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INTRODUCTION

Aims and goals of the current project are to examine whether differences in neuropsychological outcome are related to mechanism of brain injury (blast versus blunt force) as well as white matter integrity using diffusion tensor imaging (DTI). We are also collecting and analyzing data in order to determine whether imaging variables of interest are associated with psychosocial/clinical outcome, and whether there are group differences by mechanism of injury. Specifically, in the context of this study, we use novel, sophisticated MRI methods (e.g., quantitative diffusion tensor [DT] tractography) in order to characterize white matter changes seen within and across TBI subtypes, identify those at highest risk for poor outcomes, and gain knowledge about potential interventions to aid in recovery of brain functioning and cognition. In addition, we seek to identify the unique psychosocial challenges posed by differing mechanisms of injury as well as investigate the contribution of genetic factors (Apolipoprotein-E ϵ -4 [APOE ϵ 4] and brain-derived neurotrophic factor [BDNF]) to brain integrity, neuropsychological functioning, and neurobehavioral outcome.

BODY

Year 5: We have made considerable strides toward our stated goals as outlined in our Statement of Work. Our laboratory continues to grow, and we have expanded our collaborations and added key personnel, including a new UCSD/SDSU Joint-Doctoral Clinical Program graduate student (Madeleine Werhane). This year, we presented 5 studies at the International Neuropsychological Society meeting (Denver, CO) and 1 study at the Associated Sleep Societies (Seattle, WA); the full abstracts for these 6 studies from 2015 are provided in the *Reportable Outcomes* section. We now have 7 manuscripts stemming from these data published, while we have 2 manuscripts currently under review, 2 in press, and 6 manuscripts in preparation (citations for these studies are provided in the “Manuscripts Published or In Press”, “Manuscripts Under Review”, and “Manuscripts In Preparation” sections under the *Reportable Outcomes* section).

During this fifth year of our DoD study, we have recruited and tested roughly 33 participants who represent either combat controls or patients who have sustained mild to moderate TBI. There are an additional 205 participants that were screened, but not included given that they did not meet inclusion criteria (i.e., were excluded from participating). We have conducted approximately 547 phone screens of potential subjects throughout the course of the study. To date, we have enrolled a total of 122 subjects. Our recruitment rate is typically about 1-2 subjects per month. Our attrition rate is close to 0; our study subjects are informed in advance about the duration of the study, so they almost always complete both the cognitive assessment and neuroimaging sessions. After scanning, data is immediately pre-processed and prepared for analysis by skilled staff with expertise in imaging processing and analysis techniques. Fidelity checks of the data collected are thus evaluated as it is collected given that processing occurs within a day or two of data collection. Ongoing recruitment of patients and collection of relevant neuropsychological and behavioral outcome data occurs in tandem with neuroimaging (collected within one week of scanning, after obtaining appropriate consents). In addition, due to continued slowed recruitment over the past year (e.g., we have experienced considerable challenges recruiting appropriate normal control participants that meet our inclusion criteria), we requested and were approved for a second one-year no-cost extension (approved 09/29/2015). In order to fulfill our Statement of Work aims and to increase sample sizes (particularly with respect to rounding out our normal control sample to

assist in group comparisons of the neuroimaging and other data) we have taken the following steps regarding recruitment: (1) we have amended our “control” recruitment flyer, as our old control flyers featured verbiage that may have been unclear with respect to our interest in control/non-TBI veterans; our old flyers were also displayed/concentrated in VA hospital locations where otherwise “healthy” veterans might not frequent; (2) we have also better utilized word-of-mouth referral with our current TBI and control participants by asking them to share our study information with veteran friends who may qualify, emphasizing that a history of TBI is not necessary for participation, (3) we continue to give talks to various VA clinics, and we are now obtaining referrals through other research study mechanisms at the VASDHS (e.g., OEF/OIF/OND health intake study) and VA research studies that focus on female veterans with PTSD and TBI. Upkeep of regulatory approvals has also been necessary during this timeframe. Per our SOW, data analyses have continued through this past year.

Below is a summary of findings from the past year:

5 studies at the 2015 International Neuropsychological Society Meeting (Denver, CO), full abstracts provided in *REPORTABLE OUTCOMES*:

1. We examined the relationship between fatigue, sleep disturbance, depression, and quality of life in Veterans with mild-to-moderate traumatic brain injury (TBI). Results showed that physical fatigue and vegetative symptoms are the most significant symptoms associated with worse QoL related to physical health, psychological well-being, social relationships, and everyday activities within the environment (Kim et al., 2015).
2. When exploring the associations between white matter lesion (WML) pathology and cognition in Veterans with and without history of mTBI, total WML volumes did not differ between mTBI and control groups. However, poor memory was associated with increased periventricular (PVL) volume in the mTBI group only; deep white matter lesion (DMWL) volumes were not associated with cognition in either groups (Clark et al., 2015; manuscript in press).
3. We examined the associations between frontothalamic structural connectivity (FTSC) and executive functions (EF) in Veterans with or without mTBI, and results showed that, compared to the control group, the mTBI group performed worse on an EF composite score and had higher total scores across all subscales of the Frontal Systems Behavior Scale (FrSBe), a self-report questionnaire designed to measure behavioral problems caused by damage to frontal systems. Although groups did not differ on measures of FTSC, FTSC was associated with mTBI severity. Within the mTBI group, right FTSC correlated with the EF composite, while left FTSC was correlated with higher levels of reported disinhibition and executive dysfunctions; such associations were not found in the control group (Sorg et al., 2015; manuscript in preparation).
4. When examining the relationship between alcohol use in veterans and its relationship to mTBI, psychiatric symptoms, and neuropsychological performance, we found that that mTBI group reported more alcohol-related psychosocial problems (e.g., fights, poor judgment, physical injuries, emotional problems) relative to the control group. Within mTBI, more lifetime alcohol-related psychosocial problems were associated with combat exposure, longer post-traumatic amnesia from blunt injury, higher depression, anxiety, and PTSD symptoms, as well as neurobehavioral symptoms. Additionally,

greater lifetime withdrawal symptoms were associated with poorer attention and visual learning, while recent alcohol-related psychosocial problems were associated with poorer executive functioning (Hanson et al., 2015, manuscript under review).

5. When examining whether engagement in physical, mental, and social activity was related to better neurocognition in veterans with history of mild traumatic brain injury (mTBI), we found that in our sample, an active lifestyle is associated with better global neurocognition. The results reveal that greater activity engagement in everyday life is associated with enhanced objective cognitive performance, even after adjusting for depressive and PTSD symptomatology (Moore et al., 2015; manuscript in preparation).

1 study at the 2015 Associated Sleep Societies (Seattle, WA), full abstract provided in REPORTABLE OUTCOMES:

1. When examining the relationships between persistent sleep disturbances, increased sleepiness, and brain activation during a Go-NoGo inhibition task administered during functional magnetic resonance imaging, we found that mTBI Veterans reported overall greater sleep impairment when compared to control Veterans. For both groups, sleep impairment scores were negatively correlated with response in bilateral, middle, transverse, and/or inferior temporal regions. In mTBI Veterans, sleep impairment scores also correlated with middle frontal and left inferior parietal regions, as well as with the left caudate and right lateral and medial orbital-frontal regions (Orff et al., 2015; manuscript in preparation).

Please find our most recent publication citations in *REPORTABLE OUTCOMES* and *REFERENCES*, and see each publication's description below for summaries:

1. *Delano-Wood et al., 2015:*

Although possible brainstem dysfunction has been at the forefront of the TBI literature for several decades, few human studies exist, imaging studies have been very limited, and, to our knowledge, no study has examined associations between white matter integrity of the brainstem, injury severity, and postconcussive (PCS) symptoms in the context of military TBI. In this study, tractography was employed by seeding regions of interest (ROIs) along 3 brainstem white matter tracts: medial lemniscus-central tegmentum tract (ML-CTT), corticospinal tracts (CST), and pontine tegmentum (PT). Mean diffusion tensor imaging (DTI) values were derived from fractional anisotropic (FA) maps. Results showed that there were no significant differences in FA between the control and TBI groups across the 3 regions of interest; however, among the TBI group, CST FA was significantly negatively associated with loss of consciousness (LOC) duration. Additionally, lower FA of certain tracts – most especially the PT – was significantly associated with increased PCS symptoms (i.e., more severe vestibular symptoms, poorer physical functioning, and greater levels of fatigue), even after adjusting for PTSD symptoms. Our findings show that, in our sample of veterans with mTBI, tractography-based DTI indices of brainstem white matter tracts of interest are related to the presence and severity of PCS symptoms. Findings are promising as they show linkages between brainstem white matter integrity and injury severity (LOC), and they raise the possibility that the pontine tegmentum in particular may be a useful marker of PCS symptoms. Collectively, these data point to important neurobiological substrates of the chronic and complex constellation of symptoms following the ‘signature injury’ of our combat-exposed veterans.

2. Clark et al., 2015:

Failure on performance validity tests (PVTs) is common in Veterans with history of mTBI, leading to questionable validity of clinical presentations. Clarifying whether underlying brain abnormalities are present among those failing PVTs is an important clinical issue, especially given the fact that TBI is regarded as the ‘signature injury’ of the wars in Iraq and Afghanistan. Utilizing diffusion tensor imaging (DTI), we investigated cerebral white matter (WM) microstructure of mTBI Veterans and military control Veterans; our mTBI group was subdivided into 2 groups on the basis of performances above (TBI-passed) or below (TBI-failed) recommended cut-points on PVTs. We found that the TBI-failed group demonstrated significantly lower cognitive scores relative to the control and TBI-passed groups; no such differences were observed between the control and TBI-passed groups. On a global measure of WM integrity, the TBI-failed group showed more overall WM abnormalities than the other groups’ no differences were observed between the control and TBI-passed groups on WM integrity. Interestingly, regional WM analyses revealed abnormalities in the anterior internal capsule and cingulum of both TBI subgroups relative to controls; moreover, compared with the TBI-passed group, the TBI-failed group demonstrated significantly decreased WM integrity in the corpus callosum. Findings revealed that, within our sample, WM abnormalities are evident in those who fail PVTs. This study adds to the burgeoning PVT literature by suggesting that poor PVT performance does not negate the possibility of underlying WM abnormalities in military personnel with history of mTBI.

