

Award Number: W81XWH-11-1-0796

TITLE: Neural Markers and Rehabilitation of Executive Functioning in Veterans with TBI and PTSD

PRINCIPAL INVESTIGATOR: Aysenil Belger, Ph.D.

CONTRACTING ORGANIZATION: University of North Carolina-Chapel Hill
Chapel Hill, NC 27599

REPORT DATE: October 2016

TYPE OF REPORT: Annual Report

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.					
1. REPORT DATE October 2016		2. REPORT TYPE Annual		3. DATES COVERED 30Sept2015 - 29Sept2016	
4. TITLE AND SUBTITLE: Neural Markers and Rehabilitation of Executive Functioning in Veterans with TBI and PTSD				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-11-1-0796	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Aysenil Belger E-Mail: abelger@med.unc.edu				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) University of North Carolina at Chapel Hill Department of Psychiatry, CB #7160 Chapel Hill, North Carolina 27599				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT The current proposal aims to explore the relationship between brain function and connectivity in selective pathways/circuits, neuropsychological functioning, and cognitive rehabilitation response in Veterans with both Traumatic Brain Injury (TBI) and Posttraumatic Stress Disorder (PTSD). Toward this end, we propose a randomized clinical trial involving a cognitive rehabilitation intervention that targets improved executive functioning, with the participation of N=100 Veterans diagnosed with both TBI and PTSD (n=50 experimental/n=50 control). We have just begun recruitment three months ago and enrolled n=64 dyads of veterans and family members at this point.					
15. SUBJECT TERMS Cognitive Rehabilitation, Traumatic Brain Injury, Executive Function, Posttraumatic Stress Disorder					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U			USAMRMC
			UU	19	19b. TELEPHONE NUMBER (include area code)

Table of Contents

	<u>Page</u>
Introduction.....	4
Body.....	4
Key Research Accomplishments.....	10
Reportable Outcomes.....	15
Conclusion.....	17
References.....	18
Appendices.....	18

INTRODUCTION:

Section I – Introduction

The current study aims to explore the relationship between brain function and connectivity in selective pathways/circuits, neuropsychological functioning, and cognitive rehabilitation response in Veterans with both Traumatic Brain Injury (TBI) and Posttraumatic Stress Disorder (PTSD). Toward this end, we are implementing a randomized clinical trial involving a cognitive rehabilitation intervention that targets improved executive functioning, with the participation of N=100 Veterans diagnosed with both TBI and PTSD (n=50 experimental/n=50 control).

We hypothesize that executive function will significantly improve among members of the experimental group, i.e., Veterans with TBI/PTSD receiving cognitive remediation therapy. We further hypothesize that this enhanced cognitive functioning will be associated with reduced irritability/impulsivity and improved social/occupational functioning.

Functional magnetic resonance imaging (fMRI) will be used to evaluate changes in cortical function in frontostriate and frontoparietal circuits associated with executive function and cognitive control that occur as a function of cognitive remediation. We will also use electroencephalography (EEG) to evaluate changes in cortical function correlated with executive function and cognitive control that occur as a function of cognitive remediation.

Section II – Progress to Date

This annual report covers months 1-50 of the Statement of Work (SOW) for this research project. We have achieved our goals for this period, which were to commence recruitment and screening of potential study participants. Specific SOW tasks and accomplishments for each are described below.

BODY:

Task 1. Prepare for Clinical Trial (months 1-9):

1a. Submit to UNC IRB (months 1-2). We will submit a complete institutional review board (IRB) application to UNC immediately upon learning about the funding decision, so that we can rapidly get approval and submit to U.S. Army Medical Research and Materiel Command (USAMRMC) for their approval.

- UNC IRB approval was obtained at month 2.

1b. Submit to USAMRMC (months 2-9). We will submit a UNC approved IRB application, informed consent forms, data collection instruments, recruitment scripts, and all other required documentation to USAMRMC prior to implementation of the study.

- USAMRMC approval was obtained at month 4.

1c. Develop Data Collection System (months 1-9). While awaiting approval from UNC IRB and USAMRMC, we will adapt our existing Microsoft Access data collection programs to the needs

of the current Department of Defense (DOD) application. We will capitalize on the infrastructure of both the UNC Veterans Post-Deployment Adjustment Study and the UNC Biostatistics Core to ensure both high quality data collection and easy interface for Veterans and family members to provide the data in Microsoft Access.

- The data collection system was created and completed at month 9. The database is fully functional and permits research coordinators to add information from clinical interviews and cognitive testing and Veterans to add self-report data.

1d. Train Research Assistants to Facilitate Cognitive Rehabilitation (months 6-9). The Clinical Facilitator and Drs. Elbogen and Johnson will assure that research assistants are trained to a high level of fidelity to implement the components of the cognitive rehabilitation intervention. Research assistants will complete training and achieve at least 90% on the intervention fidelity checklist, as described in the clinical protocol.

- We hired research assistants and coordinators by month 6.
- Research assistants' baseline interviews/testing, interventions, and follow-up interviews/testing were observed for fidelity by month 8.
- After three sessions observed of each, all research assistants achieved 90% of fidelity criteria using a fidelity checklist by month 12.
- Research assistants can now proceed with data collection and interventions unsupervised.

