merge Data and Perform interim Data Analyses (Months 6-24)

Data merging is in the process of being performed and cleaned and made ready for interim data analyses.

7a. Merge Clinical datasets data from prior studies for brain imaging, cognitive, demographic and health symptom report data

Retrospective data sets are currently being merged for neuroimaging, cognitive, demographic and health symptom outcomes by the BEDAC data management team and interim data analysis will be performed shortly on these outcomes.

7b. Perform machine learning and/or meta-analytic techniques on common data elements from prior study epidemiological, cognitive and brain imaging data

Common data elements are being compiled from the prior clinical datasets that have been shared and will then be combined with brain imaging outcomes for Dr. Koo to perform machine learning analyses. A review paper of cognitive outcomes was published in collaboration with NOVA Southeastern investigators while waiting for the common data elements to be available for planned meta-analysis studies (Jeffrey et al., 2019).

7c. Discussion of results and preparation of abstracts for meeting presentations and initial manuscript for publication

Study results and preparation of abstracts for meeting presentations are discussed during monthly web meetings and will continue during the upcoming year.

7d. Annual reports of progress will be written

Two annual progress reports have been written and submitted for review.

OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT

- **Research Staff Training:** personnel who will be using the web systems for either direct data capture, participant tracking, or viewing reports will be trained to ensure uniformity of procedures, achieve the ultimate aim of ensuring high quality protocol implementation and data collection. As a large academic community, Boston University also provides opportunities for students to get real world experience. The BBRAIN can tap into this talent pool by taking practicum and intern students in the fields of health communication and promotion, who as part of an academic program, will create a media and outreach program for the network. Doctoral students in related fields can also be brought on to aid in this project. Finally, as has been exhibited with the GWIC, the network will be financially continued through spin-off grants in GWI and similar fields through DOD, VA and NIH and by providing the tools for talented young researchers to aid us in tackling and solving the problem of GWI. For example, in summer of 2019 we had a student from Middlebury College, VT working with us a summer intern who helped develop the BBRAIN website. This year, we had two doctoral students working with us to learn cognitive evaluations and to assist with subject recruitment efforts.

- **Participation in conferences, workshops, and seminars**: BBRAIN researchers will attend conferences, workshops and seminars to present research findings.
    - On October 3rd 2019, Drs. Sullivan and Klimas presented a talk titled, 'Military Veteran Biorepositories' where they explained available biorepositories for military research and discussed plans for BBRAIN sharing of samples for military veteran studies as part of the National Academy of Sciences (NAS) workshop on Gulf War Respiratory Health Workshop on Military Burn Pits in Washington, DC. This Committee will determine next steps for burn pit studies for Iraq war veterans and for GW veterans with respiratory problems. The NAS report has now been published and included GWIC and BBRAIN studies in their report.
    - On October 11-13th 2019, Drs. Sullivan and Klimas were invited keynote speakers at the American Academy of Environmental Medicine (AAEM) annual meeting in Louisville, KY. Dr. Sullivan's talk was titled 'Neuropathology and Toxicology of Gulf War Illness and Fatigue-related Disorders' and Dr. Klimas' presentation was titled, 'Can We "Reboot" Human Homeostasis to Cure Chronic Illness? What We Are Learning from Gulf War Illness and ME.'
    - On February 28th, 2020, Drs. Sullivan and Klimas were invited keynote speakers and presented a talk title: "Moving Knowledge to Treatment" at the State of the Science: Gulf War Illness conference in Ft. Lauderdale, FL.

- On August 18, 2020, Dr. Sullivan was invited to present the BBRAIN network at the GWI State of the Science 30th Anniversary of the Gulf War, Operation Desert Shield virtual meeting that was co-led by CDMRP and VA.

- **How results will be disseminated to communities of interest.**
  Research staff will use some of the outreach structure already in place from the Boston GWI consortium. The Facebook page has 2,500 followers, many of whom regularly interact with and share page content. This allows researchers to freely spread information among the already existing GW network on social media. GWIC also has a Twitter account and study website that will be used to disseminate information to the community and refer to the BBRAIN social media sites. Boston University also has a very proactive media team that produces text and video news stories that get widely shared. Research staff will also be aided by the Veteran Working Group in getting news out about the BBRAIN to fellow veterans and their communities. As the research team has done for GWIC, they will write professional publications that state what samples are available and who to contact. This was done for the stem cell repository that is now part of BBRAIN and was very well received in the research community. To date, a media story was written about BBRAIN in April 2019 at https://www.bu.edu/sph/2019/04/08/professor-awarded-3-2m-to-establish-biorespository-network-for-gulf-war-illness-research/ and a new larger story about BBRAIN came out on Veterans Day 2019 at https://www.bu.edu/sph/2019/11/13/the-brink-5/ to help with subject recruitment efforts and in letting investigators know about samples that will be shared for other relevant studies.

- **Plan to do during the next reporting period to accomplish the goals:** In the next reporting period, we plan to:
  - Continue to obtain Biorepository data for analysis and catalogue available biospecimens for sharing from Repository Resource Sites.
  - Continue to obtain imaging data from retrospective sites and perform post-processing of and machine learning analysis with combined common data elements.
  - Continue recruitment at the four prospective sites now that sites have gotten approval to resume in a limited capacity during the COVID pandemic. We will continue to process, store and manage samples for a total of 500 new participants. We also plan to merge data and perform interim data analyses.
  - We believe that our media stories and working with new web advertising companies will catch us up on subject recruitment by the end of year 3 barring further delays from the COVID pandemic.

4. IMPACT

- **Impact on the development of the principal discipline(s) of the project:**
  - *"Nothing to Report."*

- **Impact on other disciplines:**
  - BBRAIN investigators will collaborate with researchers external to the consortium on 10 DoD, 4 VA applications and 8 additional study sites (Harvard University, Georgetown University, Roskamp Institute, Boston VA, Bronx VA, San Francisco VA, U-Alabama, Mass General Hospital). Each site has valuable and unique samples to share within and outside the repository network that would not otherwise be available to the research community. It is the goal of the

BBRAIN to continue the expert infrastructure of scientific, laboratory and data management currently within the GWIC, include other expert scientist collaborators, and to hasten biomarker discovery and treatment development for GWI on multiple aspects of GWI disciplines (immune, neurological, respiratory, gastrointestinal etc) as well as other disciplines including comorbid conditions of ME/CFS, IBS and fibromyalgia. We also have investigators interested in studying the risk of toxicant induced Parkinson's disease and brain cancer and heavy metals exposure with our research network that we will continue to pursue.

- **Impact on technology transfer:** *If there is nothing significant to report during this reporting period, state "Nothing to Report." Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:*
    - Data shared from the biorepository will allow more investigators across the U.S to perform more research in the area of Gulf War Illness and other related health conditions. Results from studies conducted with BBRAIN samples will also make it easier for investigators to secure funding for supplemental and diverse GWI related studies and to share them for public use. This has already been shown in Dr. Sullivan and Klimas contributing our biorepository knowledge and plans for BBRAIN with the National Academy of Science (NAS) Gulf War Respiratory Health Working Group meeting in October 2019. We have also created a stem cell line with organoid brain tissue available to other researchers that is the first in this field.
- **Impact on society beyond science and technology:**
    - The demographic, exposure history, clinical data symptom assessment, diagnostic outcomes and other data gathered from prospective and retrospective sites will aid in the comprehensive understanding of the pathobiology of GWI. Results of our analysis may uncover and increase the diagnostic and treatment capability for GWI. The biorepository can also become a model for the establishment of other biorepositories in the field. Researchers may research out to us for questions regarding the setup and management of the biorepository. In fact, we have already spoken to CDC investigators studying ME/CFS and the NAS GW respiratory health working group for advice about biorepositories.

5. CHANGES/PROBLEMS:

- **Changes in approach and reasons for change**

  Due to the new restrictions and procedures following the Covid-19 pandemic, all study sites have temporarily shut down to prevent the spread of the virus. The Boston site has seen 2 participants pre-pandemic and all other sites have still been recruiting perspective participants during the year 2020 and now a list of participants that they have been approved to bring in their clinics in a limited capacity right now.

- **Actual or anticipated problems or delays and actions or plans to resolve them**

  Due to the restrictions from the Covid-19 pandemic, this study has been temporarily paused since March 2020. All sites (Boston, San Francisco, Bronx, and Miami) have re-submitted a modified version of our original IRB application to improve tester and subject safety and to perform some parts of the study remotely to reduce the in-person visit time. We are complying with each university and VA center to follow all safety measures to reduce the risk of COVID spread.

Changes that had a significant impact on expenditures

Nothing to Report

- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

  Nothing to Report

6. **PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  - **Journal publications.**

    We have published one review article to date on Neuropsychological outcomes in GW veterans and a listing of the neuropsychological Common Data Elements (CDEs) from the GWI CDE workgroup. Further CDE manuscripts are planned.

    - Jeffrey MG, Krengel M, Kibler JL, Zundel C, Klimas NG, Sullivan K, Craddock TJA. Neuropsychological Findings in Gulf War Illness: A Review. Front Psychol. 2019 Sep 26;10:2088. doi: 10.3389/fpsyg.2019.02088. eCollection 2019. Review. PMID: 31616335. Link: https://www.frontiersin.org/articles/10.3389/fpsyg.2019.02088/full

  - **Books or other non-periodical, one-time publications.**

    Nothing to Report.

  - **Other publications, conference papers, and presentations.**

    Presentations:

    - K. Sullivan. Military Biorepositories. National Academy of Science (NAS) Workshop on Gulf War Respiratory Health Committee (Invited Speaker), Washington, DC, October 3, 2019.
    - K. Sullivan. Military Occupational Health and Toxicology. American Academy of Environmental Medicine annual meeting. (Invited keynote speaker), Louisville, KY, October 12, 2019.
    - N. Klimas. Can We "Reboot" Human Homeostasis to Cure Chronic Illness? What We Are Learning from Gulf War Illness and ME. American Academy of Environmental Medicine annual meeting. (Invited keynote speaker), Louisville, KY, October 12, 2019.
    - K. Sullivan. Boston, Biorepository and Integrative Network for GWI. GWI State of the Science 30th Anniversary of the Operation Desert Storm meeting, virtual, August 18, 2020.

- **Website(s) or other Internet site(s)**
  - http://sites.bu.edu/bbrain/
  - https://wwwapp.bumc.bu.edu/BEDAC_BBrainRetro

- **Technologies or techniques**
  - **REDCap**: This primary platform utilized in the BBRAIN study is a freely available platform used extensively for collaborative multi-site research. It can be used at all sites to collect existing data and assist with data mining strategies.
  - **Laboratory Data Management System (LDMS):** Samples received by the biobank laboratory will be processed in LDMS. The LDMS (Frontier Science Foundation) system allows for the seamless management of bio-specimens from collection, processing, shipment, and storage processes. Specimens are barcoded and accessioned to ensure the integrity of the aliquot is maintained even over decades of storage.

- **Inventions, patent applications, and/or licenses**

  Nothing to Report.

- **Other Products**

Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **Individuals that have worked on the project:**

Name: Kimberly Sullivan	Project Role:	*PI of Biorepository Network and Boston site*
	Researcher Identifier (e.g. ORCID ID):	*https://orcid.org/0000-0001-7940-6123*
	Nearest person month worked:	*12*
	Contribution to Project:	*Oversee the biorepository at BUSPH; oversee the recruitment and participation at BUSPH (200 participants); oversee data and sample coordination of all prospective and retrospective BBRAIN sites.*
	Funding Support:	*BBRAIN Award,* ***W81XWH-18-1-0549***
Name: Nancy Klimas	Project Role	*Co-Investigator, PI of Miami Site*
	Researcher Identifier (e.g. ORCID ID):	*https://orcid.org/0000-0003-1459-3268*
	Nearest person month worked:	*12*
	Contribution to Project:	*Oversee the resource site at the Miami VA medical center; oversee recruitment and participation (100 participants).*
	Funding Support:	*BBRAIN Award,* ***W81XWH-18-1-0549***
Name: Julia Golier	Project Role	*Co-Investigator, PI of Bronx VA Site*
	Researcher Identifier (e.g. ORCID ID):	
	Nearest person month worked:	*12*
	Contribution to Project:	*Oversee site at Bronx VA (100 participants); serve as neuroendocrine expert for BBRAIN; oversee cortisol study protocols, analyses, and outcomes.*
	Funding Support:	*BBRAIN Award,* ***W81XWH-18-1-0549***
Name: Linda	Project Role	*Co-Investigator, PI of San Francisco VA Site*

Chao	Researcher Identifier (e.g. ORCID ID):	*https://orcid.org/0000-0002-8593-2434*
	Nearest person month worked:	*12*
	Contribution to Project:	*Serve as imaging expert for BBRAIN; oversee site in San Francisco (100 participants); share prior brain imaging data, saliva samples, and demographic, exposure, and survey data.*
	Funding Support:	*BBRAIN Award,* ***W81XWH-18-1-0549***

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

  Nothing to Report.