3. Sorg et al., 2015:

Traumatic Brain Injury (TBI) and posttraumatic stress disorder (PTSD) are highly comorbid in Veterans of the recent conflicts in Iraq and Afghanistan. In samples without history of TBI, PTSD symptoms have been associated with structural alterations within cortical and subcortical regions within the frontal and temporal lobes including prefrontal cortices, the anterior cingulate, the temporal cortex, the hippocampus, and the amygdala; damage within the white matter (WM) tracts interconnecting frontal and limbic brain regions may contribute to or exacerbate PTSD symptoms following a traumatic event. Although available studies linking white matter microstructure and PTSD symptoms have been limited, PTSD have been associated with microstructural damage within the cingulum bundle, a WM tract connecting limbic regions such as the cingulate cortex and hippocampus. This study sought to investigate WM microstructure compromise in Veterans with history of TBI and its possible contribution to PTSD symptomatology and neuropsychological functioning through the use of diffusion tensor imaging. Our results revealed that compared with controls, TBI Veterans reported higher levels of PTSD symptoms and performed worse on measures of memory and psychomotor-processing speed. TBI was associated with lower fractional anisotropy (FA) in the genu of the corpus callosum and left cingulum bundle. FA negatively correlated with processing speed and/or executive functions in 7 of the 8 tracts. Regional FA did not correlate with memory or PTSD symptom ratings, suggesting that current PTSD symptoms are independent of TBI-related white matter alterations as measured by diffusion tensor imaging. In addition, WM microstructural compromise may contribute to reduced processing speed in our sample of participants with history of neurotrauma. These findings add insight into the factors associated with complicated recovery from mild to moderate TBI.

All study-related tasks are completed by the following personnel: Dr. Delano-Wood, Dr. Dawn Schiehser, Russell Kim, and Nicole Evangelista. Russell Kim and Nicole Evangelista have actively recruited and enrolled participants. Russell Kim, and Nicole Evangelista assist Dr. Delano-Wood and Dr. Schiehser in imaging data collection, processing, and analysis. Neuropsychological testing takes

place within the Neuropsychology Unit at the VA San Diego as part of clinical care for each patient. Appropriate releases are obtained for access to those data. For any individual who was not tested clinically, we conduct a 4 hour neuropsychological battery of cognitive tests. Assessment has been coordinated by Dr. Delano-Wood, Dr. Schiehser, Russell Kim, and Nicole Evangelista. IRB continuing review has been spearheaded by Dr. Delano-Wood and Russell Kim. Finally, Nicole Evangelista and Russell Kim have coordinated the genetic testing (buccal swabbing) for the project.

KEY RESEARCH ACCOMPLISHMENTS

As requested, please find below progress on our specific aims, as well as general demographic characteristics of our samples.

Demographics and sample characteristics

Most individuals enrolled in our study have had more than one head injury during their lifetimes and were exposed to multiple blasts while on deployment. The vast majority of injuries were mild in nature (which is consistent with the extant literature). It was revealed during TBI interviewing that one individual had a severe TBI and this individual was not included in examination of the proposed aims below. When moderates are included in our analyses (they are not always), we make every effort to determine whether injury severity is a significant contributor to our findings and conduct sensitivity analyses. If we find injury severity is not a significant contributor to our analyses, we include them in our findings.

Total Sample Recruited Under DoD award:

Total recruited N=122, 3 subjects failed to complete the study in its entirety

TBI n = 76

Military Controls n = 43

TBI Sample Breakdown (Mean, SD)

of TBIs = 2.59 (1.39)

of Blast Exposures = 4.39 (15.02)

Mild TBI = 67

Moderate = 8

Severe = 1

Approximately two-thirds (n = 6) of those with moderate or severe TBI's sustained these injuries during deployment (i.e., in combat).

Most Significant TBI Type:

Blast = 19

Blunt = 44

Blast with Secondary/Tertiary Blunt = 13

Predeployment Injuries (Y = 43%), Deployment Injuries (Y = 70%), Post-deployment (Y = 20%).

Much of our work has focused on examining diffusion tensor imaging (DTI) data for several primary

regions of interest (ROI) as specified in the DoD award (i.e., anterior/posterior internal capsule; genu, body, splenium of corpus callosum; cingulum bundle). More recently, we have been working to expand upon our imaging analyses to include additional ROIs that include long-coursing fibers (e.g., superior longitudinal fasciculus) that may be vulnerable to shear/tensile forces and other tracts critical for cognition (e.g., uncinate fasciculus may be important for executive functioning and/or memory).

As stated in our aims, we examined hippocampal and temporal lobe volumes. Initial efforts have proved that volumetric analyses are not as sensitive to the effects of TBI (at least in this subset of individuals who are on average 65 months removed from their most recent injury). We are making every effort to further examine this null finding by exploring whether age might interact with TBI history to affect volumes. Initial results seem promising and additional recruitment will help clarify currently observed trends.

The purpose of this grant was to examine the potential effect of milder forms of TBI; however, during assessment of head injuries, there were several individuals ($n = 9$) that had head trauma histories that were classified as moderate ($n = 8$) or severe ($n = 1$). Per request, we include here some additional information about this small subset of individuals. Those with moderate TBI were included in Clark et al. (2016) and Delano-Wood et al. (2015) because sensitivity analyses revealed that they were not driving any white matter differences observed between the control group and individuals with history of mild TBI. We believe this likely shows that, at least within our sample, the moderate TBI group does not appear to have worse white matter alterations relative to the individuals with mild head injuries. However, this group does appear to significantly differ from controls with no head injury histories. Our volumetric findings were very similar to our white matter findings. However, the moderate group did display significantly lower temporal pole volume ($p = .004$) relative to those with mild injuries. While the small sample size of these analyses must be considered, results raise interesting questions about biomechanical models of TBI and susceptibility for certain regions to damage that may differ in those with mild vs. moderate TBI.

With respect to cognition, the moderate TBI group does significantly differ on tests of executive functioning. In particular, those with moderate TBI perform more poorly on DKEFS Inhibition scaled Score ($p = .03$), and Inhibition Switching Scaled Score ($p = .048$). However, these findings do not hold when PTSD is taken into account. It is important to note that we are vastly underpowered to include covariates in these preliminary analyses, and thus the moderate group may in fact be performing more poorly than the mild TBI group. We will therefore make every effort to further examine these preliminary results when additional individuals with moderate TBI are recruited and studied.

Specific Aim 1: To determine whether hippocampal atrophy and microstructural white matter changes can be detected in mild to moderate TBI and to assess differences by mechanism of injury (blast vs. blunt force).

Given the fact that pure-blast related TBI injury was a rare occurrence in the sample, our data analyses collapsed across subtypes of TBI for planned analyses. Moreover, disentangling the effects of blast versus blunt TBI was also made difficult by the fact that many individuals were exposed to multiple blasts during deployment and/or suffered both types of head injuries during their lifetimes.

Hypothesis 1a: Collapsed across group, TBI participants will demonstrate poorer fractional anisotropy (FA) in TBI predilection sites (i.e., anterior and posterior limbs of the internal capsule, genu and splenium of the corpus callosum, fornix) as well as lower hippocampal volumes than normal control (NC) participants.

- Sorg et al. (2014) found that TBI participants with reduced executive functions demonstrated significantly decreased fractional anisotropy (FA) of prefrontal white matter, corpus callosum, and cingulum bundle structures compared with both TBI participants without reduced executive functions and military control participants.
- Sorg et al. (2015) demonstrated that history of TBI significantly predicted lower FA values in both the genu of the corpus callosum and in the left cingulum bundle; FA also negatively correlated with processing speed. While FA was negatively associated with processing speed, it was not associated with memory or PTSD symptom ratings.
- Although we did not propose to examine effort (or even exclude individuals based on effort), we noted as the study progressed that a high number of individuals with bona fide TBI frequently fail effort, or performance validity, tests. We therefore set out to study this directly within our sample and recently published a report investigating the relationship between poor effort and white matter integrity in our sample. Interestingly, contrary to expectations, we found (Clark et al., 2015) that in mTBI veterans who failed performance validity tests (TBI-failed) demonstrated more overall WM abnormalities than the other groups (i.e., those who passed effort testing [TBI-passed]; controls with no history of TBI). Regional white matter analyses revealed abnormalities in the anterior internal capsule and cingulum of both TBI subgroups relative to controls. Moreover, compared with the TBI-passed group, the TBI-failed group demonstrated significantly decreased WM integrity in the corpus callosum.
- We have also recently submitted a manuscript (Clark et al., 2016) showing that TBI participants with poor clinical outcome (cognitive fatigue complaints) show reduced white matter integrity in a striato-thalamocortical circuit (anterior internal capsule) known to mediate fatigue. These findings build upon those from existing functional neuroimaging studies in those with history of TBI, providing further evidence for the neural basis of cognitive fatigue in head injured adults.
- We are currently writing up a manuscript (Delano-Wood et al., 2016; abstract presented at the International Neuropsychological Society, Honolulu, HI, 2013) that found that mTBI veterans differed significantly from military controls on fornix FA and fornix mean diffusivity (MD), but not on fornix volume; fornix DT indices positively correlated with performance on attention/working memory, executive functioning, and fine motor dexterity.

Hypothesis 1b: Given suggestions in the literature that DTI may be more sensitive to TBI-related diffuse axonal injury, we expect that, across mechanism of injury, white matter integrity for all regions of interest will be more strongly associated with and predictive of TBI status than hippocampal volumes.