1e. Arrange Transportation between Lab and UNC Hospital (months 6-9). To reduce participant burden, Veterans and family members will be able to park free at Dr. Elbogen's laboratory conveniently located at Carolina Crossing within 1/10 of a mile of the interstate. To further reduce participant burden, we will transport Veterans five minutes away to the Dr. Belger's lab at UNC Hospital where EEG and fMRI will be conducted and then transport Veterans back to our laboratory. We will assure transportation is running efficiently and without delays before study commencement.

- Transportation to the EEG and fMRI was arranged through the UNC-Chapel Hill School of Medicine at month 9. Participants may either take a shuttle from the research laboratory to the UNC Hospital complex, or they will be given a free parking pass.

Task 2. Baseline Interview/Data Collection (months 9-52):

2a. Recruitment (months 9-52). As outlined in project narrative and letters confirming access to military populations, we will recruit Veterans with TBI and PTSD from Dr. Elbogen's National Institute of Mental Health (NIMH) study, the Durham VA Trauma Research database, the VA Mid-Atlantic Health Care Network (VISN6) Mental Illness Research Education and Clinical Centers (MIRECC) Registry, and UNC Hospitals to meet our targeted recruitment. We will call Veterans and family members from these sources using IRB-approved protocols and phone scripts.

- We have been actively recruiting from the Durham VA and UNC since month 10. We have contacted Veterans through research registries at the Durham VA, and we have hung flyers with study information at the Durham VA and UNC Hospitals.
- We have also added recruitment from Veteran and Brain Injury organizations throughout North Carolina in month 10.
- We have presented our study at the North Carolina Veteran Service Organization annual conference in month 11.
- We participated in a Military and Veterans Networking Fair in Raleigh, NC in month 12.
- We created a Facebook Page at UNC to further advertise for the study in month 14.

- We have started recruitment through local universities and community colleges. We have had notable success at Fayetteville Community College, located near Fort Bragg Army Base.

Targeted Recruitment: By end of year one, we aim to have enrolled N=10 participants. By end of year two, we aim to have enrolled N=50 participants. By end of year three, we aim to have enrolled N=85 participants. By end of year four, we aim to have enrolled N=100+ participants.

- Since August 2012, we have enrolled n=112 Veteran-family dyads.
- We were unable to schedule participants through April and part of May 2014 due to the MRI being unavailable from 4/11/14 – 5/19/14.

2b. Informed Consent (months 9-52). The nature and the purpose of the research, the study procedures, standard protections for human subjects, and risks and benefits of the study will be explained to Veterans and family members. If both the Veteran and a family member consent, they will sign informed consent documents.

- Informed consent for both Veterans and family members has occurred. Participants have understood the protocol and no issues have arisen.
- Research assistants carefully explain the informed consent information to the Veteran dyads and make it clear that participation is voluntary.

2c. Initial Screening (months 9-52). We will ensure that Veterans meet study criteria for PTSD and TBI and ensure that Veterans are safe for EEG and fMRI procedures. We will also assess whether Veterans and/or family members have difficulties with decisional capacity that may impair their ability to provide informed consent.

- We have been conducting initial screening with success and have had few problems to report.
- Research assistants carefully use TBI and PTSD screening measures to ensure that Veterans meet study criteria.

2d. EEG/fMRI (months 9-52). The details for these procedures are provided in the project narrative. Briefly, after the initial screening confirms that Veterans meet study criteria, Veterans will be transported to UNC Hospital for EEG and fMRI procedures, which should take four to five hours.

- By month 52, we have had 101 participants successfully complete baseline MRIs and 110 successfully complete baseline EEGs.
- By month 52, we have had 67 participants successfully complete six month MRIs and 77 successfully complete six month EEGs.

2e. Interview (months 9-52). After the EEG and fMRI, Veterans will be transported back to Dr. Elbogen's lab. Depending on the time and how Veterans and family members feel, the interview portion of the data collection, which lasts 60 to 90 minutes, may be conducted the same day, or it may be rescheduled within a week if Veterans and/or family members are feeling tired at that point in time. Please note that data is entered directly by participants and research staff into Microsoft Access; thus, there is no need for data entry or double scoring on this study.

- To prevent the Veterans from becoming overtired, we have found that it works best to schedule the interview and testing in the research lab in the same week but on a different day than the MRI and EEG.

- In total, we have completed n=112 baseline interviews of veteran and family dyads by month 52.

Task 3. Implementation of Clinical Trial (months 9-52):

3a. Randomization Procedure (months 9-52). Following successful completion of the informed consent process and the baseline interview, the research coordinator will randomly assign Veterans to study conditions using a computerized procedure available to tracking systems using Microsoft Access.

- Participants are randomly assigned to study conditions by the clinical coordinator, using the Microsoft Excel RAND feature. Research assistants remain blind to participant assignment until after the baseline interview and cognitive testing have been completed. Research assistants are informed of the participant group assignment for only those veterans with whom they will be conducting individual support sessions.

3b. Initiating Intervention (months 9-52). Depending on the time and how Veterans and family members feel, initiation of the intervention may be conducted the same day as data collection, which lasts 30 to 45 minutes, or may be rescheduled within a week if Veterans and/or family members are feeling tired at that point in time. All participants will receive an iPod Touch with instructions for applications to complete as part of the study, and they will be taught how to log application use on the iPod.