- **What other organizations were involved as partners?**

  - **Organization Name:** Harvard University and New England School of Acupuncture
  - **Location of Organization:** Boston, Massachusetts
  - **Partner's contribution to the projec**t *(identify one or more)*
    - **Financial support;** *Nothing to Report*
    - **In-kind support***: Nothing to Report*
    - **Facilities**: *Nothing to Report*
    - **Collaboration**: Lisa Conboy, BBRAIN consultant affiliated with both listed institutions. Dr. Lisa Conboy is a social epidemiologist and is well-published in the area of Complementary and Alternative Medicine. She is an Instructor in Medicine at Harvard Medical School, and Research Director at the New England School of Acupuncture. Dr. Conboy has been involved in studies investigating diagnostic biomarkers and predictors of therapeutic responses in inflammatory bowel disease, irritable bowel syndrome (IBS) and GWI. Drs. Conboy have previously shared blood samples from their acupuncture study for a study of CNS autoantibodies in GWI in collaboration with Drs. Sullivan and colleagues. She has also collaborated in the Boston area PI recruitment network sharing study flyers and recruitment information with their GW veteran cohort of other local studies. Dr. Conboy will continue to participate in the Boston PI Recruitment Network as well as contribute retrospective repository blood samples and data from her successful acupuncture trial with GW veterans.
    - **Personnel exchanges**: *Nothing to Report*
    - **Other.** *Nothing to Report*

1. **Organization Name:** Harvard University and Beth Israel Hospital
2. **Location of Organization:** Boston, Massachusetts

3. **Partner's contribution to the projec**t *(identify one or more)*

    1. **Financial support;** *Nothing to Report*
    2. **In-kind support**: *Nothing to Report*
    3. **Facilities**: *Nothing to Report*
    4. **Collaboration**: Drs. Efi Kokkotou, BBRAIN Consultant affiliated with both institutions. She has previously shared blood samples from her acupuncture study for a study of CNS autoantibodies in GWI in collaboration with Drs. Sullivan and colleagues. She has also collaborated in the Boston area PI recruitment network sharing study flyers and recruitment information with their GW veteran cohort of other local studies. Dr. Kokkotou will share samples from her large biorepository of IBS and GWI samples from DOD and NIH funded studies (W81XWH-09-0064 and K01AT004916).
    5. **Personnel exchanges**: *Nothing to Report*
    6. **Other.** *Nothing to Report*

1. **Organization Name:** VA Boston Healthcare System
2. **Location of Organization:** Boston, Massachusetts
3. **Partner's contribution to the projec**t *(identify one or more)*

    1. **Financial support;** *Nothing to Report*
    2. **In-kind support**: *Nothing to Report*
    3. **Facilities**: *Nothing to Report*
    4. **Collaboration**: Drs. Christopher Brady and Neil Kowall, BBRAIN Consultant and Co-Investigator, affiliated with this institution. The VA Biorepository Brain Bank (VABBB), Gulf War Veterans' Illnesses Biorepository (GWVIB) is a collaborative effort between multiple VAs (Boston-coordinating center/diagnostic neuropathology, Tucson-biorepository) and academic medical center affiliates (Harvard, BU and the University of Arizona). GWVIB VA Boston/BU/Harvard staff are professionals that bring essential skills to the project via their collaborative work on the GWVIB and other projects: the Boston University Alzheimer's Disease Center (Dr. Kowall, Director); the Center for the Study of Chronic Traumatic Encephalopathy (Dr. Ann McKee, M.D., Director), and the VISN1 Neuropathology Laboratory (Dr. McKee, Director). Tissue is stored at the Southern Arizona VA Healthcare System (SAVAHCS) in Tucson, AZ. GWVIB Tucson/U. of Arizona staff is composed of biorepository storage, processing, management and tissue disbursement experts from the Pathology departments at SAVAHCS and the U. of Arizona. The VABBB has developed SOPs for tissue collection, processing, quality control, storage and disbursement, and developed a comprehensive tissue database annotated with relevant clinical and histopathological data. This collaboration will be leveraged for the BBRAIN and Drs. Kowall and Brady will advise Dr. Sullivan on best practices in multi-site biorepository management.

5. **Personnel exchanges**: *Nothing to Report*

6. **Other.** *Nothing to Report*

1. **Organization Name:** Boston University Medical Campus
2. **Location of Organization:** Boston, Massachusetts
3. **Partner's contribution to the projec**t *(identify one or more)*

1**. Financial support:** *Nothing to Report*

2**. In-kind support**: *Nothing to Report*

3**. Facilities**: *Nothing to Report*

4**. Collaboration**: Drs. Bang Bon Koo, Ronald Killiany and Maxine Krengel, BBRAIN Co-Investigators affiliated with Boston University Medical Campus. Dr. Bang-Bon Koo, a clinical faculty member in the Anatomy and Neurobiology department at BUMC will assist with machine-learning analyses in GWI biomarker and diagnostic analyses. Dr. Ronald Killiany, director of the BUMC Center for Biomedical Imaging will serve as the Imaging Core Director and will oversee compilation of imaging data and data mining/post-processing samples. Dr. Bang-Bon Koo, a clinical faculty member in the Anatomy and Neurobiology department at BUMC will also be available to assist with machine-learning analyses in GWI biomarker and diagnostic analyses. Dr. Maxine Krengel currently leads the Ft. Devens cohort research effort and has published several recent publications in collaboration with Drs. Sullivan and Patricia Janulewicz on long-term health outcomes in GW veterans from the DOD funded Time 5 survey (GW100046). Dr. Krengel will share repository data from the Ft. Devens Cohort survey and in-person assessment studies for collaborative BBRAIN studies.

5. **Personnel exchanges**: *Nothing to Report*

6. **Other.** *Nothing to Report*

1. **Organization Name:** CDC NIOSH
2. **Location of Organization:** Morgantown, West Virginia
3. **Partner's contribution to the projec**t *(identify one or more)*

1**. Financial support:** *Nothing to Report*

2**. In-kind support**: *Nothing to Report*

3**. Facilities**: *Nothing to Report*

4**. Collaboration**: Dr. Jim O'Callaghan, BBRAIN Co-Investigator affiliated with CDC NIOSH. Dr. James O'Callaghan serves as Distinguished Consultant, Centers for Disease Control (CDC) and Prevention, and Head of the Molecular

Neurotoxicology Laboratory in the Toxicology and Molecular Biology Branch of the Health Effects Laboratory Division at the CDC-NIOSH. He is an expert neurotoxicologist who is a member of the Boston GWIC (GW120037) and formerly served on the VA Research Advisory Committee on Gulf War Veterans' Illnesses (RAC-GWVI). He has a very active and well-funded animal GWI research program aimed at establishing the relationship among toxicant-induced changes in gene expression, growth-associated phosphorylation cascades and signaling events associated with astrocytic hypertrophy and microglial activation. He will share mouse brain samples from his GWI model for the BBRAIN studies and repository.

5. **Personnel exchanges**: *Nothing to Report*

6. **Other.** *Nothing to Report*

1. **Organization Name:** Roskamp Institute/ Tampa VAMC
2. **Location of Organization:** Sarasota, Florida
3. **Partner's contribution to the projec**t *(identify one or more)*

1**. Financial support:** *Nothing to Report*

2**. In-kind support**: *Nothing to Report*

3**. Facilities**: *Nothing to Report*

4**. Collaboration**: Drs. Laila Abdullah and Ghania Ait Ghezalia, BBRAIN Consultants affiliated with Roskamp Institute/ TAMPA VAMC. Dr. Laila Abdullah is a senior neuroscientist at the Roskamp Institute, a non-profit Research Center. Dr. Abdullah has identified novel therapies and biomarkers for GWI by applying omics (proteomics, lipidomics, and metabolomics) technology to target lipid metabolism. Dr. Abdullah has been working on identifying lipid metabolism pathways associated with mmune/inflammation and metabolic disturbances in the brains of GWI mouse models. In collaboration with Drs. Sullivan, Klimas, and Ait-Ghezala, Dr. Abdullah has been evaluating blood lipids as potential biomarkers of GWI and has successfully validated some aspects of lipid disturbances in the GWI mouse model against lipid disturbances observed in blood from veterans with GWI using Boston GWIC repository samples. Dr. Abdullah will contribute her expertise in 'omics' research, share omics data and biological samples from animal and clinical studies of GWI. Samples and data will be shared for BBRAIN through CDMRP awards (GW130045, GW150056) and a VA Merit award (RX002260-01A1).

5. **Personnel exchanges**: *Nothing to Report*

6. **Other.** *Nothing to Report*

1. **Organization Name:** Drexel University
2. **Location of Organization:** Philadelphia, Pennsylvania
3. **Partner's contribution to the projec**t *(identify one or more)*

1**. Financial support:** *Nothing to Report*

2**. In-kind support**: *Nothing to Report*

3**. Facilities**: *Nothing to Report*

4**. Collaboration**: Drs. Peter Baas and Liang Qiang, BBRAIN Co-Investigators affiliated with Drexel University. Drs. Peter Baas and Liang Qiang also Boston GWIC members from Drexel University are axonal transport, neuronal microtubule and stem cell experts. They have most recently developed a cutting-edge bank of human induced pluripotent (hiPSC) stem cells from GW veterans, in order to conduct mechanistic studies and high-throughput testing of potential therapies. The stem cell biorepository will be shared with BBRAIN and outside collaborators. Drexel and BUSPH researchers have established a repository of hiPSCs from peripheral blood mononuclear cells (PBMCs) directly from GW veterans. They have utilized contemporary stem cell technology to convert somatic cells from GW veterans into pluripotent cell lines that can be differentiated into various cell types, including neurons, glia, muscle, or other relevant cell types. They have generated hiPSCs from 2 groups of age-matched individuals: GW veterans with GWI versus those without GWI. The sets were validated for comparable and appropriate hiPSC induction, neuronal and glial differentiation, neural cell survival over time, and basic electrophysiological properties of the terminally differentiated cells. Two high profile papers have been published about this hiPSC repository. These cell lines are immortal and will be a resource for GWI researchers to pursue mechanistic hypotheses and therapies for GWI as a result of DOD funding (GW140086) to Drexel and BUSPH investigators.

5. **Personnel exchanges**: *Nothing to Report*

6. **Other.** *Nothing to Report*

1. **Organization Name:** Mass General Hospital
2. **Location of Organization:** Boston, Massachusetts
3. **Partner's contribution to the projec**t *(identify one or more)*

1**. Financial support:** *Nothing to Report*

2**. In-kind support**: *Nothing to Report*

3**. Facilities**: *Nothing to Report*

4**. Collaboration**: Dr. Marco Loggia, BBRAIN Consultant affiliated with Mass General Hospital and Harvard University. Dr. Marco Loggia is an Assistant Professor of Radiology at Harvard Medical School, the Associate Director of the Center for Integrative Pain NeuroImaging (CiPNI) at Massachusetts General Hospital, and Faculty in the MGH/HSY Athinoula A. Martinos Center for Biomedical Imaging. He is a pain expert and has been funded for a ground-breaking study of positron emission tomography (PET) markers of glial activation in GWI working in collaboration with GWIC and other Boston area investigators

(GW130100). Dr. Loggia will share blood samples and imaging, cognitive and demographic data from his DOD funded [11C]PBR28 PET/MR study of glial activation in GWI and BBRAIN will analyze his stored blood samples for cytokine markers of microglial activation to compare with his PET study outcomes.

5. **Personnel exchanges**: *Nothing to Report*

6. **Other.** *Nothing to Report*

1. **Organization Name:** Georgetown University
2. **Location of Organization:** Washington, DC
3. **Partner's contribution to the projec**t *(identify one or more)*

1**. Financial support:** *Nothing to Report*

2**. In-kind support**: *Nothing to Report*

3**. Facilities**: *Nothing to Report*

4**. Collaboration**: Drs. James Baranuik, BBRAIN Consultant is affiliated with Georgetown University. Dr. James Baraniuk is Professor of Medicine at Georgetown University and a practicing rheumatologist. He specializes in fatigue and pain management in patients with GWI, fibromyalgia and chronic fatigue syndrome (CFS)[9]. Dr. Baraniuk has been funded for multiple DOD studies of biomarkers of GWI including plasma, cerebrospinal fluid and brain imaging markers pre-and-post exercise challenge and treatment trials of GWI. Dr. Baraniuk and the GWIC are the only DOD funded sites that we are aware of that have highly valuable CSF samples in repositories. Dr. Baraniuk will share CSF, blood and brain imaging data from GWI, CFS and healthy control groups from DOD and NIH funded studies (*CDMRP* GW080053; GW140064; GW060044). Collaborative studies utilizing both Dr. Baraniuk's and Sullivan's CSF samples will be planned.

5. **Personnel exchanges**: *Nothing to Report*

6. **Other.** *Nothing to Report*

1. **Organization Name:** University of Alabama
2. **Location of Organization:** Birmingham, Alabama
3. **Partner's contribution to the projec**t *(identify one or more)*

1**. Financial support:** *Nothing to Report*

2**. In-kind support**: *Nothing to Report*

3**. Facilities**: *Nothing to Report*

4**. Collaboration**: Dr. Jared Younger, BBRAIN Consultant is affiliated with University of Alabama. Dr. Jarred Younger is Associate Professor at the University of Alabama at Birmingham (UAB), and Director of the Neuroinflammation, Pain and Fatigue Laboratory. Dr. Younger's group specializes in intensive longitudinal studies where biosamples are collected daily. This unique dataset provides measurement of self-reported symptom severity over time and biomarkers in blood. These data and samples will be shared with BBRAIN researchers. Dr. Younger maintains sera and plasma stored in 0.5mL aliquots. Crosssectional studies and 150 intensive longitudinal (daily) samples are available. Half of the samples are plasma and half sera from 6,000 GWI samples, 7,200 Healthy Controls samples, 11,200 Chronic Fatigue Syndrome samples and 4,800 Fibromyalgia samples will be shared as well as several hundred brain scans from healthy control, fibromyalgia and CFS groups.

5. **Personnel exchanges**: *Nothing to Report*

6. **Other.** *Nothing to Report*

8.SPECIAL REPORTING REQUIREMENTS

- **COLLABORATIVE AWARDS:**

  Nothing to report

- **QUAD CHARTS:** *If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.*

9. APPENDICES: *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc. Reminder: Pages shall be consecutively numbered throughout the report.* ***DO NOT RENUMBER PAGES IN THE APPENDICES.***

Appendix:

Please see attached publication:

Jeffrey MG, Krengel M, Kibler JL, Zundel C, Klimas NG, Sullivan K, Craddock TJA. Neuropsychological Findings in Gulf War Illness: A Review. Front Psychol. 2019 Sep 26;10:2088. doi: 10.3389/fpsyg.2019.02088. eCollection 2019. Review. PMID: 31616335. Link: https://www.frontiersin.org/articles/10.3389/fpsyg.2019.02088/full

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REVIEW
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Neuropsychological Findings in Gulf War Illness: A Review

Mary G. Jeffrey[1], Maxine Krengel[2], Jeffrey L. Kibler[3], Clara Zundel[2], Nancy G. Klimas[1,4,5], Kimberly Sullivan[6] and Travis J. A. Craddock[1,4,7,8]**

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This review paper summarizes the accumulation of research investigating neuropsychological outcomes in veterans with Gulf War illness (GWI). Earlier research focused on Gulf War veterans (GW) who were deployed versus non-deployed, as well as those who were symptomatic versus asymptomatic, or compared neuropsychological test results to published norms. Further research became more sophisticated, investigating specific GWI criteria, as well as the result of neurotoxicant exposure and the relationship to possible neurocognitive outcomes. As the early research supported both psychological and physiological effects on GWI; current research as summarized in this literature review supports the presence of neuropsychological deficits, particularly in the domains of attention, executive functioning, memory, and motor functioning related to chemical exposures that can be exacerbated by comorbid mood-related conditions. The same test battery has not been used consistently making it difficult to compare results among studies. Therefore, researchers created a resource to provide recommendations for the recently listed Neuropsychological Tests for Common Data Elements (CDEs) for use in all future GWI studies. Future research is necessary to further understand patterns of neuropsychological test data and how these decrements may relate to immunological or other biological markers, and the impact of trauma from physical and psychological stressors. In conclusion, there is consistent evidence that GWI is characterized by neuropsychological decrements – with future research these findings may aid in the diagnosis and assessment of treatment trial efficacy of GW veterans.