We first explored whether those with blunt vs. blast TBI differed on the following variables: right and left hippocampal volume. Next we explored Freesurfer derived volumetric indices from the following cortical areas of the temporal lobe: superior, middle, and inferior temporal; banks of the superior

temporal sulcus; fusiform; transverse temporal; entorhinal; temporal pole; parahippocampal.

--There were no significant differences between TBI subtypes (blast vs. blunt/blast) on any volumetric neuroimaging variables.

--When we compared those with history of TBI to MCs we see significant differences between the groups in the following areas: left fusiform, left inferior temporal, left transverse temporal, and right inferior temporal cortex. In particular, the TBI group has lower volumes relative to MCs. However, when we take PTSD into account in our analyses, only left the left transverse temporal cortex remains significant.

--Regression analyses revealed that hippocampal volumes were not significant predictors of TBI status.

--*However, as detailed above, WM differences were observed across multiple ROIs in those with history of TBI vs. MCs (see results for hypothesis 1a; Sorg et al., 2015). Regression analyses revealed WM microstructural integrity of the corpus callosum and cingulum bundle were significant predictors of TBI status.*

Hypothesis 1c: Since individuals with blast injury frequently experience concomitant damage related to acceleration-deceleration and CNS compromise secondary to other internal injuries (e.g., lungs), it is expected that, when directly compared to the blunt TBI subgroup, the blast TBI subgroup will show lower FA values for each white matter tract of interest.

- As stated above, pure blast related injuries were unfortunately rare in our sample and thus power is quite limited. However, when we compare the small sample of individuals with pure blast TBI (n = 19) to those with pure blunt force trauma we see no significant differences in FA across any ROIs. In general, our sample was exposed to blast multiple times throughout deployment. While the vast majority of these injuries did not result in a TBI, subconcussive blast injuries may also be playing a part in WM alterations and we are exploring ways to further examine this.

Specific Aim 2: To investigate whether differences in cognitive outcome are related to mechanism of injury as well as to hippocampal volumes and white matter DTI variables.

Hypothesis 2a: We expect blast injury to be related to greater diffuse brain effects than blunt force injury. Thus, in comparison to the blunt force TBI subgroup, the blast TBI subgroup will show more pronounced cognitive deficits, particularly in executive functioning, attention/working memory, and processing speed.

Although our pure blast group was smaller relative to the blunt force group, we explored whether those with blast only vs. blunt only differed on cognitive tests. The following tests were examined individually and there were no significant differences across the groups on any measure: Delis-Kaplan Executive Function System (D-KEFS) Color-Word Interference, Fluency, and Trails subtests; California Verbal Learning Test-2nd Edition; Wechsler Intelligence Scale for Adults 4th edition (WAIS-IV) Coding, Symbol Search, and Digit Span subtests; the Rey-Osterrieth Complex Figure Task; Reading subtest of the Wide Range Achievement Test- 4th edition (all *p*-values > .05). Furthermore, we excluded individuals that performed poorly on tests of effort in exploration of this particular hypothesis.

Next, we created the following cognitive composites from the measures to enhance power: (1) executive functions, (2) processing speed, (3) attention/working memory, and (4) memory. Contrary to expectations, across all composites, no differences were observed between the TBI groups.

Hypothesis 2b: Collapsed across group, hippocampal volumes will be positively associated with and predictive of memory performance in TBI. Additionally, in line with our preliminary DTI studies, we expect that anterior FA measures will be positively related with executive functioning and processing speed, whereas posterior FA measures will be positively associated with language and memory functions.

Hippocampal volume findings:

We examined whether hippocampal volume and temporal lobe variables were associated with cognition in the TBI group.

Significant findings are listed below:

- Rey-O Percentile was significantly associated with right ($r = -.353$, $p = .029$) and left ($r = -.369$, $p = .023$) hippocampal volumes.
- Wechsler Memory Scale-IV recognition raw was significantly associated with right hippocampal volume ($r = .332$, $p = .039$). Better performance was associated with greater volume.
- Next, we created a memory composite variable and explored hippocampal volume associations. However, the memory composites did not appear to be as sensitive as examining individual tests of memory, as there were no significant correlations.
- Interestingly, several temporal lobe ROIs were significantly associated with performance on the CVLT, and WMS-IV variables. The CVLT findings remained significant even after controlling for PTSD within the TBI group.
- **Our plan is to continue data processing and explore whether history of TBI interacts with hippocampal volume to predict memory test performance. We expect and, in fact, do see similar hippocampal volume and memory associations in military controls. However, when we test the interaction between TBI history and hippocampal volumes on cognition and control for PTSD we only find trending associations. Our plan is to follow up by increasing n (and continue processing) while also exploring the direct influence of PTSD. Additional alternative analytic avenues we plan to pursue include determining whether those with history of TBI who meet clinical criteria for PTSD differ from those who not meet criteria for this psychiatric disorder.*

White Matter Findings:

- Sorg et al. (2014) [referenced above] found that TBI participants with reduced executive functions demonstrated significantly decreased FA of prefrontal white matter, corpus callosum, and cingulum bundle structures compared with both TBI participants without reduced executive functions and military control participants.
- Sorg et al. (2015) [referenced above] demonstrated that TBI history significantly predicted lower white matter integrity in both the genu of the corpus callosum and left cingulum bundle; FA also negatively correlated with processing speed but not memory performance. Moreover, FA of these tracts was not associated with PTSD symptom ratings.

- Clark et al. (in press) found that mTBI history was not associated with increased white matter hyperintensity (WMH) pathology; however, after controlling for PTSD and intracranial volume, deep white matter hyperintensity (DWMH) pathology was associated with reduced short- and long-delayed memory performance within the mTBI group.
- Clark et al. (abstract presented at the International Neuropsychological Society, Denver, CO 2015) found that although mTBI and military control groups did not differ in total white matter lesion (WML) volumes, in the mTBI group only, poor memory was associated with increased lesion volumes.
- Sorg et al. (abstract presented at the International Neuropsychological Society, Denver, CO 2015) found that when investigating measures of frontothalamic structural connectivity (FTSC), mTBI veterans demonstrated higher levels of self-reported and objective executive functioning. Although groups did not differ in measures of FTSC, FTSC was associated with mTBI severity; within the mTBI group, right FTSC correlated with an executive function composite, while left FTSC correlated with higher levels of self-reported disinhibition and executive dysfunction.
- Delano-Wood et al. (abstract presented at the International Neuropsychological Society, Honolulu, HI, 2013) found that mTBI veterans differed significantly from military controls on fornix FA and fornix mean diffusivity (MD), but not on fornix volume; fornix DT indices positively correlated with performance on attention/working memory, executive functioning, and fine motor dexterity. mTBI subgroup analysis of blast, blunt, and military control subgroups significantly differed on fornix MD, fornix AD, and trend with fornix radial diffusivity (RD).
- Sorg et al. (abstract presented at the International Neuropsychological Society, Honolulu, HI, 2013) found that after adjusting for age and education, in the mTBI group, psychomotor processing speed was significantly positively associated with FA in the left cingulum, genu and body of the corpus callosum, and left posterior internal capsule.

Specific Aim 3: To determine whether MR variables of interest are associated with psychosocial/clinical outcome and whether there are group differences by mechanism of injury.

Hypothesis 3a: Given greater sensitivity to microstructural damage, FA of white matter in anterior regions will be more strongly associated with psychosocial clinical outcome than hippocampal volumes across TBI subgroups. Thus, in comparison to NC participants, lower FA of anterior regions will be associated with greater levels of psychological distress (i.e., depression, anxiety, and post-traumatic stress related symptomatology) and poorer functional outcomes.

- Sorg et al. (2015) [referenced above] demonstrated that TBI significantly predicted FA values in both the genu of the corpus callosum and in the left cingulum bundle; FA also negatively correlated with processing speed. While FA was negatively associated with processing speed, it was not associated with memory or PTSD symptom ratings.
- Delano-Wood et al. (2015) found that although there were no differences in FA between the TBI and military control groups across the three white matter tracts of interest (medial lemniscus-central tegmentum tract [ML-CTT], corticospinal tracts [CST], and pontine tegmentum [PT]), among the TBI group, CST FA was significantly negatively associated

with LOC duration. In addition, lower FA of certain tracts – most especially the PT – was significantly associated with increased PCS symptoms (i.e., vestibular symptoms) and poorer physical functioning, even after adjusting for PTSD symptoms; trends were also observed between lower PT FA, bodily pain, and greater fatigue. Lower FA of CST and ML-CTT was significantly associated with poorer emotional well-being after adjusting for PTSD symptoms.

- Clark et al. 2016 (submitted to *Brain Imaging and Behavior*; brief report) showed that white matter disruptions of the left anterior internal capsule is associated with greater levels of cognitive fatigue in Veterans with history of mild-to-moderate TBI.

In addition, to exploring direct relationships between MR variables and psychosocial/clinical outcome, we also sought to characterize how those with history of TBI may differ from MCs.

-Schiehser et al. (2015; manuscript) examined the relationship between postconcussive symptoms and quality of life (QOL) in Veterans with mild TBI. Results showed that perceived QOL was significantly worse in Veterans with mild-moderate TBI than in controls. In the TBI group, QOL was predominantly associated with affective symptoms, and moderate to strong correlations with fatigue and depression were evident across all QOL areas. Multivariate analyses revealed depression and fatigue to be the best predictors of Psychological, Social, and Environmental QOL, whereas sleep difficulty best predicted Physical QOL in mild-moderate TBI. Veterans with post-acute mild-moderate TBI evidence worse QOL than demographically matched Veteran controls. Affective symptoms, and specifically those of fatigue, depression, and sleep difficulty, appear to be the most relevant postconcussive symptoms predicting QOL in this population.