- To date, 112 Veteran-family dyads have successfully completed baseline individual support sessions. 56 were randomized to the experimental arm and 55 were randomized to the control arm.
- No technical difficulties concerning the iPod Touch have been reported.

3c. Experimental Group - (months 9-52). Veterans in the experimental group will be complete cognitive rehabilitation interventions that have shown empirical support in the research literature to improve executive functioning. Training for Goal Management Training lasts 45 to 60 minutes and involves both the Veteran and family member. Components of this intervention will be administered via the iPod touch, including the n-Back procedure.

- 56 baseline in-home support sessions have been conducted with participants assigned to the experimental group.
- Research assistants were observed during the first three in-home support sessions for fidelity to intervention protocols and achieved 90% fidelity.
- Ongoing random fidelity checks are being conducted at least once quarterly.

3d. Control Group (months 9-52). Veterans in the control group will also receive an iPod touch where they will be asked to practice applications that involve motor skills as well as basic memory skills.

- 55 baseline in-home visits have been conducted with participants in the control group.
- As with the experimental group, research assistants were observed during the first three in-home support sessions for fidelity to control protocols and achieved 90% fidelity.
- Ongoing random fidelity checks are being conducted at least once quarterly.

3e. Individualized Support Sessions (months 9-52). At two months and four months, a trained facilitator will visit Veterans in their homes or place of convenience in order to collect data from iPod logs, make behavioral observations, and review intervention protocols.

- By month 52, a total of 93 two-month in-home support sessions were completed. There were no problems with implementation.
- By month 52, a total of 73 four-month in-home support sessions were completed. There were no problems with implementation.

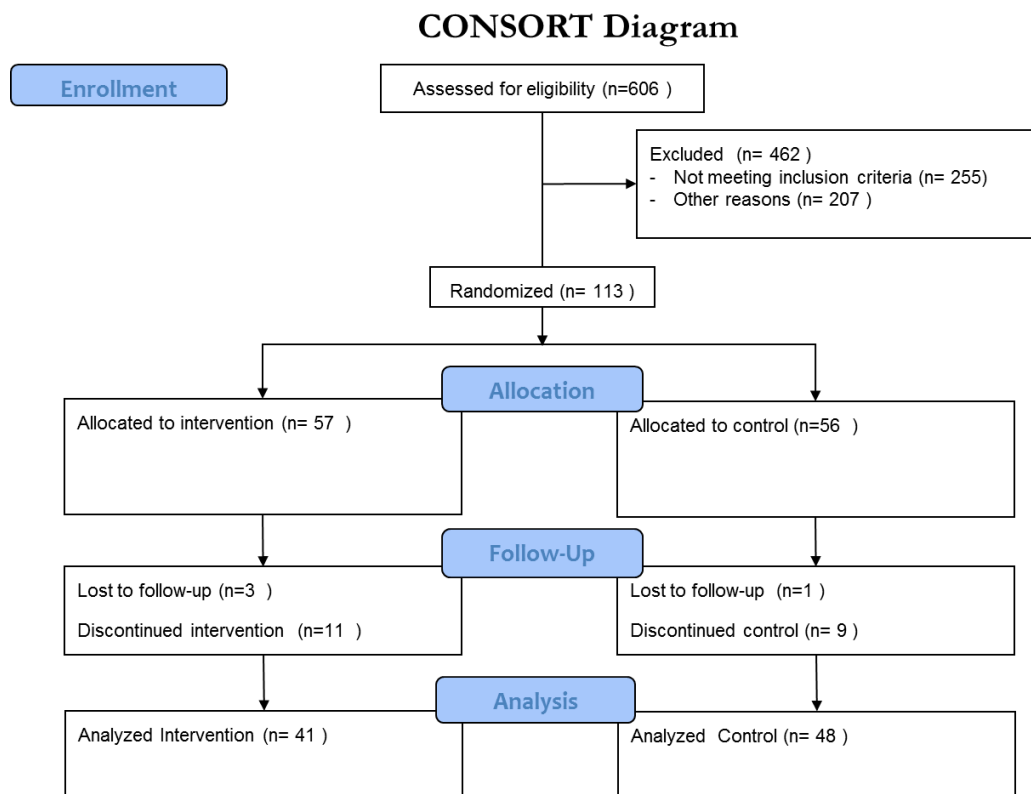
Task 4. Follow-up Interview/Data Collection (months 9-52):

4a. EEG/fMRI (timeframe, e.g., months 9-52). The details for these procedures are provided in the project narrative. Veterans will park conveniently at Carolina Crossing B and be transported to UNC Hospital for EEG and fMRI procedures, which should take about four to five hours.

- 77 Follow-up EEG sessions have been completed and 67 follow-up MRIs have been completed.

4b. Interview (timeframe, e.g., months 9-52). After the EEG and fMRI, Veterans will be transported back to Dr. Elbogen's lab at Carolina Crossing. Depending on the time and how Veterans and family members feel, the interview portion of the data collection, which lasts 60 to 90 minutes, may be conducted the same day or may be conducted within a week if Veterans and/or family members are feeling tired at that point in time.