Keywords: Gulf War illness, neurotoxicant, neuropsychology, posttraumatic stress disorder, veterans, review

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NEUROPSYCHOLOGICAL FINDINGS IN GWI: A REVIEW

Gulf War illness (GWI), also known as chronic multi-symptom illness (CMI; Fukuda et al., 1998), has impacted approximately a third of the veterans deployed to the 1990–1991 Gulf War (Research Advisory Committee on Gulf War Veteran's Illnesses [RAC-GWVI], 2008; White et al., 2016). By definition, GWI includes self-reported cognitive complaints indicative of neuropsychological impairment (Fukuda et al., 1998; Steele, 2000). Research examining the neuropsychological profile of GWI is necessary given that cognitive problems remain one of the most prevalent and distressing

symptoms of GW veterans (Smith et al., 2012; Yee et al., 2016). Early on these cognitive symptoms resulted in veterans being referred for neuropsychological evaluations soon after their return from deployment and spurred research in this area. There have now been 25 papers specifically comparing objective neuropsychological performance in GW veterans with different comparison groups (deployed vs. non-deployed, symptomatic vs. non-symptomatic veterans, toxicant vs. non-toxicant). Here we present an overview of all 25 papers and describe the trajectory of research sophistication over time.

Neuropsychological findings in veterans with GWI have varied because of the use of different comparison populations (i.e., asymptomatic versus symptomatic GW veterans, different GWI cohorts) and different neuropsychological test batteries. A recent meta-analysis of the neuropsychological decrements associated with GWI provided some clarity to the question of which neuropsychological decrements were present in GW veterans and which tests were most sensitive to identifying these decrements. This was accomplished by combining multiple study results and using aggregate data when three or more studies used the same neuropsychological test. Studies were added into the meta-analysis when GW veterans served in the war from 1990 to 1991, had neuropsychological results reported in a manner conducive to meta-analysis, when comparison groups were deployed versus non-deployed or ill versus non-ill veterans and contained a unique sample (Janulewicz et al., 2017). The meta-analysis showed that the neuropsychological domains of visuospatial abilities, attention/executive functioning, and learning/memory were significantly different in GW veterans compared with two other comparison groups (Janulewicz et al., 2017). These findings remained significant when study results were adjusted for possible effects of publication bias (Janulewicz et al., 2017). In addition, analyses indicated that the following specific tests were most sensitive in discriminating between cohorts, including Block Design from the Wechsler Adult Intelligence Scale- Third Edition (WAIS-III; Wechsler, 1997), the Trail Making Test (Reitan, 1992), the Continuous Performance Test (CPT; Letz, 1991), and the California Verbal Learning Test (CVLT). The focus of the meta-analysis was not on the methodological strengths and weaknesses of the papers across the range of publications, but rather was to combine results to increase power and effect size across studies. These statistical findings were then used to determine which neuropsychological tests were most sensitive to GWI and were recommended in the recently listed neuropsychological component of the Common Data Elements (CDEs) for use in GWI studies[1].

Recently, through the Congressionally Directed Medical Research Program (CDMRP) Gulf War Illness Research Program (GWIRP), a collaborative effort of GWI researchers was conducted to identify the CDEs or sensitive measures of cognitive functioning to guide future research and treatment trial efficacy (Gulf War Illness Research Program [GWIRP], 2019). Measures are presented in **Table 1**. These tests were chosen based on their sensitivity in distinguishing between groups in three or more prior studies with GW veterans. These tests were recommended so that future studies can compare biomarker and treatment trial outcomes between studies in a consistent manner and to use tests that are known to be sensitive to GWI.

TABLE 1 | Gulf War illness common data elements module: neuropsychological test measures.

Supplemental – Highly Recommended
Word Reading Subtest of the Wide Range Achievement Test (WRAT-4) – (Wilkinson, 1993).
Continuous Performance Test-3 (CPT) – (Conners, 2014)
Wechsler Adult Intelligence Scale-IV (WAIS-IV) – (Weschler, 2008) Recommended tests: Digit Spans, Block Design
Profile of Mood States (POMS) – (McNair et al., 1971)
Davidson Trauma Scale (DTS) – PTSD - (Davidson et al., 1997).
Delis-Kaplan Executive Function System (D-KEFS) – (Delis et al., 2001) Recommended modules: Color-Word-Interference Test, Trail Making Test, Verbal Fluency
California Verbal Learning Test – Second Edition (CVLT-II) – (Delis et al., 2000)
Rey-Osterrieth Complex Figure Test (RCFT) – (Meyers and Meyers, 1995).
Supplemental
Finger Tap Test – (Reitan and Wolfson, 1993)
Grooved Pegboard Test – (Matthews and Klove, 1964)
Hopkins Verbal Learning Test (HVLT-R)* - (Brandt and Benedict, 2001)
Brief Visual Memory Test (BVMT)* - (Benedict, 1997)
PTSD Checklist for DSM-5 (PCL-5) – (Weathers et al., 1993)
Center for Epidemiological Studies Depression Scale (CES-D) – (Radloff, 1977)
Clinician Administered PTSD Scale (CAPS-5) – (Blake et al., 1990)
Structured Clinical Interview for DSM-5 (SCID-5) – (First, 2015)

* *denotes multiple test versions available for treatment trial use.*

In addition to facilitating neuropsychological outcomes research, researchers have also been learning more about the potential risk factors leading to objective neuropsychological decrements in GW veterans, including exposure to neurotoxicants (e.g., pesticides, nerve agents, and pyridostigmine bromide [PB] anti-nerve gas pills) as well as exposure to traumatic events during the war. These risk factors also include a history of mild traumatic brain injury and psychological trauma (Posttraumatic stress disorder (PTSD or mood disorder) (Sullivan et al., 2003, 2018; Yee et al., 2016, 2017; Janulewicz et al., 2017; Chao and Zhang, 2018).

More recent studies have also focused on biomarkers that are etiologically related to the neuropsychological deficits in GW veterans. These include toxicant induced neuroinflammation as well as war-time stressors (Brimacombe et al., 2002; Sullivan et al., 2003). Relevant to these factors are the rodent studies showing increased neuroinflammation when neurotoxicants were combined with simulated war-time stressors in the models (O'Callaghan et al., 2015; Ashbrook et al., 2018; Koo et al., 2018).

REVIEW OF GENERAL NEUROPSYCHOLOGICAL FINDINGS

The neuropsychological literature has been reviewed multiple times by the RAC-GWVI (Research Advisory Committee on Gulf War Veteran's Illnesses [RAC-GWVI], 2008, 2014;

[1]https://cdmrp.army.mil/gwirp/research_highlights/19gwi_cde_initiative_highlight.aspx

White et al., 2016). Additionally, review papers were published between 2000 and 2009, including Axelrod and Milner (2000), Vasterling and Bremner (2006), and White et al. (2016). More recently, a meta-analysis of the research data was published (Janulewicz et al., 2017). The current paper reviews the methodological strengths and limitations of the neuropsychological outcome studies to date. This includes 25 papers of which 14 were included in the meta-analysis. All 25 papers included assessments with validated neuropsychological instruments and were not case studies. **Table 2** illustrates the increased sophistication in the field over time regarding case definitions and sensitive comparison groups and subsequent progress in understanding GW veterans' neuropsychological profiles.

TABLE 2 | Review papers on neuropsychological outcomes.

References	Summary and recommendations
Axelrod and Milner, 2000	• Concluded that methodological issues limited the ability to understand the data. • Recommended that future studies include more sophisticated cohort comparisons, including exposure data.
Vasterling and Bremner, 2006	• Concluded that there was no clear pattern in neuropsychological outcomes and insufficient neuroimaging evidence to draw conclusions at this point. • The impact of mood and the discrepancy between subjective reports and objective measurements made it more difficult to determine the etiology of any deficits observed. • Recommended that results need replication, objective measures of exposure should be used when applicable, baseline data should be used to investigate pre-existing vulnerabilities. • Future research should be built on more complex models that incorporate individual vulnerabilities, environmental factors and their physiological and emotional consequences and immunologic functioning.
Research Advisory Committee on Gulf War Veteran's Illnesses [RAC-GWVI], 2008	• Concluded that symptomatic veterans have a subtle "sub-clinical" CNS damage. This included deficits in attention, executive function, memory, visuospatial skills, psychomotor functioning, and mood. • Recommended that analyses of veteran subgroups, i.e., those with more pronounced cognitive deficits and those with differing exposure histories, would be most informative.
White et al., 2016	• Concluded that GW exposures are associated with decrements in cognitive function. • Future research should investigate the mechanisms and etiology of GW health problems so that biomarkers of exposure and illness may be discovered.
Janulewicz et al., 2017	• Concluded with meta-analytic methods that GW deployment is associated with deficits in visuospatial, attention, executive function, and learning and memory but not simple motor function. • Future research developing treatments or investigating biomarkers of GWI should include neuropsychological outcomes in the domains of visuospatial, attention and executive function, and learning and memory. Particularly, Block Design, Trail Making Test, Digit Span, and CVLT, were sensitive measures to use with veterans with GWI.

Axelrod and Milner (2000) summarized the neuropsychological literature to date and reported that methodological problems limited the ability to understand the data. It was recommended that neuropsychological literature would be better served by including not only analyses based on normative data, non-deployed control comparisons, or self-reported medical concerns, but by also including relative risk for neurotoxicant exposures and hypothesis driven data collection.

Vasterling and Bremner (2006) found in their review of the literature, that there was no clear pattern in neuropsychological outcomes. Additionally, the impact of mood and the discrepancy between reported symptoms and objective performance made it more difficult to elucidate etiology of any deficits that were found.

In addition, the Research Advisory Committee on Gulf War Veteran's Illnesses [RAC-GWVI] (2008) review concluded that symptomatic veterans had subtle "sub-clinical" CNS damage. This included deficits in attention, executive function, memory, visuospatial skills, psychomotor functioning, and mood. The RAC-GWVI Committee recommended that analyses of veteran subgroups, i.e., those with more pronounced cognitive deficits or those with differing exposure histories, would be most informative. When the general data regarding these studies were reviewed by the Institute of Medicine (Institute of Medicine [IOM], 2006), it was determined that overcorrecting for mood may have diminished the power to detect differences in neuropsychological variables in some prior studies.

White et al. (2016) concluded that exposures were associated with decrements in cognitive functioning in GW veterans and future research should investigate the mechanisms and etiology of GW health problems so that biomarkers of exposure and illness may be identified. In the recent GW meta-analysis by Janulewicz et al. (2017), it was reported that there were difficulties assessing domain specific findings given the sparse information reported in included studies, and the overlap between studies that prevented a more diverse sample. In addition, data were too limited to assess toxicant exposure in relation to neuropsychological deficits. Even with limitations across studies, it was found that deployed GW veterans and symptomatic GW veterans demonstrated levels of cognitive impairment, particularly in visuospatial abilities, attention/executive functioning, and learning/memory domains.

SUBJECTIVE MEMORY

Subjective memory has long been one of the most reported and debilitating symptom complaints of GW veterans. However, it has been unclear if this relates to objective memory deficits vs. attentional variability or the fatigue symptoms and sleep difficulties of those with GWI. It may also be that one-time objective neuropsychological testing in a quiet room does not fully capture functional memory concerns. The three studies that have addressed this topic to date include Binder et al. (1999), Lindem et al. (2003b), and Chao (2017).

Binder et al. (1999) incorporated measures of subjective cognitive complaints (e.g., Symptom Check List-90- Revised [SCL-90-R; Derogatis, 1992]) and affective distress (e.g., Beck

Depression Inventory [BDI; Beck and Steer, 1993], Beck Anxiety Inventory [BAI; Beck et al., 1988]) in addition to a computerized test battery (Anger et al., 1996). With a sample of 100 symptomatic GW veterans, results showed higher correlations between subjective memory complaints and affective distress versus between subjective memory complaints and objective neuropsychological results. Therefore, Binder et al. (1999) concluded that affective distress was a necessary component of GW evaluations and provided additional explanation for worse cognitive outcomes in some GW veterans.

Lindem et al. (2003b) studied the relationship between neuropsychological symptom reporting and outcomes on objective tests in GW veterans. Symptom reporting was done with the Expanded Health Symptom Checklist (HSC, Proctor et al., 1998) which included five neuropsychological symptoms (e.g., difficulty concentrating, difficulty learning new material, forgetfulness, memory lapses, and confusion). Based on responses, participants were divided into groups of no complaints, a moderate level of complaints, and a high level of complaints. The researchers predicted that higher endorsement of neuropsychological symptoms would be associated with poorer performance on measures of attention and memory. Mood–related diagnosis was assigned using the following measures: Structural clinical interview for DSM (SCID; Spitzer et al., 1990), Clinical-Administered PTSD Scale (CAPS; Blake et al., 1990), the Mississippi Scale for Desert Storm, and Brief Symptom Inventory (BSI; Derogatis, 1993). Analyses were conducted to evaluate the ability of neuropsychological performance to categorize those with no, moderate, or high neuropsychological self-reported symptoms while controlling for covariates. Analyses indicated that subjective complaints did not show a pattern consistent with predicted performance on cognitive domains; however, they were more associated with mood complaints, which aligned with findings in Binder et al. (1999). Veterans with high levels of neuropsychological symptoms also reported tension, fatigue, confusion, and decreased vigor on the Profile of Mood States (POMS). Therefore, researchers concluded that these deficits are best measured by both objective neuropsychological testing and mood assessment to elucidate a clinical picture of GWI.