-Kim et al. (2014; abstract) found that after controlling for age, effort, depression anxiety, and PTSD, TBI Veterans reported significantly greater usage of a maladaptive avoidance-oriented coping style compared to military controls. In the TBI group, avoidance coping was significantly associated with executive dysfunction, but was not associated with depression, anxiety, or PTSD symptoms. These findings suggest that targeted cognitive interventions that focus on executive dysfunction may improve coping and long-term outcomes in this population.

-Kim et al. (2015; abstract) found that when investigating the relationship between fatigue, sleep disturbance, and depression on quality of life (QoL) in veterans with history of mild-to-moderate TBI (mmTBI), elevations in fatigue and sleep problems best produced worse QoL related to physical health, fatigue alone best predicted psychological and social QoL, and depression best predicted QoL related to one's environment. Of these significant predictors, Physical fatigue, Sleep quality, and Sleep Latency best predicted QoL related to physical health, Physical fatigue best predicted Psychological and Social QoL, and Vegetative symptoms of depression best predicted QoL related to one's environment. These findings underscore the importance of neurovegetative/somatic symptoms in QoL and could provide potential treatment targets to improve specific areas of QoL in Veterans with mmTBI.

-Kim et al. (2016; abstract) found that when examining the relationship between subjective complaints of neurobehavioral symptoms and executive dysfunction/disinhibition, mood, and objective performance on an Go/No-Go inhibition task in mTBI veterans, self-reported executive dysfunction/disinhibition and depression were negatively associated with task performance. Further analyses demonstrated that higher levels of self-reported depression was the only significant predictor of task performance over and beyond the effects of subjective cognitive complaints or PTSD symptomatology. These results indicate depression as a potential treatment target for neurobehavioral symptoms related to disinhibition in mTBI veterans.

-Hanson et al., 2015 (under review) characterized alcohol use among mTBI veterans and examined its relationship to mTBI and psychiatric symptoms. The mTBI group reported more alcohol-related psychosocial problems (e.g., fights, poor judgment, physical injuries, emotional problems) relative to MCs ($p < .03$). Within mTBI, more lifetime alcohol-related psychosocial problems were associated with combat exposure, longer post-traumatic amnesia from blunt injury, and higher depression, anxiety, and PTSD symptoms, as well as neurobehavioral symptoms ($ps < .05$). Additionally, greater lifetime withdrawal symptoms were associated with poorer attention and visual learning ($ps < .03$), while recent alcohol-related psychosocial problems were associated with poorer executive functioning ($ps < .03$). Our findings suggest that lifetime alcohol-related psychosocial or withdrawal symptoms may affect post-concussive symptomatology and cognitive functioning in some veterans with a history of mTBI.

Hypothesis 3b: Since blast injury may be associated with greater psychological trauma secondary to exposure to improvised explosive devices—as well as the higher prevalence of other orthopedic injuries—it is posited that, after controlling for injury severity, individuals with blast TBI will show greater levels of psychological distress (i.e., depression, anxiety, and post traumatic related symptomatology) and poorer functional outcomes (i.e., greater deficits in work status and quality of life) than blunt force TBI.

Please see results above given our restricted sample size of blast only TBI and previously mentioned issues in teasing out the effects of blast vs. blast related TBI vs. blunt trauma in this sample.

--When we examine the TBI group as a whole, we see consistently display greater levels of depression, PTSD, anxiety and substance use when compared to military controls.

--Moreover, exploring functional outcomes, as demonstrated by Schiesher et al. (2015), perceived QOL was significantly reduced in Veterans with mild-moderate TBI than in controls. In the TBI group, QOL was predominantly associated with affective symptoms, and moderate to strong correlations with fatigue and depression were evident across all QOL areas. Multivariate analyses revealed depression and fatigue to be the best predictors of Psychological, Social, and Environmental QOL, whereas sleep difficulty best predicted Physical QOL in mild-moderate TBI. Veterans with post-acute mild-moderate TBI evidence worse QOL than demographically matched Veteran controls. Affective symptoms, and specifically those of fatigue, depression, and sleep difficulty, appear to be the most relevant postconcussive symptoms predicting QOL in this

population

Exploratory Aims:

Since genetic and neurotrophic factors have been implicated as being possibly involved in both risk for and recovery from complications secondary to TBI, an exploratory aim of the current study is to investigate two of these factors (apolipoprotein- ϵ 4 [APOE- ϵ 4] and brain-derived neurotrophic factor [BDNF]) as they relate to brain integrity, cognition functioning, and clinical/behavioral outcome. It has been suggested that APOE ϵ 4 may be associated with decreased transport of lipids, increased accumulation of beta-amyloid, increased brain inflammation, impaired brain perfusion after injury, and poorer repair.⁵⁶⁻⁵⁹ Indeed, a recent meta-analysis showed that the presence of the APOE ϵ 4 allele is associated with increased risk of poor long-term outcome at 6 months after injury,⁶⁰ and it has also been shown to be related to duration of post-traumatic coma,⁶¹ poorer neurorehabilitation outcome post TBI,⁶² impaired cognitive performance in relation non- ϵ 4 positive patients with TBI,⁶³ and slower recovery rate than those without the ϵ 4 allele over a two-year period.⁶⁴ However, effects of the APOE ϵ 4 allele are controversial as some studies have not shown any associations with neurological or cognitive outcome in TBI.⁶⁵⁻⁶⁷ Much less is known about the effect of BDNF as a possible neuroprotective factor in the context of TBI. BDNF is a critical regulator of activity-dependent synaptic plasticity,^{68,69} and it has been shown to be involved in neuronal survival and growth.⁷⁰ It has also been associated with improving cognitive and neurological deficits due to ischemia.⁷¹ To our knowledge, however, no study has investigated BDNF in mild to moderate neurotrauma, and studies investigating relationships between BDNF and white matter, cognition, and clinical outcome are needed in the literature. Thus, we plan to investigate both APOE ϵ 4 and BDNF in our sample of patients with TBI in order to better understand contributions of these genetic factors to white matter integrity and neurobehavioral outcome in blast and blunt-force TBI. We expect that, consistent with histopathological findings in the literature, participants with the APOE ϵ 4 allele will demonstrate poorer white matter integrity and cognitive/clinical outcome even after controlling for age, time since injury, and severity of injury. Additionally, we expect that higher levels of BDNF will be associated with higher white matter integrity in predilection sites as well as better cognitive and clinical long-term outcomes (adjusting for age, time since injury, and injury severity). It is hoped that data obtained will be used as pilot data for future grant applications to explore associations between APOE, BDNF and longer-term outcome in our sample.

Genotyping has been complete on 67 TBI and 38 Military Control subjects. As stated earlier, some of our studies in which we've wanted to infuse genotype data have been hampered due to low numbers of APOE- ϵ 4's in our TBI group. However, below we provide detail regarding our statistics. We hope to improve our sample size, particularly within the TBI group.

Cognition

Across our entire sample, presence of the APOE- ϵ 4 allele was significantly associated with poorer performance on measures of processing speed (i.e., DKEFS Trails—Number Sequencing, WAIS IV Coding; $p < .05$).

- Trails Number Sequencing: $F(1, 101) = 5.224$, $p = .024$

- WAIS-4 Coding: $F(1, 99) = 4.527, p = .036$

Within individuals with a history of TBI only, APOE-ε4 status was significantly associated with performance on measures of both processing speed and verbal memory, such that poorer performance was observed in ε4 carriers compared to non-carriers.

- Trails Number Sequencing: $F(1, 63) = 5.400, p = .023$
- LM I: $F(1, 64) = 7.102, p = .010$
- LM II: $F(1, 64) = 5.580, p = .021$

Importantly, while these significant associations did not survive adjustments for age, time since injury, and injury severity, this can be attributed to a lack of power due to the underrepresentation of ε4 carriers relative to non-carriers in our sample (carriers = 19, non-carriers = 86). Indeed, the direction of these observed relationships between APOE genotype and cognitive performance align with the stated hypotheses outlined in our exploratory aim, providing preliminary evidence for the role of the APOE genotype in TBI cognitive outcome.

White Matter

Across our sample, no associations have been observed between APOE status and DTI indices of WM integrity (e.g., AIC, PIC, genu, body, splenium); (all p-values > .05).

Clinical outcome

Across the sample, we have observed no associations between APOE status and various measures of clinical or functional outcome (e.g., SF-36 subscales, NSI total score, PCL total score, BAI, BDI, or WHOQOL total score). However, when the relationship between APOE status and clinical outcome was explored within TBI subjects only, APOE-ε4 status was significantly associated with poorer physical functioning (SF-36 Physical Functioning, $p = .037$) and greater role limitations due to physical disability (SF-36 Role Physical subscale, $p = .028$). However, these associations do not remain significant when corrected for age, injury severity, and time since injury.

Evangelista et al. (abstract presented at the 2016 International Neuropsychological Society in Boston, MA; manuscript in preparation) found that a history of TBI significantly modified performance on tasks of executive function across BDNF allele subtypes, such that non-Met carriers with history of TBI performed significantly worse than military control non-Met carriers ($p < .001$). There were no significant differences in cognitive test performance by BDNF allele subtype across the entire sample. These findings highlight the importance of considering the role of epigenetics when investigating TBI outcome, and provide preliminary evidence that the physiological environment following neurotrauma may negatively influence BDNF expression in non-Met carriers. As stated earlier, we are currently developing a manuscript based on the findings in this presentation.