- 88 Follow-up interviews have been completed.
- Data collection is now complete for the study.
- Below is the final CONSORT diagram for the study:



Task 5. Data Analysis and Deliverables (months 9-52)

5a. Quality Assurance (months 9-52). Throughout the data collection procedures, the research coordinator will randomly select 20% of participants and conduct an audit of Microsoft Access data and informed consent documents every six months of the project.

- MRIs have been examined for quality assurance methodologies described in Lee Friedman and Gary H. Glover (2006) Report on a Multicenter fMRI Quality Assurance Protocol, Journal of MRI, 23:827–839. All five MRI protocols showed very little participant physical movement during scanning and demonstrated MRI data was clear and could be analyzed according to the current application's protocol.
- 93% of consent forms were selected to determine if research assistants were completing these as per protocol.
- 93% of participants' interviews were selected to determine if data was entered accurately into Microsoft Access. We had 98% accuracy in data entry. The three instances of inaccuracy (e.g., '2' was entered instead of a '3') were corrected. Several times data had to be clarified for accuracy, and it was in fact determined correct.

5b. Data Analysis (months 40-48). Statistical analytics procedures, as outlined in the application, will be conducted once baseline and follow-up data are collected.

- See research accomplishments below

5c. Conference Presentations (months 12-48). Throughout the course of the grant, we will present progress on the grant at national scholarly meetings.

- See research accomplishments below.

5d. Manuscript Preparation (months 42-48). Once data is analyzed, we will prepare scientific manuscripts and submit to peer-reviewed journals.

- See research accomplishments below.

5e. Research Brief (months 44-48). We will summarize the projects in a brief to be sent to each military branch, as well as to VA Centers, including Centers of Excellence, MIRECC, VA Health Services and Development Centers and VA Quality Enhancement Research Initiative Centers.

- Not applicable at this time.

Section V - Administrative Comments (Optional) - Description of proposed site visits and participation in technical meetings, journal manuscripts in preparation, coordination with other organizations conducting related work, etc.

Specific Aim 1 – Clinical, Behavioral, Neuropsychological Variables. To evaluate neurocognitive and behavioral changes associated with cognitive rehabilitation. We hypothesize that executive function will significantly improve among members of the experimental group, i.e., veterans with TBI/PTSD receiving cognitive remediation therapy. We further hypothesize

that this enhanced cognitive functioning will be associated with reduced irritability/impulsivity and improved social/occupational functioning.

- **Hypothesis 1:** Experimental subjects will show greater improvement on tasks measuring executive function and inhibition than control subjects at six month follow-up.
- **Hypothesis 2:** Experimental subjects will show greater reduction in scores on measures of impulsivity than control subjects at six month follow-up.
- **Hypothesis 3:** Experimental subjects will have greater reduction in relationship conflict than control subjects at six month follow-up.

- Deliverable #1: For this aim, we have already published a paper examining TBI in a national database, hypothesizing per Specific Aim 1 that frontal lobe damage that corresponds to executive dysfunction would be associated with criminal behavior after the TBI. We found post-TBI criminal arrest was associated with gender, age, marital status, educational attainment, pre-TBI felony, pre-TBI drug abuse, pre-TBI alcohol abuse, and violent cause of TBI. Frontal lobe lesions from computed tomographic scans did not predict post-TBI criminal arrests. Higher numbers of post-TBI arrests were predicted by loss of consciousness (≥ 24 hours), combined with retention of motor function.
- Timeline. This paper was published in the Journal of Head Trauma Rehabilitation last year, it is attached to this report below.
 - Military Benefit/Impact: For military service members who experience TBI in the course of military service, these findings indicate that factors that occurred before the TBI are critical to consider when determining whether the service member or veteran is at risk of criminal behavior in the future. Specifically, premorbid variables, especially pre-TBI felonies, were strongly linked to post-TBI criminal arrests. The relationship between TBI and arrest was complex, and different brain functions (e.g., physical mobility) should be considered when understanding this association. Findings highlight that for post-TBI criminal behavior, many risk factors mirror those of the non-TBI general population.
- Deliverable #2: We have also submitted for publication an analysis of TBI and clinical/behavioral correlates associated with Specific Aim 1. In a national dataset of post-9/11 military veterans, we found 17.3% met criteria for TBI during military service, 48.8% of whom reported multiple head injuries. The most common mechanisms of injury included blast (33.1%), object hitting head (31.7%), and fall (13.5%). In multivariable analyses, probable TBI during military service was associated with enlisted rank, male gender, high combat exposure, and sustaining TBI prior to military service. Veterans sustaining multiple head injuries had significantly higher rates of PTSD, depression, back pain, and suicidal ideation.
- Timeline. This paper has been accepted for publication in The Journal of Neuropsychiatry and Clinical Neurosciences and will be in print this month.