More recently, Chao (2017) conducted a study aimed at examining how subjective memory complaints (1 query of difficulty remembering) correspond with the likelihood of objective test results using the CVLT-II with a sample of 428 deployed GW veterans. Chao (2017) found significant impairment in verbal learning, retention, and recall in veterans with subjective complaints, even when accounting for age, sex, years of education, and mood-related diagnoses (e.g., major depressive disorder [MDD], PTSD, and anxiety). However, those with subjective memory complaints were more likely to have a PTSD diagnosis. Regression analyses also demonstrated poorer retention in association with subjective memory complaints. These results contrast with previous research (Binder et al., 2001; White et al., 2001) that did not find a connection between subjective complaints and objective impairment. Chao (2017) concluded that subjective memory complaints are sensitive to neuropsychological deficits and, as subjective memory complaints are linked to dementia risk, a necessary component of GW neuropsychological assessment.

These three studies did not show consistency in regard to objective tests (**Table 3**). Binder et al. (1999) and Lindem et al. (2003b) found results that linked subjective complaints to more mood-related factors, whereas Chao (2017) found evidence of objective memory impairment with subjective complaints. Given the discrepancy between subjective complaints and objective test performance, more validation research is needed with tests sensitive to memory impairment in GW veterans as delineated in the CDE protocol (**Table 1**). Also, none of these studies used the same subjective question of memory functioning making comparisons with objective measures difficult. Future studies should incorporate a validated subjective measure of cognitive functioning such as the Everyday Cognition Scale. In addition, careful use of statistical measures must be implemented to understand the unique contribution that mood and cognitive factors play in neuropsychological performance.

NEUROPSYCHOLOGICAL PERFORMANCE AS COMPARED BY NORMATIVE DATA

The following two early studies (Axelrod and Milner, 1997; Sillanpaa et al., 1997) examined those deployed in the GW in comparison to normative data. Axelrod and Milner (1997), tested 44 male GW veterans on a comprehensive neuropsychological exam (**Table 3**). Compared to normative data, deficits were found on only a motor test; Grooved Pegboard and a test of executive function; Stroop Color and Word Test (Matthews and Klove, 1964; Heaton et al., 1992). The researchers attributed the neuropsychological issues to elevations on selected subtests of a personality measure the Minnesota Multiphasic Personality Inventory Second Edition (MMPI-2; Graham, 1990). However, Janulewicz et al. (2017) found through examination of effect sizes, that cognitive flexibility as measured by the Trail Making Test- Trail B had a large effect size, while a small to medium effect was seen in motor tests, which may show some deficits that were masked by a small sample size. Other limitations were the lack of a control group (i.e., comparison to normative data collected from a non-military population), and lack of control regarding covariates of cognitive performance (i.e., age, gender, developmental history), and psychopathology (i.e., PTSD).

Sillanpaa et al. (1997) investigated neuropsychological and neurological functioning in 49 GW veterans from an Army Reserve Military Police unit. Each veteran completed personality and neuropsychological testing (**Table 3**). Neuropsychological performance was evaluated in comparison to normative data and models were created to test variables associated with a syndrome and to test variables associated with mood. The syndrome model included demographic factors, self-reported exposure to toxicants and a composite score of subjective complaint (i.e., composed of scores from the SCL-90-R and MMPI-2), and a clinical signs index (i.e., composite score of laboratory tests for liver and immune functioning or infection presence). The model of mood-related issues included indices of trait anxiety, subjective

TABLE 3 | Neuropsychological studies with Gulf War veterans.

References	Group (N)	Neuropsychological Tests	Strengths	Limitations	Conclusions
Goldstein et al., 1996	29 GWV, 39 non-veterans	WAIS-R Information WAIS-R Similarities WAIS-R Digit Span WAIS-R Arithmetic WAIS-R Digit Symbol WAIS-R Picture Completion WAIS-R Block Design COWAT Incidental Memory Verbal Associative Learning Short-Term Memory Symbol Digit Learning Trail Making Test CPT Grooved Pegboard	– GWVs compared to demographically matched controls on neuropsychological tests – Test battery included some measurements sensitive to GWI (i.e., Block Design)	– No case designation based on GWI – Limited measurement of mood	– Found that GWVs performed worse on impairment index in compared to controls – However, the level of impairments (1 SD) was not consistent with subjective cognitive complaints – Effect size Cohen's d calculation* show small effect for Trails B (d = 0.25) and pegboard dominant (d = 0.18).
Axelrod and Milner, 1997	44 male GWV from Army Guard unit	Reitan-Indiana Aphasia Screening Test WAIS-R AVLT Stroop* Trail Making Test WMS-R Finger Tapping Grooved Pegboard* Grip Strength COWAT Category Fluency PIAT-R WCST	– Veterans compared via normative data and grouped by both objective (i.e., Grooved Pegboard, Stroop) and subjective (i.e., health complaint) measures	– Small sample size – Lack of correction for Type 1 error – Volunteer sample – No hypotheses	– No evidence of deficits – Differences in subjective complaints in psychological measures – Effect size Cohen's d calculation* show large effect for Trails B (d = 1.28), and small/medium effect for motor tests (d = −0.63 to −0.48)
Hom et al., 1997	26 GWV with Haley Syndromes, 10 GWV and 10 non-deployed veteran controls	WAIS* Halstead Category Test* Tactual Performance Test Seashore Rhythm Test Speech-Sounds Perception Test Finger Oscillation Test Trail Making Test* Reitan-Indiana Aphasia Screening Examination, Reitan-Klove Sensory Perceptual Examination Reitean-Klove Lateral Dominance Examination Reitan Word Finding Test WMS-R* WRAT3*	– Matched GWV group – GWI criteria used with a factor derived technique	– Small sample size – Limitations of those with fitting factor criteria – Multiple hypothesis testing Initial differences between control group and cases	– Differences between GWI and GWVs in global neurocognitive functioning – Cohen's d calculation* showed a large effect size for Block Design (d = −1.57) and a medium effect size for Trail Making Test- Trail B (d = 0.69) – Psychological responding was consistent with other medical patients
Sillanpaa et al., 1997	49 GWV from a single Army reserve military police unit	NES-2 CPT* Grip Strength Grooved Pegboard* Neurological Screen Fingertip Number Writing perception* WCST* AVLT WAIS-R *	– Examiner blind to participant's medical history – Exposure to toxins measured via self-report – Models tested to mimic GWI and psychological functioning	– Small sample size – Low variance and range in scores – Multicollinearity problems present	– Psychological model accounted for neuropsychological performance with a R^2 of at least a 0.03 (at or above a small effect) for all domains – At least a small effect for exposure and symptoms seen in nearly all domains – Cohen's d calculation* showed a medium effect for motor functioning (d = 0.76)
Vasterling et al., 1998	43 GWVs: 19 with PTSD and 24 without	Letter Cancelation Stroop CPT* WCST WAIS-R Digit Span WAIS-R Arithmetic* Rey-AVLT* CVMT*	– Investigated GWVs with PTSD	– Small sample size – Lack of comparison sample of participants with differing mental disorders – Unable to manipulate trauma exposure	– Veterans with PTSD had deficiencies in sustained attention, mental manipulation, information acquisition, and retroactive interference

(Continued)

TABLE 3 | Continued

References	Group (N)	Neuropsychological Tests	Strengths	Limitations	Conclusions
Anger et al., 1999	66 GWV with unexplained symptoms from WA and OR, 35 GWV controls	Behavioral Assessment and Research System (BARS): Simple Reaction Time* Selective Attention Test Digit Span* Symbol Digit* Serial Digit Learning ODTP*	– Compared those with GWI with controls – Physician blind to participant status	– Volunteer sample Self-selection bias	– Specific problems demonstrated in processing speed – Individuals compared based on processing speed differences also found that those with slower processing speed had deficits in memory and attention
Binder et al., 1999	100 GWV with unexplained symptoms	CPT ODTP*	– Investigated self-report of cognitive ability and affective distress in conjunction with objective cognitive performance	– Cognitive measures may lack sensitivity	– Subjective complaints associated with psychological distress over objective cognitive performance
Bunegin et al., 2001	8 symptomatic GWV, 8 GWV controls	NES-2: Hand-Eye Coordination Simple Reaction Time Visual Digit Span Forward and Backward* Horizontal Addition Pattern Memory* Switching Attention*	– Compared symptomatic GWVs with non-symptomatic GWVs – Investigated blood flow	– Small sample size – Less sensitive measures used	– Symptomatic GWVs had worse performance in memory and executive function tasks – Exposure to acetone also impacted cognitive performance in GWVs – Cohen's d calculation* showed a small effect size for CPT, reaction time (d = −0.14)
Lange et al., 2001	48 symptomatic GWV, 39 GWV controls	NES* PASAT* WAIS-R Digit Span* CVLT RCFT Trails Making Test Category Test* Judgment of Line Orientation Test WAIS-R Block Design Grooved Pegboard	– Compared those with GWI with matched controls	– Volunteer sample of health-care seeking veterans – Small sample size CFS sample – Unequal cells comparisons	– Impairment found in attention (R^2 = 0.12–0.19) and executive functioning tasks (R^2 = 0.07) even after controlling for mood – Cohen's d calculation* showed a large effect size for CPT reaction time (d = 0.85).
White et al., 2001	193 GWV, 47 Germany deployed veterans	WAIS-R CPT Trail Making Test PASAT WCST Digit Span CVLT* WMS-R* Finger Tapping Purdue Pegboard POMS* TOMM	– Compared deployed and non-deployed veterans – Detailed account of toxin exposure – Stratified Random sample	– TOMM scores evidenced possible poor effort in some participants – Multiple comparisons	– Initially, mood was only significant with adjustment for multiple comparisons – Comparing those with and without exposure, had worse performance in short term memory (R^2 = 0.315–0.399), attention (R^2 = 0.381), and mood ((R^2 = 0.202–0.315) – Cohen's d calculation* showed small effect sizes for all neuropsych tests (d = −0.47 to 0.22
David et al., 2002	209 British GWV, 132 non-deployed era veterans	WAIS-R NART WAIS-III Letter Sequencing PASAT SART Stroop Trail Making Test WMS-R Purdue Pegboard	– Compared Gulf War deployment and medical status against other deployments (Bosnia) and controls – Stratified Random sample Blind raters Statistical analyses	– Cross-over effects Self-report symptoms	– Significance only found in PTSD measure – Cohen's d calculation* showed a large effect size for Block Design (d = −2.53)

(Continued)

TABLE 3 | Continued

References	Group (N)	Neuropsychological Tests	Strengths	Limitations	Conclusions
Lindem et al., 2003a	193 GWV, 47 Germany deployed veterans	WAIS-R Information subscale* WAIS-R Digit Span* WMS-R Digit span CPT* Trail Making Test WCST PASAT* Finger Tapping* Purdue Pegboard* WAIS-R Block Design WMS-R Verbal Paired Associate Learning CVLT* Visual Reproduction* POMS*	– Investigated PTSD in relation to exposure to chemical agents – Investigated symptom severity – Better generalization with use of overall cohorts in Gulf War – Large sample size	– Correlational analyses – Lack of baseline performance or known preexisting conditions	– PTSD symptoms severity correlated with greater deficits in a wide array of neuropsychological measures in GW deployed veterans (Partial R^2 = 0.02–0.10) – CBW exposure and PTSD severity in GWVs associated with deficits in sustained attention (Partial R^2 = 0.0004–0.0015), motor speed/motor coordination (0.0000–0.0007)
Lindem et al., 2003b	193 GWV, 47 Germany deployed veterans	WAIS-R Information subscale WAIS-R Digit Span WMS-R Digit span CPT Trail Making Test A Trail Making Test B WCST PASAT Finger Tapping Purdue Pegboard WAIS-R Block Design WMS-R Verbal Paired Associate Learning CVLT Visual Reproduction POMS*	– Investigated GWVs discrepancy between subject complaints and objective performance	– Multiple comparisons	– Subjective complaints more associated with mood symptoms
Lindem et al., 2003c	58 GWV and 19 Germany-deployed veterans	WAIS-R Information subscale WAIS-R Digit Span WMS-R Digit span CPT Trail Making Test* WCST* PASAT Finger Tapping Purdue Pegboard WAIS-R Block Design WMS-R Verbal Paired Associate Learning* CVLT* Visual Reproduction* TOMM* POMS	– Investigated motivation in GWVs	– Small sample size – Difficult to ascertain the reason behind lower TOMM scores – Low amount of those with low TOMM scores	– Variability was seen in those with lower TOMM scores particularly in attention, executive functioning, and memory
Proctor et al., 2003	Danish GWVs (215), comparing deployed (143) and non-deployed veterans (72)	WAIS-R Information CPT Trail-making Test Wisconsin Card Sorting Test Purdue Pegboard WAIS-R Block Designs California Verbal Learning Test WMS Visual Reproductions POMS* TOMM	– Blind to categorization of "higher or lower" symptom status during all phases of recruitment, testing, and interviewing – Differences in deployment missions between Danish and American groups	– Significant mean age difference between deployed (38.8 years) and non-deployed (34.8 years) – Self-report of exposure	– Evidence of increased mood complaints related to GW service – no significant domain-specific evidence of CNS dysfunction was found – No associations between reported GW Environmental exposures related to the Danish GW deployment mission and objective measures of cognitive functioning were observed

(Continued)