Citations or full abstracts for all key research accomplishments stated below are provided in *REPORTABLE OUTCOMES*:

Submitted Abstracts from 2015:

1. When examining the relationship between fatigue, sleep disturbance, depression, and quality of life in Veterans with mild-to-moderate traumatic brain injury (TBI), we found that physical fatigue and vegetative symptoms are the most significant symptoms associated with worse QoL related to physical health, psychological well-being, social relationships, and everyday activities within the environment. Sleep quality and latency are also associated, albeit to a lesser degree, to physical health QoL. These findings underscore the importance of neurovegetative/somatic symptoms in QoL and could provide potential treatment targets to improve specific areas of QoL in Veterans with mmTBI (Kim et al., 2015).
2. When exploring the associations between white matter lesion (WML) pathology and cognition in Veterans with and without history of mTBI, total WML volumes did not differ between mTBI and control groups. However, poor memory was associated with increased periventricular (PVL) volume in the mTBI group only; deep white matter lesion (DMWL) volumes were not associated with cognition in either groups. Findings suggest that PVLs may exert a more deleterious effect on cognition in those with a history of mild neurotrauma (Clark et al., 2015).
3. When examining the associations between frontothalamic structural connectivity (FTSC) and executive functions (EF) in Veterans with or without mTBI, we found that compared to the control group, the mTBI group performed worse on an EF composite score and had higher total scores across all subscales of the Frontal Systems Behavior Scale (FrSBe), a self-report questionnaire designed to measure behavioral problems caused by damage to frontal systems. Although groups did not differ on measures of FTSC, FTSC was associated with mTBI severity. Within the mTBI group, right FTSC correlated with the EF composite, while left FTSC was correlated with higher levels of reported disinhibition and executive dysfunctions; such associations were not found in the control group (Sorg et al., 2015). These data suggest that altered structural connectivity of frontothalamic white matter pathways may disrupt processes vital to executive functions in Veterans with mTBI.
4. When examining the relationship between alcohol use in veterans and its relationship to mTBI, psychiatric symptoms, and neuropsychological performance, we found that that mTBI group reported more alcohol-related psychosocial problems (e.g., fights, poor judgment, physical injuries, emotional problems) relative to the control group. Within mTBI, more lifetime alcohol-related psychosocial problems were associated with combat exposure, longer post-traumatic amnesia from blunt injury, higher depression, anxiety, and PTSD symptoms, as well as neurobehavioral symptoms. Additionally, greater lifetime withdrawal symptoms were associated with poorer attention and visual learning, while recent alcohol-related psychosocial problems were associated with poorer executive functioning. A thorough assessment of alcohol-related problems may be important for understanding the sequela of mTBI in veterans. Additional research on pre- and post-mTBI alcohol-use patterns is needed (Hanson et al., 2015).
5. When examining whether engagement in physical, mental, and social activity was related to better neurocognition in veterans with history of mild traumatic brain injury (mTBI), we found that in our

sample, an active lifestyle is associated with better global neurocognition; this relationship was most pronounced for executive dysfunction. The results reveal that greater activity engagement in everyday life is associated with enhanced objective cognitive performance, even after adjusting for depressive and PTSD symptomatology. Findings have implications for the refinement of intervention strategies to optimize clinical outcome in Veterans with mild traumatic brain injury (Moore et al., 2015).

6. When examining the relationships between persistent sleep disturbances, increased sleepiness, and brain activation during a Go-NoGo inhibition task administered during functional magnetic resonance imaging, we found that mTBI Veterans reported overall greater sleep impairment when compared to control Veterans. Sleep disturbance and sleepiness were associated with more numerous areas of inhibitory brain response in mTBI relative to non-TBI Veterans. In addition, sleep disturbance was associated with lower responsiveness of middle frontal and parietal regions, and sleepiness was associated with higher inhibition-related response in the basal ganglia/orbitofrontal regions, and these associations were not evident in controls. Overall, these results suggest that sleep disturbance and sleepiness following mTBI may lead to differing and more widespread cortical demands during cognitive tasks requiring executive function/inhibitory response (Orff et al., 2015).

Published Papers from 2015:

1. When examining the relationships between white matter integrity of the brainstem, injury severity, and postconcussive (PCS) symptoms in Veterans with or without history of TBI, we found no differences in fractional anisotropy (FA) values between groups across 3 regions of interest: medial lemniscus-central tegmentum tract (ML-CTT), corticospinal tracts (CST), and pontine tegmentum (PT). However, among the TBI group, CST FA was significantly and negatively associated with loss of consciousness (LOC) duration. Also, lower FA of certain tracts was significantly associated with increased PCS symptoms, even after adjusting for PTSD symptoms. The findings demonstrate linkages between brainstem white matter integrity and injury severity (LOC), and they raise the possible utility of assessing the pontine tegmentum as a marker of PCS symptoms in Veterans with TBI (Delano-Wood et al., 2015).

2. When investigating cerebral white matter (WM) microstructure in Veterans with or without mTBI, we found that mTBI Veterans who failed (TBI-failed) at least one performance validity test (PVT) demonstrated significantly lower cognitive scores relative to mTBI Veterans who passed (TBI-passed) all PVTs and control Veterans. On a global measure of WM integrity, the TBI-failed group showed more overall WM abnormalities than the other groups. Regional WM analyses revealed abnormalities in the anterior internal capsule and cingulum of both TBI subgroups relative to controls. Moreover, compared with the TBI-passed group, the TBI-failed group demonstrated significantly decreased WM integrity in the corpus callosum. The results of this study suggest that poor PVT performance does not negate the possibility of underlying WM abnormalities in Veterans with mTBI (Clark et al., 2015).

3. When investigating white matter (WM) microstructure compromise in Veterans with history of TBI and its possible contribution to posttraumatic stress disorder (PTSD) symptomatology and neuropsychological functioning through the use of diffusion tensor imaging, we found that compared with controls, TBI Veterans reported higher levels of PTSD symptoms and performed worse on measures of memory and psychomotor-processing speed. TBI was associated with lower fractional

anisotropy (FA) in the genu of the corpus callosum and left cingulum bundle. FA negatively correlated with processing speed and/or executive functions in 7 of the 8 tracts. Regional FA did not correlate with memory or PTSD symptom ratings, suggesting that current PTSD symptoms are independent of TBI-related white matter alterations as measured by diffusion tensor imaging. In addition, WM microstructural compromise may contribute to reduced processing speed in our sample of participants with history of neurotrauma. These findings add insight into the factors associated with complicated recovery from mild to moderate TBI (Sorg et al., 2015).

REPORTABLE OUTCOMES

We have the following manuscripts and abstracts. The following studies were completed with joint funding from the VA and DoD.

5 Abstracts presented at the International Neuropsychological Society, Denver, CO, February 2015:

1. Physical Fatigue and Vegetative Symptoms Best Predict Quality of Life (QoL) in Veterans with Mild to Moderate Traumatic Brain Injury: (Russell T. Kim, Alexandra L. Clark, Scott F. Sorg, Amy J. Jak, Karen L. Hanson, Henry J. Orff, Lisa Delano-Wood, & Dawn M. Schiehser)

Objective: Fatigue, sleep disturbance, and depression have been found to be the most relevant post-concussive symptoms related to poor quality of life (QoL) in Veterans with mild-moderate traumatic brain injury (mmTBI). However, little is known about which aspects of these multi-factorial symptoms may be most associated with different facets of QoL in this population.

Participants and Methods: mmTBI Veterans (n = 50) were administered the World Health Organization Quality of Life (WHOQOL)-BREF as a measure of QoL as well as measures of fatigue (Modified Fatigue Impact Scale; MFIS), sleep (Pittsburgh Sleep Quality Index; PSQI), and depression (Beck Depression Inventory-II; BDI-II). Four WHOQOL-BREF subscales and factor-analytic-derived subscales of the MFIS, PSQI and BDI-II were examined.

Results: Stepwise regressions revealed that overall elevations in fatigue (MFIS) and sleep problems (PSQI) best predicted worse Physical QoL, while fatigue alone best predicted Psychological and Social QoL and depression (BDI-II) best predicted Environmental QoL (p 's<.03). Of these significant predictors, Physical Fatigue, Sleep Quality, and Sleep Latency best predicted Physical QoL (p 's<.02) and Physical Fatigue best predicted both Psychological and Social QoL (p 's<.001); while Vegetative Symptoms of the BDI-II alone predicted Environmental QoL (p <.001).

Conclusions: Physical fatigue and vegetative symptoms are the most significant symptoms associated with worse QoL related to physical health, psychological well-being, social relationships, and everyday activities within the environment. Sleep quality and latency are also associated, albeit to a lesser degree, to physical health QoL. These findings underscore the importance of neurovegetative/somatic symptoms in QoL and could provide potential treatment targets to improve specific areas of QoL in Veterans with mmTBI.

2. Mild Traumatic Brain Injury (mTBI) Moderates the Association Between

White Matter Lesion Burden and Memory Performance: (Alexandra L. Clark, Dawn M. Schiehser, Scott F. Sorg, Mark W. Bondi, Norman Luc, Russell Kim, & Lisa Delano-Wood)

Objective: Accumulating evidence has shown that diffuse axonal injury (DAI) results in white matter lesion (WML) pathology after severe head trauma; however, little is known about WMLs in mild TBI

(mTBI). Additionally, few studies have investigated the relationship between WMLs and cognitive dysfunction in individuals with head trauma. The current study therefore explored associations between WML pathology and cognition in Veterans with and without history of mild TBI.

Methods: 45 Veterans (mTBI=23, Military Controls [MCs]=22) underwent structural magnetic resonance scanning (MRI) and cognitive assessment. Fluid attenuated inversion recovery images were examined for deep white matter lesion (DWML) and periventricular lesion (PVL) volumes. Memory performance was assessed using the California Verbal Learning Test-II, and psychiatric symptoms were rated using the Beck Depression Inventory-II and the Posttraumatic Stress Checklist.

Results: WML volumes were not associated with age or psychiatric symptomatology ($p's > .05$).

MC and mTBI groups did not differ in Total WML or WML subtype volumes ($p's > .05$). MANOVAs revealed a significant Group x PVL volume interaction on memory performance (Wilk's $\lambda = .743$, $p = .04$), such that poor memory was associated with increased PVL volume in the mTBI group, but not the MCs. There were no significant associations between DWML volume and cognition in either group ($p > .05$).

Conclusions: Results show that mTBI may not result in increased WML pathology. However, PVL, but not DWML, volumes were associated with memory impairment in participants with history of mTBI. Findings suggest that PVLs may exert a more deleterious effect on cognition in those with a history of mild neurotrauma.