- *Military Benefit/Impact:* TBI was characterized by a number of mechanisms, of which blast is most common but does not represent the majority. Treatment for veterans would be improved by clinical interventions to address both mechanism of injury and repeated TBI. Clinical and research as well as suicide prevention efforts in Iraq and Afghanistan Veterans should account for the majority TBIs being non-blast related and nearly half reporting multiple head injuries. As pre-military TBI was a significant risk factor for military sustained TBI, and as found in Deliverable #1 above, screening for pre-military TBI and related risk factors is warranted.
- Deliverable #3: We have already analyzed and presented at a national conference baseline neurocognitive and behavioral data from the current DOD-funded study. As indicated in Specific Aim 1, we found executive functioning tasks were significantly related to impulsive and aggressive behaviors in N=116 Iraq/Afghanistan Veterans with TBI and PTSD. Performance on the Dellis Kaplan Executive Function System (DKEFS) Color-Word task was significantly associated with impulsive behaviors ($p=0.0018$) on the Barratt Impulsivity Scale (BIS) and violence/aggression ($p=0.0099$) on the Conflict Tactics Scale (CTS). Veterans who committed commission errors—anticipating targets when they were not present— on a continuous performance task had higher scores of aggressive behaviors on the CTS ($p=0.01$).
- Timeline. We currently have a draft of this paper, will copyedit a final manuscript and submit for publication January 2017.
 - *Military Benefit/Impact:* Disinhibition associated with TBI and functioning in the frontal-striate system contributes to increased risk of aggression. Anticipating targets erroneously could be associated with hypervigilance in PTSD, suggesting the frontal-limbic system, particularly regarding perceived (or misperceived) threats, plays a role in aggression in TBI+PTSD. Both sets of findings confirm broad diagnoses are less important than particular cognitive deficits associated with them with respect to accuracy in cognitive performance tasks as well as disinhibited behavior in those with TBI+PTSD which have direct implications for military combat performance as well as social adjustment in service-members with TBI and PTSD.
- Deliverable #4: For the follow-up of neurocognitive and behavioral data from the current DOD-funded study and testing of the Study Aim 1 hypotheses, we completed six month follow-up data collection from a total of N=88 pairs of veterans-family dyads in February 2016. Specifically, we are examining whether the cognitive rehabilitation intervention (called Cognitive Apps for Life Management or “CALM”) led to reduced executive dysfunction, impulsivity, anger, and aggression in veterans with PTSD and TBI. We created data sets in March 2016, and rendered a clean dataset of clinical, neuropsychological, and behavioral measures in April 2016. Preliminary analyses on hypotheses started May 2016 and are currently being run in SAS 9.4.

- ***Timeline.*** We have already drafted the paper and we plan to submit the paper in February, with expected revisions to make in Spring 2017.
 - ***Military Benefit/Impact:*** CALM is a clearly defined, feasible, portable rehabilitative intervention with OIF/OEF veterans suffering from the effects of TBI and PTSD. The intervention requires already available technology with commercially available, low cost applications and can be customized to the specific needs of the individual veteran. Family members or significant others will be integrated in the rehabilitation process, with the goal of helping them to become key support persons in the veteran's recovery efforts. The intervention itself is without side effects, does not draw unnecessary attention to one's disabilities, and does not require frequent clinical contact outside of the home environment. Positive findings from the RCT will demonstrate CALM as a mobile technology based method by which service members and veterans with TBI and PTSD can effectively improve functioning in multiple domains of living and reduce emotional dysregulation and disinhibition associated with the co-occurring disorders.

Specific Aim 2. fMRI Outcomes. We will use fMRI imaging to evaluate changes in cortical function in frontostriate and frontoparietal circuits associated with executive function and cognitive control that occur as a function of cognitive remediation.

- **Hypothesis 1:** We hypothesize that as a group, veterans participating in the cognitive rehabilitation program will show significantly larger changes in neural activity associated with executive functions when comparing pre- and post-treatment fMRI responses.
- **Hypothesis 2:** We further hypothesize that a subgroup of veterans may have alterations in the neural substrates and circuitry, particularly in frontostriate and frontoparietal brain systems that may prevent successful implementation of cognitive rehabilitation, while others may benefit from these interventions because their pathways are intact and can be reactivated with cognitive rehabilitation. We will therefore conduct exploratory analyses to examine differences in neural activity and connectivity between treatment responders and nonresponders.
- **Deliverable #5:** We have completed acquisition of fMRI data from 100 veterans on 2 activation tasks: 1) Cognitive Inhibition Task and 2) Emotional 1-back Working memory task. Pearson's correlation analyses revealed significant correlations between activation in the posterior cingulate cortex ($r=-.23, p=.03$), left hippocampus ($r=-.23, p=.03$), right hippocampus ($r=-.25, p=.01$), right amygdala ($r=-.28, p=.009$) and performance on *color-word inhibition*; activation in the left hippocampus ($r=-.21, p=.04$) and *avoidance* (CAPS); activation in the inferior frontal gyrus ($r=.21, p=.04$) and *numbing* (CAPS), and activation in the medial prefrontal cortex ($r=.22, p=.03$), insula ($r=.22, p=.03$), and fusiform gyrus ($r=.21, p=.04$) and *verbal working memory performance*. In brief the results-to-date revealed that activity in cortico-limbic regions, and regions associated with striatal, default mode, and salience networks were significantly associated with increased symptom severity and greater impairments in neurocognition. Activation during the *DKEFS color word interference* performance negatively correlated with the

posterior cingulate gyrus ($r = -.30$, $p = .004$) and the right thalamus ($r = -.21$, $p = .035$). *Numbing* (CAPS sub-score) negatively correlated significantly with the left pallidum ($r = -.29$, $p = .005$).