TABLE 3 | Continued

References	Group (N)	Neuropsychological Tests	Strengths	Limitations	Conclusions
Sullivan et al., 2003	207 treatment seeking GWV (120 referred for neuropsych evaluation), 53 treatment seeking non-deployed veterans	WAIS-R Information WAIS-R Digit Span* Trail Making Test NES CPT Stroop Test Paced Auditory Serial Addition Test Wisconsin Card Sort Test* CVLT WMS-R Paired Associate Learning WMS-R Visual Reproductions* Hooper Visual Organization Test WAIS-R Block Design* Finger tapping Purdue Pegboard RCFT* POMS* TOMM	– Investigated deployment, treatment seeking, use of pyridostigmine bromide (PB) and PTSD on cognitive functioning – Matched by control group that was also treatment seeking	– Self-report of exposure – Sample size small for comparisons	– GW deployed worse than controls on attention, visuospatial skills, visual memory, and mood – PB use in GWVs worse in executive system tasks – GWVs with PTSD versus those without PTSD showed no differences – Cohen's d calculation* showed a large effect sizes for block design and digit span forward (d = −2.43 to −1.00), small effect sizes for Trails A and B, digit span backward, CVLT, WMS, immediate recall, and finger tapping (d = −0.090 to 0.43), and a medium effect size for WMS, delay recall (d = −0.55).
Vasterling et al., 2003	72 GWVs deployed and 33 non-deployed GWVs	WAIS-R Digit Span WCST AVLT CVMT Purdue Pegboard WAIS-R Information	– Selection of a non-treatment seeking group of GWVs – Comparison of deployed GWVs to a group of GWVs mobilized but no deployed – Use of olfactory and neurocognitive measures with demonstrated sensitivity to neurotoxic exposures	– Sample was regionally recruited	– No evidence that performance on olfactory or neurocognitive measures were related to war-zone duty or to self-reported exposure to GW toxicants – Symptoms of emotional distress were positively correlated with self-report of health and cognitive complaints
Proctor et al., 2006	140 Army GWV with modeled estimates of nerve agent exposure	CPT Trail Making Test WAIS-R Digit Span WCST Finger Tapping Purdue Pegboard* WAIS-R Block Design* CVLT WMS-R verbal paired associate learning WMS visual reproduction	– Stratified random sampling – Examined performance by exposure to sarin and cyclosarin – Sample was unaware of sarin and cyclosarin components, analyses were conducted a prior to exposure knowledge	– Etiology undetermined given the risk of another illness between exposure and measurement (i.e., no baseline health information) – Limited objective information about exposures	– Exposure associated with poor fine psychomotor dexterity (d = 0.44) and visuospatial abilities (d = 0.43)
Barrash, 2007	301 GWV, 99 era veterans deployed elsewhere	WAIS-III Similarities* Block Design* Digit Symbol Digit Span North American Reading Test – Revised Starry Night Test COWAT AVLT* Benton Visual Retention Test* RMT-Words and Faces* Stroop Grooved Pegboard*	– Study of effort and neurocognitive performance in GWVs – Grouped by credible or non-credible impairment	– Small sample of non-credible group – Decreased statistical power – Lack of measures investigating reason behind low effort	– Non-credible impairment associated with more variability in tests and worse emotional/cognitive functioning

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TABLE 3 | Continued

References	Group (N)	Neuropsychological Tests	Strengths	Limitations	Conclusions
Wallin et al., 2009	41 GWVs: 25 with GWI and 16 controls	WRAT reading Block Design Trail Making Test CVLT Pegboard	– Stratified random sampling – Used GWI criteria to divide groups	– Small sample size – Gap between deployment and time of study – Multiple analyses	– Differences only seen in mood and health measures – Cohen's d calculation* showed a medium effect size for block design, Trails B, and CVLT long delay, (d = −0.73 to 0.51), and a small effect size for WRAT reading, Trails A, and Pegboard (d = −0.13 to 0.39).
Toomey et al., 2009	1061 deployed GWV and 1128 non-deployed GWV	WAIS-III Digit Span Trail Making Test* PASAT CPT* WCST CVLT* RCFT* Finger Tapping* Purdue Pegboard* TOMM WRAT-III	– Investigated differences in deployment, toxin exposure, and GWI status – Large sample size, stratified random sampling method – Use of factor analysis – Use of Khamisiyah exposure data	– Low study participation rates – Cross-sectional design – Neuropsychology raters were not blind to condition	– Deployed veterans had worse performance on motor speed (OR = 2.35) and sustained attention (OR = 2.64) – Those with Khamisiyah exposure showed poor motor speed after controlling for mood – Cohen's d calculation* showed small effect sizes for all neuropsych tests (d = −0.09 to 0.06).
Chao et al., 2010	40 GWV with a history of DOD notified sarin cyclosarin exposure risk and 40 non-exposed matched GW veteran controls	CPT Trail Making Test WAIS-III Digit Span Short Category Test COWAT Grooved Pegboard WAIS-III Digit Symbol, matching WAIS-III Block Design WAIS-III Verbal Comprehension Index CVLT-II WMS-III Logical Memory BVMT-R TOMM*	– Used matched cohort sample – Use of Khamisiyah exposure data	– Lack of information regarding the unit and rank of veterans – Lack of information regarding symptom severity (i.e., CMI, smoking status, head injuries) – Lack of cumulative exposure for all GW veterans – Plume estimates only by unit	– No differences in cognitive measures after controlling for poor effort (i.e., failure of TOMM). – Cohen's d calculation* showed a small effect sizes for all neuropsych tests (d = 0.22 to 0.26).
Chao et al., 2011	64 sarin and cyclosarin exposed GWVs and 64 "matched" unexposed GWVs	CPT* WAIS-III Digit Span* Trail Making Test Short Category Test CVLT-II* Grooved Pegboard TOMM	– Used matched controls to compare structural and functional differences in veterans with suspected neurotoxicant exposure – Use of more sensitive MRI (4T) – Use of some sensitive tests for neuropsychological and mood outcomes	– Lack of information regarding veteran's unit, severity of GWI symptoms, smoking status, or history of head injury – Neurotoxicant exposure measured at unit over individual level	– Reduced gray matter and white matter in exposed veterans which was linked to neurotoxicant exposure – Exposed veterans made more omission errors and had slower responses times; omission errors was also linked to neurotoxicant exposure – Cohen's d calculations* showed a medium effect size for Trails A (d = −0.64), and small effect sizes for CPT, Trails B, CVLT, and pegboard (d = −0.36 to 0.38).
Chao et al., 2016	136 GWVs: 106 who reported hearing chemical alarms sound	WAIS III Block Design* Digit Span* CVLT		– Had to rely on self-reports of deployment-related exposures – Lack of pre-GW measurements of brain structure and function – Small sample size – Lack of a non-deployed GW-era veteran control group	– Self-reported frequency of hearing chemical alarms was inversely associated with and significantly predicted performance on the Block Design visuospatial task. – This effect was partially mediated by the relationship between hearing chemical alarms and lateral occipital cortex volume.

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TABLE 3 | Continued

References	Group (N)	Neuropsychological Tests	Strengths	Limitations	Conclusions
Chao, 2017	428 deployed GWVs: 272 which met CDC criteria for CMI	CVLT-II*	– Tested verbal memory with GWVs presenting with subjective memory complaints – Large sample size	– Only measured one domain to control for Type 1 error	– Worse performance on verbal memory associated subjective complaints over and above mood, however, there was higher endorsement of PTSD symptoms
Sullivan et al., 2018	159 GW-deployed preventative medicine personnel who had varying levels of pesticide exposure	WAIS-III information subtest Boston Naming Test Trail Making Test* CPT* WCST Finger Tapping Grooved Pegboard HVOT RCFT* Stanford-Binet Copying Test CVLT II POMS* TOMM	– Grouped veterans by exposure (low/high) to PB and pesticides – Sample had sophisticated knowledge of exposure as they were part of the medical team	– Multiple analyses – Exposures of PB and pesticide may be correlated – Classifications of groups based on self-report	– High pesticide/high PB had worse information processing speed, attention (i.e., errors), visual memory, and increased mood complaints

*See original journal articles in first column for test references. *Denotes significance of $p < 0.05$.*

complaints, depression, and state anxiety. Results indicated that mood-related factors (i.e., anxiety, depression) accounted for more variance in neuropsychological performance measuring attention, motor coordination, and executive functioning in comparison to the syndrome model. However, limitations of the study included a small sample size and the use of a syndrome model that does not represent the current case criteria for GWI (i.e., CMI or Kansas GWI criteria).

These two studies (Axelrod and Milner, 1997; Sillanpaa et al., 1997) were similar in that they attributed more mood-altering factors to neuropsychological functioning as measured by the MMPI-2. However, comparison of effect sizes may point toward a trend in relatively impaired motor coordination and executive functioning.

DEPLOYMENT STATUS AND NEUROPSYCHOLOGICAL FINDINGS

Goldstein et al. (1996) tested 21 GW deployed veterans with a battery of neuropsychological tests and compared their performance to results from 38 demographically matched non-military controls. Cognition was measured via an extended version of the Pittsburgh Occupational Exposure Test battery (**Table 3**). Psychological distress was measured via the SCL-90-R. An impairment index was composed of 14 total neuropsychological tests (**Table 3**). Differences were found in the overall impairment index with significantly poorer performance in deployed compared to the control group. When controlling for mood, the impairment index difference was no longer significant. Specific impairments were found on the Controlled Oral Word Association Test (COWAT) and the Continuous Performance Test (CPT) reaction time. Notable limitations of this study are the small sample size utilized as well as the use of matched controls from a non-military population. Effect sizes noted in the recent meta-analysis by Janulewicz et al. (2017) reported a small effect (0.25) in the Trail Making Test -Part B between the groups, while the Grooved Pegboard (dominant) score approached a small effect size (0.18).

White et al. (2001) performed neuropsychological testing and compared the outcomes in those with specific self-reported neurotoxicant exposures. Veterans (n = 240) were recruited from 2 deployed and one non-deployed cohorts (Proctor et al., 1998). Veterans underwent an environmental interview, mood surveys, a full neuropsychological test battery (**Table 3**) and a psychological diagnostic interview. Neuropsychological outcomes showed differences in CPT when mood covariates were not controlled for; however, no individual measure achieved statistical significance when controlling for mood. Of note, additional tests showed moderate effect sizes in measures of attention, executive, and motor function (Paced Auditory Serial Addition Test (PASAT), Wisconsin Card Sort Test (WCST), Trail Making Test- Part A, Purdue Pegboard) which suggest that those deployed in the GW had poorer cognitive performance.

David et al. (2002) investigated neuropsychological patterns among 341 veterans who served in the United Kingdom military forces. Out of 341 participants, 98 were designated "Gulf well," 111 were designated "Gulf ill," 78 were designated "Era ill" and 54 were designated "Bosnia ill." David et al. (2002) assessed general functioning through a complete neuropsychological battery (**Table 3**). In regard to neuropsychological test performance, the GW ill group had poorer performance on WAIS-R Performance IQ, the digit symbol test, the Trail Making Test, and Sustained Attention to Response Task (SART) accuracy. After adjusting for the BDI score and multiple comparisons, no significant differences were found between healthy and GW ill on cognitive performance measures. David et al. (2002) found that the ill group had higher scores on the Mississippi Combat Related

PTSD Scale. When testing the main effect of deployment, it was found that participants in the Gulf group had significantly lower Verbal IQ and Performance IQ scores (i.e., most notably, in Block Design) compared to the Era ill Group. Additionally, the Gulf ill group had the lowest pegboard performance compared to the other groups. After controlling for BDI scores, there were still significant differences in Verbal IQ and the Purdue Pegboard when comparing the Gulf ill group to other groups. However, these contrasts were not significant after adjusting for multiple comparisons. Therefore, David et al. (2002) concluded that there was no major neuropsychological impairment, but rather, more associations with mood related impairment in deployed veterans which may better account for poor performance on neuropsychological measures. However, by controlling these factors, they may have discounted the mood symptoms may have resulted from neurological impairment and/or neurotoxicant exposures. Additionally, before correction, there was indication that individuals who were GW ill may have difficulties associated with performance in Performance IQ, Digit Symbol, Trail Making Test- Part A and B, and SART errors. Additionally, GW ill was also associated with poorer performance in Verbal IQ, Performance IQ, Block Design, and the Purdue Pegboard. Furthermore, these studies highlight the importance of overcorrection for emotional symptoms that may lead to underestimating true neuropsychological deficit that can also lead to mood symptoms as stated by Institute of Medicine [IOM] (2006).

Lindem et al. (2003a) investigated neuropsychological performance in conjunction with chemical exposure and severity of trauma symptoms with a sample of 225 deployed and non-deployed participants. Participants were administered the CAPS to determine the level of trauma symptoms. In addition, the veterans underwent a full neuropsychological test battery White et al. (2001). Chemical exposure was assessed through self-report measures and a clinical interview. Results indicated that the severity of PTSD symptoms in the full sample after controlling for covariates was directly correlated with poorer performance in general intellectual ability, attention, motor, memory, and mood measures. In GW deployed veterans, partial correlations were significant for those with PTSD and worse performance on general intellectual ability, sustained attention, motor functioning, verbal learning, and all mood scales.

Proctor et al. (2003) studied neuropsychological measures in deployed (n = 143) and non-deployed veterans (n = 72) Danish GW veterans. Researchers compared groups across neuropsychological measures (White et al., 2001), controlling for age. It was found that there were significant differences for neuropsychological domains; such that individual tests of executive functioning and verbal memory showed poorer performance in the deployed veterans. There was significant difference on the POMS Fatigue and Confusion scales, with deployed groups reporting a moderate to high number of symptoms. Therefore, the researchers concluded that, as there was no connection between deployed and non-deployed groups on neuropsychological measures, there was no evidence in this study of toxicant exposure leading to neurocognitive deficits. Rather, mood related symptoms were more likely to be reported. However, this study was composed of Danish soldiers who were not exposed to combat and were not in chemical warfare areas indicating that they likely differed from other cohorts (e.g., British, American) given differential exposure to GW neurotoxicants (less endorsement of exposure to chemical warfare agents and no use of anti-nerve gas pills) and less trauma. However, further investigation of the effect sizes via Janulewicz et al. (2017) found small effects in the Trail Making Test (d = 0.22 to 0.31) and in a memory measure (CVLT; d = −0.32 to −0.20). Block Design approached a small effect as well (d = −0.18).

Sullivan et al. (2003) evaluated a sample of 260 veterans including GW deployed and seeking treatment (i.e., for cognitive or health symptoms) and a control group of GW non-deployed veterans seeking neuropsychological evaluations. All veterans underwent a neuropsychological battery (**Table 3**) in addition to a structured clinical interview. In comparison to non-deployed veterans, deployed veterans had worse performance in measures of attention, visuospatial skills, and visual memory. In addition, deployed veterans endorsed worse mood symptoms. Therefore, the researchers concluded that GW deployment led to the significant neuropsychological decrements. Effect size analysis performed by Janulewicz et al. (2017) found a small effect in Trail Making Test- Part A (d = 0.43), Trail Making Test- Part B (d = 0.36), CVLT Trials 1–5 (d = −0.26), CVLT short delay (d = −0.47), CVLT long delay (d = −0.42), CVLT recognition (d = −0.33), and WMS immediate recall (d = −0.55). A medium effect was seen in WMS delayed recall (d = −0.55). A large effect or higher was seen in Digit Span backward (d = −1.00), and Block Design (d = −2.43).