3. Frontothalamic Structural Connectivity in Veterans with Mild Traumatic Brain Injury:

Associations with Executive Functions: (Scott F. Sorg, Norman Luc, Alexandra L. Clark, Dawn M. Schiehser, Mark W. Bondi, Russell Kim, & Lisa Delano-Wood)

Objective: White matter pathology is common in traumatic brain injury and is evident even in mild cases (mTBI). This damage may cause a disconnection syndrome via disruption of functional networks that mediate cognitive processes. The thalamus is a key relay station for many neural networks, and damage within frontothalamic white matter pathways may contribute to executive dysfunction following mTBI. In this study we computed measures of frontothalamic structural connectivity (FTSC) and examined its association with mTBI and measures of executive functions (EF) in a sample of US military Veterans.

Methods: Thirty-nine Veterans (mTBI=21, Military Controls [MCs]=18) completed cognitive testing, the Frontal Systems of Behavior Scale (FrSBe), and structural and DTI MRI scanning. Seed and target regions were identified via FreeSurfer and frontothalamic pathways were produced via probabilistic tractography. Measures of FTSC (i.e., proportion of streamlines from the thalamus reaching the frontal lobes) were extracted from the resultant tracks.

Results: Compared to MC, the mTBI group had higher FrSBe scores across all subscales ($p < .01$) and performed worse on an EF composite score ($p < .01$). MC and mTBI groups did not differ in measures of FTSC ($p's > .05$), however, FTSC was associated with mTBI severity ($p < .05$). Within the mTBI group, right FTSC correlated with the EF composite ($r = .57$, $p = .02$), while left FTSC was correlated with higher levels of reported disinhibition ($r = .57$, $p = .01$) and executive dysfunctions ($r = .57$, $p = .01$). Such associations were not found in MCs.

Conclusions: Results show that altered structural connectivity of frontothalamic white matter pathways may disrupt processes vital to executive functions in Veterans with mTBI. While group differences in FTSC were not found, FTSC was associated with objective and subjective measures of executive functions and may be related to mTBI severity.

4. Alcohol-Related Psychosocial Problems are Associated with TBI Injury Characteristics, Greater Post-Concussive Symptomatology, and Poorer Cognition in Veterans with a History of Mild TBI:

(Karen L. Hanson, Dawn M. Schiehser, Russell Kim, Norman Luc, Alexandra L. Clark, Scott Sorg, & Lisa Delano-Wood)

Objectives: Since little is known about alcohol use patterns and associations with cognitive and psychiatric functioning among veterans with a history of mild traumatic brain injury (mTBI), we aimed to (1) characterize alcohol use among mTBI veterans, (2) examine its relationship to mTBI and psychiatric symptoms, and (3) determine associations with neuropsychological performance.

Participants and Methods: Thirty-seven veterans ($n=21$ mTBI; $n=16$ military controls [MCs]; mean age=32.11; 22% women; 55% Caucasian) were assessed for problem alcohol use (modified Customary Drinking and Drug Use Record [CDDR]), psychiatric (depression, anxiety, and post-traumatic stress disorder [PTSD]) symptoms, and cognition. Participants reporting current DSM-IV alcohol or substance dependence were excluded.

Results: The mTBI group reported more alcohol-related psychosocial problems (e.g., fights, poor judgment, physical injuries, emotional problems) relative to MCs ($p<.03$). Within mTBI, more lifetime alcohol-related psychosocial problems were associated with combat exposure, longer post-traumatic amnesia from blunt injury, and higher depression, anxiety, and PTSD symptoms, as well as neurobehavioral symptoms ($rhos=.33$ to $.55$, $ps<.05$). Additionally, greater lifetime withdrawal symptoms were associated with poorer attention and visual learning ($rhos=-.52$ to $-.57$, $ps<.03$), while recent alcohol-related psychosocial problems were associated with poorer executive functioning ($rhos=-.53$ to $-.73$, $ps<.03$).

Conclusions: Our findings suggest that lifetime alcohol-related psychosocial or withdrawal symptoms may affect post-concussive symptomatology and cognitive functioning in some veterans with a history of mTBI. Veterans with mTBI who are combat-exposed or with a longer post-traumatic amnesia may be at higher risk for alcohol-related psychosocial problems. A thorough assessment of alcohol-related problems may be important for understanding the sequela of mTBI in veterans. Additional research on pre- and post-mTBI alcohol-use patterns is needed.

5. Engagement in an Active Lifestyle is Associated with Better Neurocognitive Functioning Among Veterans with Mild Traumatic Brain Injury:

(Raeanne C. Moore, Lisa Delano-Wood, Russell T. Kim, Karen L. Hanson, Scott F. Sorg, Alexandra L. Clark, Zvinka Z. Zlata, Pariya L. Fazeli, Lisa T. Eyler, & Dawn M. Schiehser)

Objective: Mild traumatic brain injury (mTBI) is common among military personnel, and there is mounting evidence that a history of mTBI elevate risk for poor long-term cognitive outcomes. We therefore examined whether engagement in physical, mental, and social activity was related to better neurocognition (NC) among a well-characterized cohort of Veterans with a history of mTBI.

Participants and Methods: 41 mTBI Veterans (mean age=33, 88% male) underwent a comprehensive assessment of neurobehavioral and cognitive functioning. Participants were excluded if they failed symptom validity tests. A global NC score was derived using demographically-adjusted scores from the following domains: executive functioning, learning and memory, attention and processing speed, and language. Participants were classified based on the number of self-reported Active Lifestyle Factors (ALFs; Mental, Physical, and Social), and relationships to global NC and specific cognitive domains were explored.

Results: Participating in more ALFs was associated with better global NC ($F=3.7$; $p=0.02$), executive functioning ($F=3.0$, $p=0.04$), and attention and processing speed ($F=2.9$, $p=0.05$). Post hoc analyses

revealed engagement in all 3 ALFs was related to the highest NC. The relationships with ALFs and global NC ($F=3.3$, $p=0.03$) and executive functioning ($F=2.8$, $p=0.05$) remained significant after controlling for depressed mood and post-traumatic stress disorder (PTSD).

Conclusions: In our sample of Veterans with mTBI, cross-sectional findings suggest that an active lifestyle is associated with better global NC. This relationship was most pronounced for executive dysfunction. Specifically, results show that greater activity engagement in everyday life is associated with enhanced objective cognitive performance, even after adjusting for levels of depressive symptomatology and PTSD in patients with history of head trauma. Findings have implications for the refinement of intervention strategies to optimize clinical outcome in Veterans in the aftermath of head injury.

1 study at the Associated Sleep Societies, Seattle, Washington, June, 2015:

1. Association of Sleep Disturbance, Insomnia, and Sleepiness with Cortical Activation on a Go-NoGo Task in Veterans with and without History of Mild-Moderate Traumatic Brain Injury:

(Henry Orff, Lisa T. Eyler, Lisa Delano-Wood, Scott F. Sorg, Russell T. Kim, Norm Luc, & Dawn M., Schiehser)

Objective: For many Veterans, mild-moderate traumatic brain injury (mTBI) can be associated with persistent sleep disturbances and increased sleepiness, which are not always synonymous. Dissociating these symptoms at a neural level may help identify underlying mechanisms of symptomatology and could have beneficial prognostic and diagnostic implications.

Participants and Methods: 53 Veterans with a history of mTBI (age: 32.5 ± 6.7 ; education: 14.3 ± 1.4 ; 94% male) and 25 Veterans with no history of mTBI (age: 31.8 ± 8.1 ; education: 14.6 ± 1.7 ; 68% male) were studied. The Pittsburgh Sleep Quality Inventory (PSQI), Insomnia Severity Index (ISI), and Epworth Sleepiness Scale (ESS), and a Functional Magnetic Resonance Imaging (fMRI) Go-No-Task were administered. BOLD signal from the NoGo condition (inhibition) relative to non-NoGo condition was obtained for several regions of interest and correlated with sleep scores.

Results: mTBI Veterans reported greater impairments on the PSQI ($p = 0.009$), ISI ($p < 0.001$), and ESS ($p < 0.001$). For both groups, PSQI and ISI scores were negatively correlated with response in bilateral middle, transverse, and/or inferior temporal regions ($r's = -0.577$ to -0.279 ; $p's \leq 0.01-0.05$). In mTBI Veterans, additional significant correlations were observed, namely, between the PSQI and ISI and middle frontal and left inferior parietal regions ($r's = -0.29$ to -0.38) and between the ESS and response in the left caudate and right lateral and medial orbital-frontal regions ($r's = 0.28-0.35$; $p's \leq 0.01-0.05$).

Conclusions: Two novel findings emerged in this preliminary investigation: 1) Sleep disturbance and sleepiness were associated with more numerous areas of inhibitory brain response in mTBI relative to non-TBI Veterans; 2) Sleep disturbance was associated with lower responsiveness of middle frontal and parietal regions, and sleepiness was associated with higher inhibition-related response in the basal ganglia/orbitofrontal regions, and these associations were not evident in controls. Overall, these results suggest that sleep disturbance and sleepiness following mTBI may lead to differing and more widespread cortical demands during cognitive tasks requiring executive function/inhibitory response.