- *Timeline.* Results have been presented at the annual meeting of the Society for Neuroscience in October 2016. The baseline fMRI manuscript # 1 has been completed, and being submitted to “Biological Psychiatry: Cognitive Neuroscience and Neuroimaging”, in January 2017. We examined the association between PTSD symptom severity, impulsivity, working memory deficits and regional functional brain activation in a large sample of veterans with co-morbid PTSD/TBI. Brain activation patterns during an affective 1-back working memory task was assessed with fMRI in 100 veterans with comorbid PTSD-TBI. Before scans, clinical measures of PTSD symptom severity were assessed using the CAPS, as well as measures of impulsivity using the Barratt Impulsivity scale. Digit span performance was also assessed prior to scans. Regression analyses were performed to examine the association between clinical PTSD symptom severity, impulsivity and fronto-limbic activation. An additional 20 control subjects were also evaluated with functional MRI to explore neural activation characteristics of the PTSD sample and confirm replication of previously reported group differences. FMRI group comparisons revealed significantly greater activation during the emotional face working memory condition in PTSD/TBI individuals relative to controls in multiple frontal and limbic regions (cluster thresholded $z > 2.3$). Multiple regression analyses revealed that CAPS avoidance severity scores significantly positively correlated with limbic activation, including right amygdala ($p < .01$), hippocampus (right $p < .03$, left $p < .003$), and insula ($p < .04$). Limbic hyperactivation to emotional faces compared to object stimuli during working memory was also significantly correlated with increased impulsivity and self-control (amygdala right $p < .01$; insula $p < .02$; hippocampus $p < .03$). Finally, working memory capacity was significantly higher in subjects who showed higher activation across frontal-limbic and sensory cortical processing regions (amygdala left $p < .02$, right $p < .007$; hippocampus left $p < .009$, right $p < .005$; insula $p < .001$; CG $p < .003$; MFG $p < .03$; IFG $p < .01$; FG $p < .007$; TaFG $p < .01$; TpFG $p < .007$, TOG $p < .01$). These findings indicate that greater PTSD clinical symptom severity in comorbid PTSD/TBI is associated with hyperactivation in multiple limbic regions, including the hippocampus, amygdala, and insula, during emotional information processing. Exploratory analyses further suggest that this hypersensitivity to emotional stimuli extends beyond limbic regions, and can be observed in early sensory regions, including inferior temporal and fusiform areas, consistent with hyperarousal and aberrant salience attribution to affective stimuli. Our study also reveals that relatively greater orienting to emotional stimuli and activation in limbic brain regions, including amygdala, insula and inferior frontal regions, are significantly predictive of greater impulsivity in PTSD/TBI subjects. Finally, our findings also indicate that PTSD/TBI patients with better working memory capacity, as measured by the backwards digit span task, show significantly greater fMRI activation across a distributed network of fronto-limbic and sensory cortical regions. Overall, these results suggest that hyperarousal and aberrant allocation of

salience to emotional stimuli and associated fronto-limbic activation in PTSD/TBI veterans significantly contributes to the severity of PTSD avoidance symptoms and higher levels of impulsivity. Interventions targeting front-limbic regions may reduce aberrant orienting and responding to emotional stimuli, while decreasing impulsivity and improving self-control, thereby leading to improve emotion regulation in comorbid PTSD/TBI.

- *Military Benefit/Impact:* Our findings revealed for the first time that specific symptom dimensions of PTSD can be associated with specific brain circuits, thereby indicating specific neural targets for intervention. Our findings also suggest that both severity of TBI (measured by number TBI and severity of PTSD symptoms) are associated with impairments across a wide network of frontal and limbic brain regions. The compounded effect of TBI severity on PTSD symptom severity and neurocognitive and behavioral disinhibition further suggest that objectively measuring, documenting and remediating TBI on the field, as well as identifying immediate neural correlates of TBI will significantly reduce the severity of ensuing PTSD symptoms, and the severity of emotional and behavioral dysregulations associated with TBI/PTSD.
- *Deliverable #6:* For the follow-up of fMRI data from the current DOD-funded study and testing of the Study Aim 2 hypotheses, we finished six month follow-up data collection in February 2016 and had complete fMRI data from N=68 veterans. Specifically, we are examining whether the cognitive rehabilitation intervention led to improved fronto-striate and fronto-parietal activations, in association with reduced executive dysfunction, impulsivity, anger, and aggression in veterans with PTSD and TBI.
- *Timeline:* We have completed analysis of the fMRI data for this follow-up time point, to examine changes in fronto-striate and fronto-limbic activation in experimental and control treatment groups. In the next 3 months we expect to have completed the analysis of the functional MRI data (both whole brain and region of interest analyses) (by end of September), allowing us to begin composing the manuscript. All image processing outcomes (region of interest activations in frontostriate and fronto-parietal brain systems) will be added to the dataset of clinical, neuropsychological, and behavioral measures in October 2016. We are currently running statistical analyses in SAS 9.4, and draft the introduction and methods sections of this treatment fMRI analysis paper by November 2016, and will write the Results end of January 2017. The Discussion will be completed February 2017 and we plan to submit the paper in March 2017, with expected revisions to make in late Spring 2017.
 - *Military Benefit/Impact:* Changes in brain function as measured by fMRI, specifically in the fronto-striate and fronto-limbic systems, from the RCT will demonstrate CALM as a mobile technology based method by which service members and veterans with TBI and PTSD can effectively improve functioning in multiple domains of living and reduce emotional dysregulation and disinhibition associated with the co-occurring disorders.