Toomey et al. (2009) conducted a study examining GW veterans (deployed n = 1061, and non-deployed 1,128) on several measures of neuropsychological performance. Veterans underwent a neuropsychological battery (White et al., 2001). Results indicated that deployed veterans performed significantly worse on a measure of attention flexibility (i.e., Trails A-B) in comparison to non-deployed veterans. The meta-analysis completed by Janulewicz et al. (2017) did not return any notable effect sizes.

Overall, these studies comparing deployed GW veterans to non-deployed veterans showed some consistency in relative impairment within major cognitive domains, including simple and sustained attention, complex tracking, working memory, acquisition and retention of information when simply comparing deployment status rather than symptomatic vs. non-symptomatic groupings.

SYMPTOMATIC VS. NON-SYMPTOMATIC DEPLOYED GW VETERANS AND NEUROPSYCHOLOGICAL PERFORMANCE

Hom et al. (1997) first investigated symptomatic GW veterans (n = 26) in comparison to healthy GW veteran controls (n = 20) on neuropsychological and psychological measures (**Table 3**).

Psychological functioning was measured using validated surveys and a clinical interview. Symptomatic veterans showed significantly worse performance on measures of overall brain function or derived composite scores from neuropsychological measures (Halstead Retain Impairment Index). In addition, symptomatic veterans showed greater impairment than controls on the Halsted Category Test and Trails Making Test- Part B (d = 0.69 per Janulewicz et al., 2017), indicating poor abstract reasoning and problem solving/flexibility; measures of executive functioning. Of note, Janulewicz et al. (2017) also found a large effect size for Block Design (d = −1.57) for this study. The researchers concluded that these results supported the presence of worse neuropsychological and mood functioning in veterans with GWI as classified by Haley syndromes (Haley et al., 1997). However, these researchers hypothesized that mood complaints were secondary to the physical dysfunction consistent with GWI symptoms and did not solely account for GWI presentation. This study exhibited several limitations including a small sample size.

Anger et al. (1999) investigated mood and neuropsychological differences in GW veterans with unexplained medical symptoms. Veterans underwent a medical examination conducted by a physician blind to case/control designation; controls were determined as those not endorsing any GW related symptoms. Symptomatic and non-symptomatic veterans (N = 101) completed a series of tests assessing psychological and neuropsychological functioning (**Table 3**). Anger et al. (1999) found statistically significant differences on neuropsychological testing only for the Oregon Dual Task Procedure (ODTP) computerized test measure after controlling for multiple comparisons. Using these results, researchers divided groups based on speed as "slow cases" and "other cases." Consistent with performance on the ODTP, veterans in the "slow case" group showed slower responses than controls on Symbol Digit, Simple Reaction Time, Digit Span Forward, and Digit Span Backward. Therefore, Anger et al. (1999) reported slower neurobehavioral performance on digit recall tasks and increased psychological distress in those with GWI symptoms. However, slow performance was exhibited in a sub group of GW cases ("slow cases"). These "slow cases" also showed deficits in working memory, attention and response speed indicating a more severe subgroup. These results were also not otherwise explained by mood or PTSD and were consistent with the literature investigating deficits in those with organophosphate poisoning.

Storzbach et al. (2000) conducted a study investigating the performance of GW veterans with unexplained symptoms (n = 241) on psychosocial and neurobehavioral measures in comparison to a veteran control group (n = 113). In regard to the mood measures, there was a significant difference between groups in that symptomatic veterans were higher on nearly all mood measures with nearly all measures demonstrating a large effect size. Additionally, the case group endorsed worse physical, mental, and health-related functioning (SF-36), greater combat exposure scale measures, and PTSD symptoms. In regard to neuropsychological testing, the case group had worse performance on Symbol Digit and ODTP forced choice and forced latency scores with a small effect size (Smith, 1968; Binder, 1993). The researchers concluded that, as they found differences in psychosocial and cognitive tests, stress has a major role in GW symptoms as either a precursor or a result of the experienced symptoms. However, these conclusions are limited in that the researchers did not control for mood when investigating neuropsychological performance.

Storzbach et al. (2001) expanded upon these findings using the same measures to assess psychosocial and cognitive functioning in 239 symptomatic GW veterans and 112 control veterans. However, they identified a "slow group" using a modified cutoff as established by Anger et al. (1999). The slow group had worse performance in comparison to controls in all measures, except the Serial Digit Learning Test again indicating a more impaired subgroup.

Binder et al. (2001) investigated cognitive performance in symptomatic GW veterans (n = 94) as defined by chronic fatigue syndrome (CFS). Groups were divided based on CFS criteria (Fukuda et al., 1994) with 32 participants comprising the case group and 62 participants comprising the control group. Neuropsychological testing was conducted using the same battery described in Anger et al. (1999). Results indicated that those in the case group performed worse on reaction time ODTP latency, and ODTP number correct. Limitations of this study include the use of a computerized measure that may have been less sensitive then measures with an examiner and a shorter battery with less global neurocognitive implications and the classification of GWI as CFS.

Bunegin et al. (2001) built their hypothesis on the premise that GW symptoms are linked to CNS dysfunction. Previous research has shown that GW veterans experience cognitive issues and headaches from chemical odors (Bell et al., 1990; Miller and Prihoda, 1999) which is similar to transient ischemia. Therefore, researchers investigated cognitive performance and middle cerebral artery blood flow velocity (MCABFV) in both symptomatic (n = 8) and asymptomatic GW veterans (n = 8) when exposed to different air conditions (i.e., clean air, placebo acetone condition, and low levels of acetone). All participants were tested using NES-2 computerized assessment (Letz, 1991). The results of the study suggested that both symptomatic and asymptomatic GW veterans performed similarly in cognitive tests when comparing the performance across different air exposures. However, pooled data across conditions revealed significantly lower performances in measures of memory and executive functioning in symptomatic GW veterans. Additionally, there were statistically significant differences between asymptomatic and symptomatic GW veterans in MCABFV as symptomatic GW veterans demonstrated a depressed response across all conditions.

Lange et al. (2001) conducted a study examining symptomatic and healthy GW veterans on cognitive functioning; however, symptomatic was defined using established criteria for CFS and Multiple Chemical Sensitivity (Cullen, 1987; Fukuda et al., 1998). Additionally, Lange et al. (2001) identified and accounted for presence of PTSD and major depression in a group of 87 GW veterans (healthy controls = 39; GWI = 48). Both healthy and symptomatic GW veteran groups were administered tests sensitive to attention, concentration or information processing, verbal and visual memory, abstraction and conceptualization, visuo-perceptual and perceptual-motor functions, and fine motor functioning. Analyses found significant results in attention,

concentration, and information processing, as well as abstraction and conceptualization. Tests reflecting attention and information processing as well as tests of abstraction and concentration were significantly different with symptomatic veterans showing worse performance than non-symptomatic controls. In addition, regression analyses were conducted controlling for mood outcomes; results indicated the symptomatic group remained significant on some tests (NES simple reaction time) but were no longer significant for other tests. Mood-related diagnoses were not correlated with performance on the CPT; therefore, case status was the only predictor and remained significant in symptomatic GW veterans. Lange et al. (2001) concluded that symptomatic veterans exhibited deficits on attention, concentration, and information processing over and above the impact of mood related disorders. Limitations of the study include using GWI terminology inconsistent with the field where current case criteria is determined using Kansas or CDC criteria rather than CFS and MCS.

Wallin et al. (2009) investigated neuropsychological performance in a small sample derived from the National Health Survey of GW veterans (Case group with CDC criteria = 25, Control = 16). Veterans underwent neuropsychological testing (**Table 3**) in addition to psychological testing. Wallin et al. (2009) found no significant differences between groups on neuropsychological testing. However, there were differences in GWI cases on measures of depression, somatic complaints, and anxiety. Wallin et al. (2009) concluded a stronger influence of psychological factors over neurological factors. Several limitations were present in this study including a small sample size. Correspondingly, an effect size analysis conducted by Janulewicz et al. (2017) found meaningful effects (>0.20) in Block Design (d = −0.73), Trail Making Test, Part-A (d = 0.39), Trail Making Test, Part-B (d = 0.51), CVLT, long delay (d = −0.66), Pegboard, dominant (d = 0.37) and Pegboard, non-dominant (d = 0.31) that would have shown significant differences in a larger study sample.

These eight studies had similar findings regarding cognitive domains when investigating symptomatic vs. non-symptomatic veterans indicating the more refined criteria than deployed vs. non-deployed. In the symptomatic groups there was consistency in attention deficits as measured Digit Span Forward in several studies (**Table 3**). Additionally, psychomotor speed as measured by Symbol Digit and Simple Reaction Time was sensitive to symptomatic veterans (**Table 3**). Finally, the most consistent finding regarding attention was in a measure of sustained attention – CPT, which was observed in several studies. Executive functioning was more variable with less consistency in test measures used. Therefore, there was few similarities between studies (i.e., no more than two studies had similar findings in Category Test and Trail Making Test- Part B). In regard to memory, several studies found memory impairment as measured by the CVLT-II (**Table 1**). These findings are supported by both imaging and animal models of memory. Regarding visuospatial functioning, there was consistency of results in that the symptomatic group showed worse performance on Block Design in multiple studies (Hom et al., 1997; Proctor et al., 2006; Chao et al., 2010). Finally, there was some consistency in motor coordination as measured by a Pegboard test in several studies (Proctor et al., 2006; Chao et al., 2010, 2011). In terms of mood measures, these studies did not have more than two studies that were consistent in mood results. However, health outcomes as measured by the SF-36 were different in the case symptomatic groups (Anger et al., 1999; Storzbach et al., 2000; Wallin et al., 2009).

These studies were able to demonstrate a stronger argument for neurological dysfunction given the clear operational definitions of symptomatic vs. non-symptomatic groups. However, these studies were still very diverse in regard to the measurement style (i.e., computer versus paper and pencil) and test battery and what determined 'caseness.' These studies also highlight the importance of using more objective measures of neurological biomarkers to make a stronger argument for behavioral and neurological connections. As noted before, future research using CDEs for case criteria and neuropsychological batteries would be highly beneficial given their sensitivity to changes in veterans with GWI as well as creating more consistency across studies.

NEUROTOXICANT EXPOSURE AND NEUROPSYCHOLOGICAL PERFORMANCE

Several studies have assessed neuropsychological functioning in relation to neurotoxicant exposures during the war including sarin, pesticides and pyridostigmine bromide (PB) anti-nerve gas pills. Results of these studies are reported below and in **Table 4**.

In the Proctor et al. (1998) paper described above, when comparing those exposed or not exposed to self-reported chemical warfare agents, significant differences were found in measures of tension and confusion (POMS), long term visual memory (WMS-R Visual Reproduction), short term verbal memory (CVLT), and attention/working memory (Digit Span). However, those that reported exposure to chemical warfare agents during the war also had lower scores in comparison to the unexposed group. When controlling for mood or malingering, the results did not change, indicating performances were not fully explained by mood disorders and likely represented sequelae from toxicant exposures.

Lindem et al. (2003a) as described above assessed veterans with PTSD and chemical exposure, analyses showed worse performance in sustained attention, motor speed, and motor coordination. Furthermore, researchers concluded that severity of PTSD was a contributing factor to issues with short-term verbal memory (acquisition, retrieval, semantic clustering). Additionally, this pattern suggested difficulties with sustained attention, planning, and executive functioning that may point toward issues with hypervigilance. Finally, self-reported chemical weapons exposure showed specific deficits in sustained attention, perseverative responses, visual memory, and mood measures.

Proctor et al. (2006) examined the relationship between DOD-estimated levels of sarin and cyclosarin exposure and neuropsychological functioning. A stratified random sample of GW veterans completed a medical and history questionnaire,

TABLE 4 | Neurotoxicants and Neuropsychological Performance.

References	Group (N)	Neuropsychological Tests	Strengths	Limitations	Key Findings and Conclusions
White et al., 2001	193 GWV, 47 Germany deployed veterans	WAIS-R CPT Trail Making Test PASAT WCST Digit Span CVLT* WMS-R* Finger Tapping Purdue Pegboard POMS* TOMM	– Compared deployed and non-deployed veterans – Detailed account of toxicant exposure – Stratified Random sample	– TOMM scores evidenced possible poor effort in some participants – Multiple comparisons	– Pesticide exposure by self-report was associated with worse mood functioning on all POMS subscales. – Chemical weapons exposure by self-report was associated with worse mood functioning on the POMS subscales of tension and confusion as well as poorer – performance on attention/executive functioning, memory and mood measures.
Sullivan et al., 2003	207 treatment seeking GWV (120 referred for neuropsych evaluation), 53 treatment seeking non-deployed veterans	WAIS-R Information WAIS-R Digit Span Trail Making Test NES CPT Stroop Test Paced Auditory Serial Addition Test Wisconsin Card Sort Test* CVLT WMS-R Paired Associate Learning WMS-R Visual Reproductions Hooper Visual Organization Test WAIS-R Block Design Finger tapping Purdue Pegboard POMS TOMM	– Investigated deployment, treatment seeking, use of pyridostigmine bromide (PB) and PTSD on cognitive functioning – Matched by control group that was also treatment seeking	– Self-report of exposure – Sample size small for exposure comparisons	– PB use in GWVs showed worse performance on an executive system task. – GWVs with PTSD versus those without PTSD showed no significant differences – There were no significant interaction effects of PB and PTSD on cognitive functioning.
Vasterling et al., 2003	72 GWVs deployed and 33 non-deployed GWVs	WAIS-R Digit Span WCST AVLT CVMT Purdue Pegboard WAIS-R Information	– Selection of a non-treatment seeking group of GWVs – Comparison of deployed GWVs to a group of GWVs mobilized but not deployed – Use of olfactory and neurocognitive measures with demonstrated sensitivity to neurotoxic exposures but not to organophosphates	– Sample was regionally recruited	– No evidence that performance on olfactory or neurocognitive measures were related to self-reported exposure to GW toxicants – GWVs reporting more significant exposures reported greater severity of health symptoms and more severe cognitive symptoms, than those reporting less significant exposures – Symptoms of emotional distress were positively correlated with self-report of health and cognitive complaints
Proctor et al., 2006	140 Army GWV with modeled estimates of nerve agent exposure	CPT Trail Making Test WAIS-R Digit Span WCST Finger Tapping Purdue Pegboard* WAIS-R Block Design* CVLT WMS-R verbal paired associate learning WMS visual reproduction	– Stratified random sampling strategy – Examined performance by exposure to sarin and cyclosarin by DOD modeling – Sample was unaware of sarin and cyclosarin components, analyses were conducted prior to exposure knowledge	– Etiology undetermined given the risk of another illness between exposure and measurement (i.e., no baseline health information) – Limited objective information about exposures – Plume estimates only by unit	– Exposure associated with poor fine psychomotor dexterity (d = 0.44) and visuospatial abilities (d = 0.43) in a dose-response manner – The difference on the motor task was equivalent to the performance effect of being approximately 20 years older and for the block design task, being 15 years older. – Higher exposure was not significantly related to mood state.