Manuscripts Published or In Press:

Published in 2015 or In Press:

1. Delano-Wood, L., Bangen, K.J., Sorg, S.F., Clark, A.L., Schiehser, D.M., Luc, N., Bondi, M.W., Werhane, M., Kim, R.T., & Bigler, E.D. (2015). Brainstem white matter integrity is related to loss of consciousness and postconcussive symptomatology in veterans with chronic mild to moderate traumatic brain injury. *Brain Imaging and Behavior*, 9, 500-512.
2. Clark, A.L., Sorg, S.F., Schiehser, D.M., Bigler, E., Bondi, M.W., Luc, N., Kim, R.T., Jacobson, M.W., Jak, A.J., & Delano-Wood, L. (2015). White Matter Associations with Performance Validity Testing in Veterans with Mild Traumatic Brain Injury: The Utility of Biomarkers in Complicated Assessment. *Journal of Head Trauma Rehabilitation* [epub ahead of print].
3. Sorg, S. F., Schiehser, D. M., Bondi, M. W., Luc, N., Clark, A. L., Jacobson, M. W., ... & Delano-Wood, L. (2015). White Matter Microstructural Compromise Is Associated With Cognition But Not Posttraumatic Stress Disorder Symptoms in Military Veterans With Traumatic Brain Injury. *The Journal of Head Trauma Rehabilitation* [epub ahead of print].
4. Clark, A.L., Sorg, S.F., Schiehser, D.M., Luc, N., Bondi, M.W., Sanderson, M., Werhane, M.L., & Delano-Wood, L. (In Press). Deep White Matter Hyperintensities Affect Verbal Memory Independent of PTSD Symptoms in Veterans with Mild Traumatic Brain Injury. *Brain Injury*.
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Updated citations for 4 papers originally published in 2014:

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executive function performance following mild to moderate traumatic brain injury? *Journal of Clinical and Experimental Neuropsychology*, 33(6), 704-714.

Manuscripts Under Review:

1. Hanson, K.L., Schiehser, D.M., Kim, R.T., Sorg, S.F., Clark, A.L., Werhane, M., Twamley, E.B., Jak, A.J., & Delano-Wood, L. (Under Revised Review). Problem Alcohol Use is Associated with Increased Psychiatric Symptomatology and Reduced Processing Speed in Veterans with Mild Traumatic Brain Injury. *Journal of Clinical and Experimental Neuropsychology*.
2. Clark, A.L., Sorg, S.F., Delano-Wood, D.M., Werhane, M., & Schiehser, D.M (Under review). A Brief Report on the Association Between Cognitive Fatigue and White Matter in Veterans with History of Mild to Moderate Traumatic Brain Injury. *Brain Imaging and Behavior*.

Manuscripts In Preparation:

1. Sorg, S.F., Clark, A.L., Schiehser, D.M., Bondi, M.W., & Delano-Wood, L. (In preparation). Brain Derived Neurotrophic Factor (BDNF) Genotypes Moderate the Relationship between PTSD symptoms and Cortical Thickness in Veterans with Mild TBI.
2. Sorg, S.F., Luc, N., Clark, A.L., Kim, R.T., Bondi, M.W., Schiehser, D.M., & Delano-Wood, L. (In preparation). Frontothalamic Structural Connectivity in Veterans with Mild Traumatic Brain Injury: Associations with Executive Functions.
3. Werhane, M., Clark, A.L., Sorg, S.F., Schiehser, D.M., Bondi, M.W., Baker, D., Hauger, R., & Delano-Wood, L. (A review in preparation). Biomarkers of Chronic Traumatic Brain Injury Associated with Protracted Pathological Vascular and Inflammatory Processes.
4. Evangelista, D., Clark, A.L., Werhane, M.L., Sorg, S.F., Schiehser, D.M., Kim, R.T., Bondi, M.W., Bangen, K.J., & Delano-Wood, L. (In Preparation). Brain-Derived Neurotrophic Factor (BDNF) Genotype is Related to Executive Function But Not Memory Performance in Veterans with History of Mild Traumatic Brain Injury
5. Orff, H, Eyler, L.T., Delano-Wood, L., Sorg, S.F., Kim, R.T., Luc, N., & Schiehser, D.M. (In Preparation) Association of Sleep Disturbance, Insomnia, and Sleepiness with Cortical Activation on a Go-NoGo Task in Veterans with and without History of Mild-Moderate Traumatic Brain Injury:
6. Moore, R.C., Delano-Wood, L., Kim, R.T., Hanson, K.L., Sorg, S.F., Clark, A.C., Zlatar, Z.Z., Fazeli, P.L., Eyler, L.T., & Schiehser, D.M. (In Preparation). Engagement in an Active Lifestyle is Associated with Better Neurocognitive Functioning Among Veterans with Mild Traumatic Brain Injury.

Presentations:

- As part of her duties as Chair of APA Division 40, Dr. Schiehser gave the following presentations:

“Comprehensive Neuropsychological Assessment of Veterans with TBI”; Invited Symposium Speaker, APA Division 22; APA Annual Convention, Toronto, Canada; August 7, 2015.

“Fatigue in Traumatic Brain Injury”; Invited Address (CE Course), APA Division 40; APA Annual Convention, Toronto, Canada; August 9, 2015.

- As part of a VA-sponsored National Webinar, Dr. Dawn Schiehser presented “Diagnosis, Mechanism, and Management of Fatigue in Mild Traumatic Brain Injury” (June 24, 2014). The web URL for this presentation is provided below in *References*.

CONCLUSION

We continue to make considerable progress toward our stated goals as outlined in our Introduction above. Given greater collaborations with other VA TBI investigators, our laboratory has grown considerably and productivity has increased significantly. Collectively, my laboratory has completed several studies, 7 that are now published, 2 that are currently under review in peer-reviewed journals, 2 in press, and 6 manuscripts under preparation. We have tested and scanned 33 additional participants this past year. We expect to be especially productive this year and next, especially in regard to increased recruitment efforts, as we continue to grow our lab while also rounding out our data collection so that we can then embark upon large-scale studies to test many of the hypotheses set forth in the original proposal.

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2. Clark, A.L., Sorg, S.F., Schiehser, D.M., Bigler, E., Bondi, M.W., Luc, N., Kim, R.T., Jacobson, M.W., Jak, A.J., & Delano-Wood, L. (2015). White Matter Associations with Performance Validity Testing in Veterans with Mild Traumatic Brain Injury: The Utility of Biomarkers in Complicated Assessment. *Journal of Head Trauma Rehabilitation* [epub ahead of print].
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APPENDICES

We list below publications and abstracts that were submitted since the start of the study.

6 Abstracts presented at the International Neuropsychological Society, Seattle, WA, February 2014:

1. Cognitive and Psychiatric Dissociations between Fractional Anisotropy and Cortical Thickness in Veterans with Mild TBI: (Scott F. Sorg, Mark W. Bondi, Dawn M. Schiehser, Norman Luc, Amy J. Jak, Alexandra L. Clark, Karen L. Hanson, James B. Lohr, & Lisa Delano-Wood)

Objective: Studies using diffusion tensor imaging (DTI) have shown lower white matter integrity in veterans with history of mild TBI (mTBI). However, the effect of mTBI on gray matter regions remains understudied in this population. Thus, in a sample of veterans with mTBI, we investigated the relationships among the cognitive effects of mTBI, PTSD symptom severity, and brain structure in terms of gray matter measured via cortical thickness (CT) and white matter integrity measured via fractional anisotropy (FA).

Participants and Methods: Thirty-eight mild TBI and 17 normal control (NC) veteran participants completed neuropsychological and psychiatric testing (e.g., PTSD Check List) with adequate effort, and underwent MRI scanning an average of 4 years following their TBI event(s). Mean CT measures were extracted from 6 frontal and temporal cortical regions of interest and FA measures were extracted from 10 white matter tracts of interest.

Results: Adjusting for age, education, depression, and PTSD symptoms, mTBI participants performed worse than NCs on a memory composite and a test of psychomotor processing speed ($p's < .05$). CT did not differ between the mTBI and NC groups or correlate with cognitive test scores ($p's > .05$). Thinner left orbitofrontal CT was associated with higher PCL scores ($p < .05$). FA was lower in the TBI group than NCs in the left cingulum bundle ($p < .05$) and genu of the corpus callosum ($p < .05$). FA correlated with processing speed in seven tracts including the left cingulum ($r = .38, p < .05$) and genu ($r = .50, p < .01$). FA did not correlate with PCL scores ($p > .05$). Left cingulum bundle FA correlated with CT in the left middle frontal ($r = .31, p < .05$) and orbitofrontal cortices ($r = .38, p < .01$).

Conclusions: Results demonstrated that gray matter thickness was associated with PTSD symptom severity but not cognition, whereas white matter anisotropy was associated with cognition but not PTSD symptom severity, suggesting dissociable neurobiologic substrates for the cognitive and psychological sequelae following mTBI.

2. Poor Effort is Associated with Increased Reporting of Injury Characteristics and Postconcussive Symptomatology but not Structural Brain Changes: A Multidisciplinary Study of OEF/OIF Veterans with History of Mild TBI: (Alexandra L. Clark, Scott F. Sorg, Mark W. Bondi, Norman Luc, Dawn M. Schiehser, Karen L. Hanson, Dean C. Delis, Lawrence R. Frank, Amy J. Jak, James B. Lohr, & Lisa Delano-Wood)

Objective: Studies investigating the role of effort in OEF/OIF Veterans with history of mild TBI (mTBI) have generally shown that poor effort is strongly associated with inflation on symptom rating scales, increased rates of clinical diagnoses, and decreased neurocognitive test performance. However, whether there are neurobiological abnormalities that underlie this pattern of increased symptom endorsement and clinical presentation in those who fail effort measures has not been studied. Therefore, the current study sought to explore the relationship between effort, symptom reporting, and structural brain changes

(Freesurfer-derived values of cortical thickness and indices of white matter integrity using DTI) in OEF/OIF veterans with history of mTBI.

Participants and Methods: Ninety-seven (83M/14F) OEF/OIF Veterans (mean age = 31; mean time since injury = 2.3 years) underwent neuropsychological assessment and 3T MRI scanning. Participants were divided into those with history of mTBI who passed effort measures (mTBI-Pass: $n = 52$), those with mTBI who failed effort measures (mTBI-Fail: $n = 16$), and military combat controls (NC: $n = 28$) with no history of mTBI. Poor effort was defined by failure on the Test of Memory Malingering (TOMM) (Trial 1 score < 45) or CVLT Forced Choice Recognition (total score < 15). Mean cortical thickness measures were extracted from 6 frontal and temporal cortical regions of interest and FA measures were extracted from 10 white matter tracts of interests.