Specific Aim 3 - EEG Outcomes. We will use EEG to evaluate changes in cortical function correlated with executive function and cognitive control that occur as a function of cognitive remediation (n2/p3a/p3b).

Hypothesis that as a group, veterans participating in the cognitive rehabilitation program will show significantly larger changes in neural activity associated with executive functions (N2, P3 components) when comparing pre- and post-treatment event-related potential (ERP) responses.

- Deliverable #7. We have completed all EEG data collection and processing related to the N2 and P3 events on 112 baseline visits. So far, the results suggest that in the Emotional Oddball task CAPS (numbing, D, and total, in particular), BIS (total, cont) and ANGER all generally predict the level of neural responses related to cognitive control (N2) to standard images in the emotional oddball task. Further, this prediction is shifted (change in intercept) when the stimulus follows a distractor images, regardless of the emotional valence of that image. However, when the image presented is a target, or goal driven, this relationship is only shifted following negative distractors. Results further revealed that number of TBIs significant impacted the severity of electrophysiological event-related potentials.
- Timeline. The manuscript for the baseline EEG data has been submitted to Biological Psychiatry on 11/22/2016. We are currently revising the manuscript for a resubmission.
 - Military Benefit/Impact: These findings have benefit because they suggest that the brain is hyperresponsive to stimuli of no goal relevance, which also dilutes the impact of goal-related information. This could have implication as to how information is presented to veterans with PTSD and TBI and how to treat them. Our findings suggest that both severity of TBI (measured by number TBI and severity of PTSD symptoms are associated with impairments across a wide network of frontal and limbic brain regions.
- Deliverable #8. We have completed the time 2 follow-up EEG data acquisition in February 2016, and all follow-up EEG data has been processed. We are currently conducting the peak-picking to identify amplitudes of the N2/P3 ERP components for each stimulus type. The values obtained from these analyses will be submitted to our statistical models and analyzed using SAS.
- Timeline. In the next 3 months we expect to have completed the analysis of the follow-up EEG data (by end of September), allowing us to begin composing the manuscript. All ERP peak amplitude and latency measures from the follow-up EEG scans will be added to the dataset of clinical, neuropsychological, and behavioral measures in October 2016. We will run statistical analyses in SAS 9.4, and draft the introduction and methods sections of this treatment fMRI analysis paper by November 2016, and will write the

Results January 2017. The Discussion will be completed February 2017 and we plan to submit the paper in March 2017, with expected revisions to make in late Spring 2017. We expect that these results will be critical for assessing the changes in neural communication due to treatment intervention.

- *Military Benefit/Impact:* Changes in EEG, as well as identifying immediate neural correlates of TBI will show the potential and promise to significantly reduce the severity of ensuing PTSD symptoms, and the severity of emotional and behavioral dysregulations associated with TBI/PTSD using a mobile technology based cognitive rehabilitation intervention.

REPORTABLE OUTCOMES: Provide a list of reportable outcomes that have resulted from this research to include:

We have met enrollment targets and successfully completed a randomized clinical trial of cognitive rehabilitation for Iraq/Afghanistan veterans with TBI and PTSD. As stated above, we have just begun to analyze this data, so the following results are presented as preliminary and are subject to change as we continue analysis, submit to peer-reviewed journals, and respond to reviewer feedback. Here are the highlights of reportable outcomes for this study:

At baseline, we enrolled N=113 pairs of veterans and family members and collected clinical, behavioral, neuropsychological, fMRI and EEG data. This exceeded our target of 100 pairs, meaning that we have adequate power to test hypotheses. Moreover, to our knowledge, this represents the largest sample of fMRI and EEG neuroimaging data ever collected for individuals with co-occurring TBI and PTSD.

At six month follow-up, we collected data from N=89 pairs of veterans and family members. This represents a 76% retention rate which to our knowledge is equivalent to or better than other studies testing clinical interventions in veterans with TBI and PTSD and attests to the potential for mobile-based cognitive rehabilitation to be seen as feasible and viable to implement among those with TBI and PTSD.

We are in the process of conducting preliminary analyses on the effectiveness of the randomized clinical trial of the Cognitive Apps for Life Management (CALM) intervention on the main clinical outcomes. We have thus far found the following:

- **The CALM intervention had a significant effect on lowering anger and aggressive impulses in veterans with PTSD and TBI.** Specifically, we used the Dimensions of Anger Reactions (DAR) scale which has been validated in combat veterans with PTSD to measure anger disposition directed toward others. Forbes, D, Hawthorne, G, Elliott, P, McHugh T, Biddle, D, Creamer, M, Novaco, RW (2004) A concise measure of anger in posttraumatic stress disorder. *Journal of Traumatic Stress*, 17, 249-256. In our study, preliminary analysis demonstrates that veterans with TBI and PTSD in the CALM intervention condition scored significantly lower on the DAR at six month follow-up than participants in the control condition ($F(1, 86) = 7.47, p = 0.0076$). We further analyzed

the data to control for gender, age, and number of TBI events and still continued to uncover that the CALM intervention led to substantially lower anger and aggressive impulses among veterans with TBI and PTSD ($F(1, 86) = 7.21, p = 0.0088$).