(Continued)

TABLE 4 | Continued

References	Group (N)	Neuropsychological Tests	Strengths	Limitations	Key Findings and Conclusions
Toomey et al., 2009	1061 deployed GWV and 1128 non-deployed GWV	WAIS-III Digit Span Trail Making Test* PASAT CPT WCST CVLT* RCFT* Finger Tapping* Purdue Pegboard* TOMM WRAT-III	– Investigated differences in deployment, toxicant exposure, and GWI status – Large sample size, stratified random sampling method – Use of factor analysis – Use of Khamisiyah exposure data	– Low study participation rates from overall larger sample – Cross-sectional design – Neuropsychology raters were not blind to condition – Self-reported PB, pesticide, oil well fire, vaccine exposure	– Those with Khamisiyah exposure modeled sarin exposure showed poor motor speed after controlling for mood – Those reporting proximity to SCUD missiles had lower motor speed – Those reporting CARC paint exposure had worse visual memory – Khamisiyah exposure was associated with poorer verbal memory, beyond emotional distress and demographic variables
Chao et al., 2010	40 GWV with a history of DOD notified sarin cyclosarin exposure risk and 40 non-exposed matched GW veteran controls	CPT Trail Making Test* WAIS-III Digit Span Short Category Test COWAT* Grooved Pegboard* WAIS-III Digit Symbol, matching WAIS-III Block Design* WAIS-III Verbal Comprehension Index* CVLT-II WMS-III Logical Memory BVMT-R TOMM	– Use of DOD modeled Khamisiyah data for sarin/cyclosarin exposure – Demographically matched groups	– Lack of information regarding the unit and rank of veterans – Lack of information regarding symptom severity (i.e., CMI, smoking status, head injuries) – Lack of cumulative exposure for all GW veterans – Plume estimates only by unit	– No differences in cognitive measures after controlling for poor effort (i.e., failure of TOMM). – No correlation between unit-level dose-estimates and neuropsychological data in the exposed veterans. – In exposed veterans, hippocampal volume correlate positively with verbal comprehension scores, while total GM volume correlated positively with performance on verbal fluency and visuospatial ability and negatively with time to complete the Trail Making Test and time to place all pegs in the pegboard with the non-dominant hand. – In exposed veterans, total WM volume correlated positively with verbal fluency, and visuospatial function.
Chao et al., 2011	64 sarin and cyclosarin exposed GWVs and 64 "matched" unexposed GWVs	CPT* WAIS-III Digit Span* Trail Making Test Short Category Test CVLT-II* Grooved Pegboard TOMM	– Used matched controls to compare structural and functional differences in veterans with suspected neurotoxicant exposure – Use of more sensitive MRI (4T) – Use of sensitive tests for neuropsychological and mood outcomes	– Lack of information regarding veteran's unit, severity of GWI symptoms, smoking status, or history of head injury – Neurotoxicant exposure measured at unit over individual level	– Reduced gray matter and white matter in exposed veterans which was linked to sarin/cyclosarin exposure, over and above confounding demographic, clinical, and psychosocial variables. – Exposed veterans made more omission errors and had slower response times on CPT; omission errors was also linked to sarin neurotoxicant exposure – Positive correlation between GM and WM volume, on CVLT performance and digit span backward in the exposed veterans.

(Continued)

TABLE 4 | Continued

References	Group (N)	Neuropsychological Tests	Strengths	Limitations	Key Findings and Conclusions
Chao et al., 2016	136 GWVs: 106 who reported hearing chemical alarms sound	WAIS III Block Design* Digit Span* CVLT		– Had to rely on self-reports of deployment-related exposures – Lack of pre-GW measurements of brain structure and function – Didn't measure experience and exposure that took place *after* the GW – Small sample size – Lack of a non-deployed GW-era veteran control group	– Self-reported frequency of hearing chemical alarms was inversely associated with and significantly predicted performance on the Block Design visuospatial task. – This effect was partially mediated by the relationship between hearing chemical alarms and lateral occipital cortex volume. – Volumes of the lateral occipital cortex, right inferior frontal cortex, and right supramarginal gyrus were positively correlated with Block design raw scores. – Volumes of lateral occipital cortex, right supramarginal gyrus and right precuneus were negatively correlated with the frequency of hearing chemical alarms. – No dose-effect relationship between Khamisiyah exposures and Block Design raw scores – Frequency of hearing chemical alarms sound was inversely correlated with Backward Digit Span raw scores but not with raw scores on CVLT learning trial 2 or with CVLT short-delay free recall.
Sullivan et al., 2018	159 GW-deployed preventative medicine personnel who had varying levels of pesticide exposure	WAIS-III information subtest Boston Naming Test Trail Making Test* CPT* WCST Finger Tapping Grooved Pegboard HVOT RCFT* Stanford-Binet Copying Test CVLT II POMS* TOMM	– Grouped veterans by exposure (low/high) to PB and pesticides – Sample had sophisticated knowledge of exposure as they were part of the medical team	– Multiple analyses – Exposures of PB and pesticide may be correlated – Classifications of groups based on self-report	– High pesticide/high PB had worse information processing speed, attention (i.e., errors), visual memory, and increased mood complaints, after controlling for either CMI, PTSD, or depression. – High pesticides/low PB group was the worst performing in terms of visual memory recall while the low pesticides/low PB and low pesticides/high PB group performed significantly better. – Dichlorvos (pest strips) exposure was the best predictor of poorer performance in the attention and psychomotor domains. Methomyl (fly bait) exposure and lindane (delouser) were the best predictors of affective complaints in the mood domain. Bendiocarb and lindane were the best predictors for the visuospatial domain.

*See original journal articles in first column for test references. *Denotes significance of $p < 0.05$.*

a semi-structured environmental interview, neuropsychological testing, and psychological testing. Veterans were grouped based on exposed vs. non-exposed status as determined by modeled plume exposure estimates obtained from the DoD (from the Khamisiyah weapons depot detonations in March 1991). Results indicated significant differences in groups on psychomotor and visuospatial abilities (e.g., Purdue Pegboard and Block Design) with higher exposure associated with worse outcomes, or a dose response effect with exposure. However, one limitation is the gap between exposure and outcome measurement (4–5 years), thereby making it impossible to determine if it was a delayed or immediate exposure effect. Importantly however, this was the only study conducted before awareness of possible sarin exposure and before DOD notification letters were sent to those exposed at Khamisiyah, Iraq thus reducing bias based on knowledge of exposures.

Toomey et al. (2009) compared 2,000 veterans as described above and additionally performed analyses within the deployed veterans with and without sarin exposure from the Khamisiyah weapons depot detonations as classified by DOD notification (Winkenwerder, 2003). Results showed toxicant exposure was associated with motor speed deficits on CPT over and above mood related effects. In addition, depressive symptoms and exposure to self-reported contaminated food and water were related to worse scores of sustained attention measures. Veterans self-reporting CARC paint exposures had worse visual memory functioning. Veterans reporting being exposed to nerve agents during the war had worse verbal memory functioning and those reporting being near SCUD missiles had lower motor speed.

Chao et al. (2010) investigated neuropsychological performance (White et al., 2001) and MRI results between 40 GW veterans with a history of DOD notified sarin/cyclosarin exposure risk from Khamisiyah and 40 non-exposed matched GW veteran controls. When comparing the controls to the group exposed to sarin/cyclosarin, there were no differences in cognitive measures after controlling for poor effort (i.e., failure on the TOMM). However, the group with sarin exposure had less total gray matter and hippocampal volume on brain imaging. Limitations included lack of information regarding the unit and rank of veterans, lack of information regarding symptom severity (i.e., CMI, smoking status, head injuries), lack of cumulative exposure for all GW veterans, and plume estimates only by unit. Per Janulewicz et al. (2017), there were meaningful effects for Block Design ($d = -0.32$), CPT, reaction time ($d = 0.42$), CVLT long delay ($d = -0.34$), and Pegboard, non-dominant ($d = 0.27$).

Chao et al. (2011) then expanded on these prior findings using a different and larger cohort of veterans (sarin exposed $n = 65$; unexposed controls = 64) and a stronger 4T magnet MRI. Group comparisons on neuropsychological tests showed that sarin exposed veterans had more omission errors and slower reaction time on the CPT. Additionally, there was reduced gray matter and white matter volume in comparison to the control group. Regression analyses also revealed that GWI status was associated with errors of omission, as well as reduced gray matter and white matter volume. Janulewicz et al. (2017) also found meaningful effects in CPT reaction time ($d = 0.38$), Trail Making Test, Part A ($d = -0.64$), Pegboard, dominant ($d = -0.28$), and pegboard non-dominant ($d = -0.036$).

Sullivan et al. (2003) used a sample of 260 veterans including GW deployed and treatment seeking and a control group of GW non-deployed veterans not seeking treatment. Veterans were also compared based on PTSD and the use of pyridostigmine bromide (PB) anti-nerve gas pill usage during the war. All veterans underwent a neuropsychological battery (**Table 1**) in addition to a structured clinical interview to determine PTSD status. Veterans exposed to PB showed worse performance on a measure of executive system functioning. However, there was no difference between those with and without PTSD on neuropsychological measures and no interaction effect of PB use and PTSD diagnosis. Therefore, the researchers concluded that GW deployment and PB exposure led to the significant neuropsychological decrements.

White et al. (2001) – compared deployed and non-deployed veterans as described above. In this study, pesticide exposure by self-report was associated with worse mood functioning on POMS mood scales. Chemical weapons exposure by self-report was also associated with worse performance on attention/executive functioning, memory and mood measures.

Sullivan et al. (2018) investigated how differing levels of pesticide exposure and PB intake contributed to neuropsychological outcomes in GW veterans. The researchers recruited veterans with functional knowledge of their exposure to neurotoxicants based on their military occupational specialties as military pesticide applicators and/or preventative medical personnel. The four veteran comparison groups were based on pesticide and PB exposures. Participants completed a full neuropsychological test battery (**Table 4**). Veterans were also assessed for psychological functioning. GWI was determined by CMI criteria (Fukuda et al., 1998). Results showed that high pesticide/high PB exposed group showed significantly slower CPT reaction time and higher POMS symptoms. These neuropsychological decrements remained significant with PTSD as a covariate, demonstrating a main effect on attention reaction time in comparison to the low pesticide/low PB group. Additionally, the high pesticide exposure/low PB group was significantly worse on a measure of visual memory compared to the low pesticide/high PB and low pesticide/low PB groups. Significant differences were found in psychomotor, mood, attention, and memory domains when controlling for covariates (i.e., age, education, gender). Researchers found that a higher rate of CMI was associated with the high pesticide/high PB group which evidenced worse cognitive performance in attention, motor, and memory domains. Overall, results showed that high pesticide/high PB exposure had worse performance on information processing reaction times, attentional errors and visual memory accompanied by increased mood complaints. Limitations of this study include multiple analysis with a smaller sample size, increasing the chance of finding significance. Additionally, it is possible that, although the sample had a sophisticated knowledge of their exposure, their exposures were correlated (i.e., exposure to PB associated with exposure to nerve agents, and pesticides). Additionally, pesticide and PB classifications were reliant on self-report exposure.

Vasterling et al. (2003) compared 72 GW deployed veterans and 33 non-deployed veterans. They compared a full neuropsychological battery and used an olfactory test as a sensitivity measure of toxicant exposure. Results showed no evidence that performance on olfactory or neurocognitive measures were related to war-zone duty or to self-reported exposure to GW toxicants. Symptoms of emotional distress were positively correlated with self-report of health and cognitive complaints. However, the olfactory test has not been shown to be sensitive to organophosphate exposures, the most commonly associated exposure with GWI.

Research on neurotoxicant exposures varied in regard to the toxicant explored (i.e., PB, pesticides or cyclosarin/sarin) and methodology used (i.e., objective or subjective measures). Research would be improved by including more objective biomarkers of past toxicant exposure when comparing deployed and non-deployed troops. Suggested objective biomarkers could be immunological, genetic, or metabolic in nature and would strengthen the link between toxicant exposure and neurological dysfunction given these variables reflect compromised functioning at the time of the study rather than retrospective measures such as self-report or military dose estimate reports. Although markers of past organophosphate exposures have previously been elusive, more recent downstream effects from these exposures have been preliminarily identified and can be utilized (Abou-Donia et al., 2017). Additionally, some studies also addressed investigating illness status or treatment seeking groups (David et al., 2002; Sullivan et al., 2003). Research would improve with more consistent grouping of individuals based on established criteria for GWI (i.e., Steele, 2000). Finally, utilizing recommended CDEs consistently across studies for assessing mood and neuropsychological performance and consistent questions about neurotoxicant exposures would benefit future research as study results would be more comparable.

MOOD AND PTSD CONTRIBUTIONS TO NEUROPSYCHOLOGICAL PERFORMANCE

The following five studies that were previously reviewed above concluded that neuropsychological performance was either attributable to mood symptoms or equivalent to controls after accounting for mood-related symptoms (Axelrod and Milner, 1997; Sillanpaa et al., 1997; Storzbach et al., 2000; David et al., 2002; Proctor et al., 2003). Axelrod and Milner (1997) found that GW veterans had elevated scores in a MMPI measure thought to represent body complaints. Sillanpaa et al. (1997), using a model of psychological factors, found that depression (as measured by the MMPI) and anxiety (as measured by the STAI) significantly predicted neuropsychological performance in attention, motor, and executive functioning while an early model of GWI failed to produce significance. Storzbach et al. (2000) found that there was a significant predominately large effect difference in the case group on scores from multiple PTSD and psychological scales. David et al. (2002) found that symptomatic individuals had higher scores on depression, PTSD and anger scales. Finally, Proctor et al. (2003) found that there was significant difference in the POMS mood scales (Fatigue and Confusion) between those reporting GWI symptoms versus controls.

Vasterling et al. (1998) examined GW veterans with (n = 19) versus without PTSD (n = 24) on measures of attention and memory dysfunction. GW veterans with PTSD performed worse on the WAIS-R Arithmetic test and made more commission errors on the CPT. The GW veterans with PTSD also had worse performance in the Auditory Verbal Learning Test (AVLT) and Continuous Visual Memory Test (CVMT). Vasterling et al. (1998) hypothesized that the presence of intrusions (i.e., inability to inhibit thoughts or experiences related to trauma) could contribute to these patterns of symptoms. Using a principal component analyses, the researchers found that cognitive intrusions symptoms, particularly re-experiencing phenomenon, was related to poorer performance on memory and attention measures (**Table 2**). Therefore, they hypothesized that PTSD may lead to problems inhibiting inaccurate answers and filtering information unrelated to the task at hand. Of note, the study was limited given that the sample was specifically chosen to have PTSD and they also had other co-morbid diagnoses (i.e., major depression, dysthymia, panic disorder, social phobia, obsessive-compulsive disorder, and somatoform disorder), and included a small sample size making it difficult to control for potential confounds.

In these five studies, there was a lack of consistent use of the same psychological measures making comparing across studies difficult. In addition, some of these psychological tests that measure body complaints and pain, can be interpreted as representing physical or psychological impairments. However, these results showed that depression and PTSD are noteworthy covariates that should be accounted for when investigating neuropsychological performance in GW veterans. Nevertheless, many studies of toxicant exposure and GWI status show neuropsychological deficits even after controlling for mood (Vasterling and Bremner, 2006; Research Advisory Committee on Gulf War Veteran's Illnesses [RAC-GWVI], 2008). Correspondingly, mood can also be affected by toxicant exposures such as those experienced in the GW indicating another reason why mood should also be assessed in neuropsychological assessments (Sullivan et al., 2018). The recently recommended CDEs for GW research also include measures of PTSD, depression and mood (**Table 1**).

MOTIVATION AND MALINGERING EFFECTS ON NEUROPSYCHOLOGICAL FUNCTIONING

Lindem et al. (2003c) investigated motivation as a contributing factor impacting neuropsychological results in GW veterans. Using a test of malingering and motivation performance validity test (TOMM), the veterans were grouped by those with high scores ($\geq$48) and those with low scores ($\leq$47). Mood related disorders were established using the structured clinical interviews (SCID and CAPS). Results indicated a significant

difference on measures of attention, executive functioning, and memory between those with high and low scores on the TOMM. Results also showed some inconsistency across performance given expected patterns with deficits in cognition. Specifically, veterans with lower TOMM scores had lower scores on a verbal memory measure (i.e., Verbal Paired Associates on WMS-R) whilst having higher scores on another test of verbal memory (i.e., CVLT), highlighting the variability that is associated with lower motivation. Additionally, more cognitively challenging items (Trails B, WCST) were more sensitive to low motivation as they required more effort than other tests of simple attention and concentration (Trails A, Digit Span Forward and Backward). Limitations included a small sample of veterans with poor effort (n = 18) and a lack of significant clinical measures. The researchers concluded that motivation was an important factor to consider when assessing cognitive performance in GW veterans.

Barrash (2007) proposed that neuropsychological examinations of GW veterans may be unreliable given possible poor effort, invalidating neuropsychological results. A sample of 399 veterans deployed in the GW were divided into three groups: participants without impairments, participants exhibiting impairment with credible results or participants with impaired and non-credible results. Participants underwent a full neuropsychological battery with results adjusted based on age, gender, and estimated premorbid intellect. In addition, veterans completed measures assessing psychological functioning and subjective cognitive complaints. Malingering was measured using the Exaggeration Index of the AVLT (Rey, 1964), Recognition Memory Test (RMT), performance across cognitive domains, error types, and MMPI-2 validity indices. Researchers found lower levels of non-credible performance among GW veterans, and those with non-credible validity results had worse impairment on nearly all neuropsychological tests. In addition, those in the non-credible group were more likely to endorse worse subjective cognitive symptoms and emotional and social impairment. Therefore, Barrash (2007) concluded that non-credible results are relatively rare in GW populations (<1%). In addition, researchers found consistently worse performance patterns in non-credible profiles indicating that a malingering measure should be used in neuropsychological assessments. Barrash (2007) noted some limitations including a small sample of the non-credible group, decreased statistical power, and a lack of measures indicating the reason for poor effort.

Both of these studies show a lower rate than expected in GW veterans for malingering or lowered motivation performances. However, it was demonstrated that low effort can lead to worse outcomes on neuropsychological testing as well as variable test performances that makes it difficult to interpret the true cognitive profile of GW veterans with low effort. Therefore, it is recommended that all neuropsychological batteries include measures of motivation and malingering that can be used as covariates in analyses or where those performing sub-optimally on these measures can be removed from data analyses. An element of the recent CDEs for neuropsychological assessment includes a motivational measure (CVLT Forced Choice, **Table 1**).

DISCUSSION

Gulf War illness is a CMI, impacting the health of a significant amount of GW veterans; however, the etiology and treatment of GWI remains somewhat elusive, prompting the demand for more research. Research investigating the neuropsychological underpinnings of GWI is especially needed given the prevalence of cognitive symptoms in GW veterans, possibly the second most reported symptom in GWI (Smith et al., 2012).

Early studies of neuropsychological functioning and GW veterans focused more on the etiology of these symptoms with conflicting results pointing either toward a mood related or neurological cause. These studies did not use an established criterion and compared groups based on their deployment status (deployed, non-deployed) and/or symptom presence (reporting symptoms, not reporting symptoms). Therefore, early review papers such as Axelrod and Milner (2000) recommended that further research should use more testable operational definitions of GWI (see **Table 2**).

Despite the efforts to establish criteria for GWI, researchers continued to find mixed results on the etiology of GWI centering on the debate of a mood related or neurotoxicant underpinning or both. Vasterling and Bremner (2006) highlighted that the impact of mood and the discrepancy between subjective reports and objective measurements made it more difficult to determine the etiology of any deficits observed. Further studies controlled for mood effects in analyses (i.e., PTSD or depression), however, different outcomes and case criteria used continued to make clear comparisons across studies difficult to interpret. For example, David et al. (2002) found substantial evidence of mood related nature of GWI using the Fukuda et al. (1998) CDC criteria in United Kingdom veterans,. Wallin et al. (2009) expanded on these findings using the CDC criteria in United States veterans and only found differences in GWI on depression, somatic complaints, and anxiety and were underpowered to detect neuropsychological impairments. Further research using the Haley GW syndromes eluded to more physiological causes (Hom et al., 1997). Nevertheless, focusing on these criteria or the presence of GW-related symptoms did not necessarily clarify the etiology of GWI. However, no study to date has compared the IOM and Kansas case criteria when comparing neuropsychological outcomes. Because the Kansas criteria has been shown to be a more specific case criteria than other measures used in prior studies (CDC, ME/CFS, 'slow' cases), this may provide more clarity with regard to neuropsychological impairment profiles in veterans with GWI.

In addition, there is now consistent evidence across nine papers comparing neurotoxicant exposures and neuropsychological outcomes (see **Table 4**). Seven out of the nine studies found significant neuropsychological differences when comparing exposures through either sarin/cyclosarin, organophosphate pesticides or PB anti-nerve gas pills. These studies point toward a pattern of neurotoxicant exposure and neurocognitive decline given their relative similarity to other occupationally exposed groups of agricultural workers or pesticide applicators (Ismail et al., 2012; Mackenzie Ross et al., 2013). Therefore, neurotoxicant exposures may have an impact

on particular neuropsychological domains including attention, executive system, memory and motor functioning as a result of chemicals that impact acetylcholine inhibition and induce neuroinflammation (Sullivan et al., 2003, 2018; Proctor et al., 2006; Toomey et al., 2009).

Additional research focused on other pertinent topics in GWI including subjective memory and effort. Briefly, one of the three studies found a correlation between subjective memory and objective memory functioning. Future research would benefit from consistency of subjective and objective cognitive queries.

As PTSD can be a relevant comorbidity in GW veterans, this review also included research investigating PTSD and GW veterans in relation to neuropsychological performance. In two out of three smaller studies, veterans with PTSD who had served in the GW showed worse performance in verbal memory (i.e., working memory, intrusions, recognition, and interference), visual memory, general intellectual ability, sustained attention, motor speed, and visuospatial skills (Vasterling et al., 1998, Lindem et al., 2003a). However, these findings were not replicated in a larger study of treatment seeking veterans (Sullivan et al., 2003).

The GW was a short combat mission of just 4 days of actual ground war, resulting in a PTSD prevalence rate of less than 10% of GW veterans in population-based studies (Research Advisory Committee on Gulf War Veteran's Illnesses [RAC-GWVI], 2008). Although studies of convenience samples with self-referred participants generally have higher PTSD rates. Prevalence rates of comorbidity between those with GWI and PTSD need to be fully investigated. Given the significant overlap of comorbidity in convenience sample studies, treatment studies should consider comorbid therapies where both disorders can be treated at the same time.

Correspondingly, GWI and stress or PTSD symptoms as a comorbid condition is supported by neuroinflammation and HPA axis research. O'Callaghan et al. (2015) and Koo et al. (2018) found that stress, as induced via corticosterone exposure, extended the impact of neuroinflammation from diisopropyl fluorophosphate (i.e., DFP sarin surrogate), in a rat model of GWI. This suggests that the effect of the neurotoxicant is worsened by the stressor rather than the cause. Furthermore, O'Callaghan et al. (2015) identified cytokine biomarkers (i.e., TNF-alpha, interleukin 6) which were more highly elevated after corticosterone exposure. Additionally, they found that treatment with anti-inflammatory antibiotic minocycline reduced the inflammatory response. Koo et al. (2018) found that DFP exposure was associated with wide spread microstructural integrity changes on diffusion imaging in the thalamus, amygdala, piriform cortex, and ventral tegmentum area whereas the rats also treated with corticosterone had more restricted patterns within the hypothalamus and hippocampus. Ashbrook et al. (2018) supported this finding identifying epigenetic biomarkers or transcriptional histone modification and DNA methylation in genes possibility linked to neuroinflammation and cognition in a rat model of GWI with DFP and corticosterone.

In research with human participants, Golier et al. (2012) found that GW veterans with PTSD were more likely to have higher plasma adrenocorticotropic hormone after exposure to corticotropin-releasing factor. Additionally, this change was associated with higher exposure to PB. Golier et al. (2012) concluded that this reflects HPA dysfunction in GW veterans. Furthermore, Golier et al. (2016) found that treatment via mifepristone was associated with improvements in verbal learning in GW veterans with CMI which was mediated by cortisol change levels suggesting some overlap with cognitive functioning and HPA axis health.

Suggestions for future research include using measures consistent across studies. Additionally, future research should continue to utilize more objective measures of neurological dysfunction (i.e., imaging, genetic studies, immunological factors) in conjunction with recommended neuropsychological and psychological test measures. These studies show the importance of controlling for PTSD and other mood effects when comparing neuropsychological outcomes in veterans with GWI. Although research is varied on GWI and its sub components (i.e., PTSD, effort, and subjective reporting), there remains strong evidence of neuropsychological decrements. The etiology of these results remains unclear but has been further linked to neurological dysfunction.

Mood factors remain relevant given their potential to exacerbate neurological dysfunction by possibly proliferating neuroinflammation (O'Callaghan et al., 2015; Koo et al., 2018). Despite these efforts, the heterogenous nature of methodologies investigating neuropsychological deficits limits the ability to truly identify the etiology of the neuropsychological decline without instituting common data elements of core tests used in all future neuropsychological studies. However, research has been improved to support evidence of GWI leading to deficits measurable through neuropsychological batteries, particularly in areas including attention, memory, motor functioning, and executive functioning. Notable improvements include the use of established criteria and measuring toxicant exposure especially through objective biomarkers (Abou-Donia et al., 2017). However, future research would benefit from continuing to use established criteria when investigating neuropsychological performance in GWI. Linking objective biomarkers with neuropsychological outcomes could provide potential markers for treatment development. For instance, research on cytokine profiles of GWI have shown immunological homeostatic shifts, which lends credence to a neurological etiology in GWI and treatment avenues to pursue (Golier et al., 2012; Craddock et al., 2015; Abou-Donia et al., 2017). Finally, there has been a lack of research investigating GWI and PTSD comorbidity.

CONCLUSION

In conclusion, neuropsychological research in GWI has improved in methodology but continues to leave questions regarding the etiology and cognitive difficulties in veterans. Future research should utilize improved methods with the use of standardized methodology and assessment batteries, increase measurement sensitivity and increase consistency while expanding into additional realms of study

(i.e., immunological and neuroimaging biomarkers) that could further explain the underlying pathobiology of GWI. Through this research, clinicians can utilize sensitive neuropsychological instruments which in turn will more effectively inform treatment efficacy for the multitude of veterans impacted by GWI and its co-morbidities.

Therefore, the neuropsychological CDEs (Gulf War Illness Research Program [GWIRP], 2019) is an excellent resource for identifying highly recommended measures for future research to allow direct comparison of study results. It is also imperative that these measures are adapted for use in imaging studies to understand the functional and structural underpinnings of cognitive impairments and changes over time in this aging group of veterans who are at higher risk for chronic medical conditions (Zundel et al., 2019).

Our recent meta-analysis of neuropsychological studies found impairments in visuospatial, attention, executive function, and learning and memory domains which were found in three or more prior studies (Janulewicz et al., 2017). This literature review supports these findings while considering the impact of neurotoxicant and mood factors. Future research assessing treatments or investigating biomarkers of GWI should include neuropsychological outcomes in the domains of visuospatial, attention and executive function, and learning and memory. Specifically, tests to include are Block Design, Trail Making Test, Digit Span, and CVLT, as these are known sensitive measures in GW veterans. For the clinician, GW veterans are an aging population at higher risk for chronic medical conditions and therefore their subjective cognitive complaints should be documented and evaluation with the sensitive neuropsychological measures recommended in this review.

AUTHOR CONTRIBUTIONS

MJ, JK, NK, MK, KS, and TC contributed to the conception and design of the review. MJ, CZ, and TC compiled review materials. MJ wrote the first draft of the manuscript. JK, NK, MK, CZ, KS, and TC wrote sections of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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