- Military Benefit/Impact: TBI and PTSD in Veterans has also been linked to problems with anger, aggression, and violence, which are often complaints of Veterans seeking mental health services post-deployment and have been shown to predict poor treatment outcomes in Iraq and Afghanistan Veterans. A recent national study (Sippel et al, 2016) showed that the majority of veterans (61.2%) reported experiencing difficulties controlling anger and a sizable minority of veterans (23.9%) reported experiencing aggressive urges over a two-year period. To our knowledge, data from the current DOD-funded study are the first to yield empirical support for an intervention to effectively decrease anger and aggressive impulses in veterans with TBI and PTSD. This mobile-technology based approach is also feasible, portable, low-cost, and showed high adherence.
- **At this stage, we have not yet found that the CALM intervention had significant effect on executive function and impulsivity.** Close examination of the data reveal why this was probably the case. Specifically, we found that the majority of the sample did not have executive dysfunction despite meeting criteria for TBI; for instance, only 12% of the veterans with TBI and PTSD demonstrated impaired functioning on the main cognitive measure we used, the Dellis Kaplan Executive Function System (DKEFS) Color-Word task. As such, there were likely ceiling effects regarding the ability to improve scores among a sample of participants of whom 88% already showed normal functioning in this area of cognition. Similarly, veterans in the sample generally showed low levels of impulsivity, 75% were below the cut-off of 74 on the Barratt Impulsivity Scale; thus, our ability to reduce already low impulsivity may correspondingly be due to floor effects (i.e., only a quarter of our sample showed high impulsivity).
 - Military Benefit/Impact: These null results, if we continue to find this in subsequent analyses, have important implications for DOD and enrolling participants with TBI in future cognitive rehabilitation studies. When we designed the study in 2010, it was less well known that the majority of TBIs in veterans were mild TBIs. As a result, these findings suggest that TBI may be an insufficient inclusion criteria for studies of cognitive rehabilitation; rather, future DOD research on TBI should use cognitive or behavioral criteria (as opposed to diagnostic criteria alone) for inclusion when determining effects of interventions and rehabilitation in veterans and military personnel with TBI.

CONCLUSION: Summarize the results to include the importance and/or implications of the completed research and when necessary, recommend changes on future work to better address the problem. A "so what section" which evaluates the knowledge as a scientific or medical product shall also be included in the conclusion of the report.

It is estimated that up to half of all military service members with combat-related traumatic brain injury (TBI) also meet criteria for Posttraumatic Stress Disorder (PTSD). TBI and PTSD are both characterized by deficits in multiple cognitive domains, including attention, executive function, and affective and cognitive control. However, cognitive and affective sequelae associated with TBI are compounded by the presence of PTSD symptoms in returning Veterans. Specifically, it has been shown that significant frontal lobe dysfunction, particularly disinhibition, occurs more often among Veterans with both TBI and PTSD than among Veterans diagnosed with only one of these conditions. The combination of TBI and PTSD in Veterans has also been linked to problems with anger and violence, which are common complaints of Veterans seeking mental health services post-deployment and have been shown to predict poor treatment outcomes in Iraq and Afghanistan Veterans. Executive dysfunction, especially difficulty with attentional processing, is strongly related to hostility and aggressiveness in Iraq and Afghanistan Veterans; increasingly so in the presence of TBI and PTSD.

Understanding the neurobiology and neuropsychology associated with an evidence-based cognitive rehabilitation intervention will allow us to identify Veterans with both TBI and PTSD who are predisposed to positive treatment outcomes. To our knowledge, this will be the first attempt to integrate neurobiological and neurocognitive techniques with information about the efficacy of a theoretically and empirically driven cognitive rehabilitation intervention in Veterans with combined TBI/PTSD diagnoses. Additionally, this research may suggest additional avenues for assessment of clinical intervention efficacy and the identification of therapeutic targets (e.g. alteration of function in fronto-limbic circuits) relevant to the military population. Future studies could investigate whether adjunctive treatment with antianxiety agents, such as oxytocin, may have additional implications for effective cognitive rehabilitation of Veterans with both TBI and PTSD, by either increasing efficacy in the responders or facilitating processing along fronto-limbic pathways critical for attention and executive function.

Our goal is to identify subgroups of individuals who are more or less likely to benefit from specific intervention strategies and thus be better able to develop individualized treatment protocols with a higher likelihood of success for the individual Veteran. Better understanding of the cognitive rehabilitation process in these TBI patients who are also suffering from PTSD will help define resources and costs of medical care necessary to adequately address many of the issues raised in this population. Given the links between TBI/PTSD, executive dysfunction, and anger, impulsivity, and aggression, efforts to rehabilitate cognitive function will be particularly important to ensure that current and future Veterans adjust successfully when they return home to their families, workplaces, and communities.

REFERENCES:

- Not applicable at this time.

APPENDICES:

- Published Article attached.

SUPPORTING DATA: All figures and/or tables shall include legends and be clearly marked with figure/table numbers.

- See research accomplishments and reportable outcomes above