Results: Collapsed across effort, when compared to the NCs, the overall mTBI group showed significantly elevated scores on measures of PTSD ($p = .001$), depression ($p = .01$), and anxiety ($p = .015$). Within the mTBI group, in comparison to the mTBI-Pass subgroup, the mTBI-Fail subgroup reported less time since their most recent TBI ($p = .03$) and higher levels on all psychiatric measures (PTSD, depression, and anxiety; all p -values $< .002$). Additionally, the mTBI-Fail subgroup reported significantly more severe injury characteristics (LOC, AOC, PTA; all p -values $< .05$) and increased postconcussive severity ($p < .015$) in the context of reduced performance across multiple cognitive domains measured (all p -values $< .05$). However, although the overall mTBI group showed greater white matter and cortical thickness abnormalities when compared to NCs, there were no significant differences between the mTBI-Pass and mTBI-Fail groups on any of the imaging indices examined.

Conclusions: Despite considerably elevated subjective complaints, injury severity reporting, and symptom endorsement in those with mTBI with low vs. high effort results of this study show that, in our cohort of mTBI veterans with poor effort, there are no objective gray or white matter differences – above and beyond those attributable to mTBI—that might explain this pattern of exaggerated injury and symptom reporting. Future research focusing on symptom attribution and illness perception may aid in understanding more about the relationship between reduced effort and increased symptom endorsement patterns following neurotrauma in this vulnerable population.

3. Alcohol Misuse is Associated with Increased Psychiatric Symptomatology and Reduced Processing Speed in Veterans with Mild Traumatic Brain Injury:

(Karen L. Hanson, Dawn M. Schiehser, Elizabeth Twamley, Amy J. Jak, Alexandra L. Clark, James B. Lohr, Dean C. Delis, & Lisa Delano-Wood)

Objective: Given that little is known about the role of alcohol misuse in the cognitive and psychiatric outcomes among veterans with mild traumatic brain injury (mTBI), we aimed to: (1) characterize how veterans with mTBI differ from military combat controls on measures of alcohol misuse, psychiatric symptomatology, and cognition; (2) determine the risk factors for problematic alcohol use among veterans with mTBI; and (3) examine whether problematic alcohol use is associated with increased psychiatric symptoms and reduced cognition among veterans with mTBI.

Participants and Methods: 77 veterans ($n=48$ with mTBI history; $n=29$ veteran combat normal controls [NCs]; mean age = 31.9; 14% women) completed an assessment of problematic alcohol use (Alcohol Use Disorders Identification Test: AUDIT), psychiatric symptoms, and neuropsychological (NP) functioning. Participants who reported current (within 30 days) alcohol or substance dependence (DSM-IV criteria) or a positive toxicology screen taken on the day of testing were excluded from the study. Only participants who demonstrated optimal effort (64/77) upon testing were included in the cognitive analyses.

Results: Compared to NCs, there was a trend revealing that the mTBI group was more likely to score above the AUDIT cut-off score of 8 ($p=.066$). Within the mTBI group, higher AUDIT scores correlated with younger age at testing ($r= -.45, p=.001$) and lower education ($r=-.30, p=.007$), as well as the following injury characteristic variables: younger age at last TBI ($\rho=-.38, p=.01$), shorter (?) post-traumatic amnesia duration ($\rho=-.60, p=.001$), and increased blast-related quaternary effects ($\rho=.45, p=.019$). When compared to the mTBI group with low AUDIT scores, the mTBI group scoring above the AUDIT cutoff reported higher levels of depression ($p=.005$) and anxiety ($p=.02$), and increased neurobehavioral symptoms ($p=.026$), but there were no differences on PTSD symptoms ($p = .11$). Finally, higher AUDIT scores were associated with slower visuomotor processing speed ($p = .02$) but not other NP domains. *Conclusions:* Findings suggest that (1) compared to NCs, mTBI veterans are more likely to report alcohol-related problems, (2) younger and less educated mTBI veterans appear to be at higher risk for alcohol abuse and (3) alcohol abuse among mTBI veterans is associated with elevated psychiatric symptoms and slower visuomotor processing speed. These results emphasize the importance of assessing for and treating problematic alcohol use among veterans with history of neurotrauma.

4. Memory Deficits Differ by Working Memory Performance in Mild to Moderate Traumatic Brain Injury: (Adelina Matevosyan, Lisa Delano-Wood, Omar Alhassoon, Vincent J. Filoteo, Elisa B. Lanni, Russell T. Kim, Karen L. Hanson, & Dawn M. Schiehser)

Objective: Memory problems are common in the context of mild to moderate traumatic brain injury (mmTBI); however, the nature of memory deficits in this population is not entirely clear. Given the relationship between working memory/executive function (WM/EF) and organization of information for adequate retrieval, we hypothesized that individuals with mmTBI who demonstrate poor WM/EF will present with a retrieval deficit, which is characterized by better recognition or cued recall as compared to free recall.

Participants and Methods: Veterans with a history of mmTBI ($n=46$; mean years since injury=6.6) and 17 demographically-matched veteran normal controls (VNC) with optimal effort were administered the California Verbal Learning Test (CVLT-II) and the Wechsler Adult Intelligence Scale Digit Span Backwards (DSB) test. The mmTBI group was divided into low WM/EF (LDSB) and high WM/EF (HDSB) using a median split of the DSB scores ($raw \leq 8.5$). *Results:* A One-Way MANOVA revealed significant differences between LDSB, HDSB, and VNC on measures of total (Trials 1-5), free, and cued recall (all $p's \leq .01$), but not recognition ($p=.08$). Post-hoc analyses revealed that LDSB participants performed significantly worse on total, free, and cued recall compared to VNC, while they performed significantly worse on total and free recall compared to the HDSB group (all $p's < .02$); no differences in recognition were found between either groups. No significant differences were found on any of the memory measures between HDSB and VNC (all $p's > .25$).

Conclusions: Results indicate that a subset of mmTBI individuals with poor WM/EF show a retrieval deficit, which is marked by reduced recall relative to recognition. As greater retrieval demands are required for semantic cueing compared to recognition, our results are consistent with a severe retrieval deficit in this particular subgroup. These findings highlight the role of WM/EF in retrieval of information and have implications for targeted assessment and cognitive interventions for specific mmTBI subgroups.

5. Executive Dysfunction is Associated with Avoidance Coping Style in Veterans with Mild to Moderate Traumatic Brain Injury: (Russell T. Kim, Lisa Delano-Wood, Mark W. Bondi, Karen L. Hanson, Adelina Matevosyan, Elisa B. Lanni, Norman Luc, & Dawn M. Schiehser)

Objective: Preliminary evidence suggests that individuals with traumatic brain injury (TBI) may utilize maladaptive coping styles, such as avoidance or emotional reaction (e.g., self-blame), more than functional task-oriented coping styles. Since executive dysfunction is frequently observed in veterans with history of TBI, we sought to investigate the relationship between coping style and performance on executive tasks in this population.

Participants and Methods: Participants were veterans ($n = 20$) with a history of mild to moderate TBI (6.9 mean years since injury) and veteran combat normal controls (NCs: $n = 18$) without a history of TBI. All participants were administered measures of coping (Coping Inventory for Stressful Situations), executive function (Color-Word Interference Test; CWIT), depression (Beck Depression Inventory-II), anxiety (Beck Anxiety Inventory), and Post-traumatic Stress Disorder (PTSD) symptoms (PTSD Checklist-Military Version).

Results: Controlling for age, depression, anxiety, and PTSD, the TBI group reported significantly greater usage of Avoidance coping when compared to NCs; groups did not differ in their use of Task or Emotional coping (all p 's $> .05$). In the mTBI group, Avoidance coping was significantly associated with worse CWIT Inhibition/Switching ($p = .03$), but was not related to depression, anxiety, or PTSD (all p 's $> .56$). Both Task and Emotional coping were associated with mood (all p 's $< .01$), but were unrelated to executive function.

Conclusions: Taken together, our findings demonstrate that veterans with history of mild to moderate TBI endorsed greater avoidance coping compared to combat controls with no history of neurotrauma. In TBI veterans, greater use of avoidance coping was associated with poorer executive function. Additionally, task and emotional coping was related to increased psychiatric symptomatology (depression, anxiety, and PTSD). These findings underscore the impact of reduced executive function on maladaptive coping, and they suggest that proper assessment and targeted cognitive and psychological interventions may improve long-term outcomes in this vulnerable population.

6. Correlates of TBI History in Aging Veterans Presenting with Cognitive Difficulties: A Clinical

Case Series: (Daniel A. Nation, Tony Abuyo, Lisa Delano-Wood, Amy J. Jak, & Mark W. Bondi)

Objective: We sought to investigate the relationship between cognitive aging and history of traumatic brain injury (TBI) among aging veterans in order to further our understanding of the interaction between TBI and age-related cognitive disorders.

Participants and Methods: A case series of 104 Veterans (age mean=70.5, range=46-89; 94.2% male) referred for neuropsychological evaluation of cognitive difficulties (self- or informant-report) were compared on demographics, cognition, and psychiatric history based on whether there was history of TBI ($n=54$) or not ($n=50$). No participants were referred because of a known TBI, but history of TBI was assessed during clinical interview and chart review. Analyses were performed across the entire sample and after stratification by clinical diagnosis [normal cognition, Cognitive Disorder, or Dementia].

The main effects of TBI history and the interaction of TBI history with clinical diagnoses were evaluated by ANOVA. Chi-square analyses compared rates of anxiety, depression, PTSD, and alcohol/substance abuse history. *Results:* There was a main effect of TBI history on age at presentation, such that Veterans with a history of TBI were younger than those without a history of TBI ($p=.001$). Veterans with a history of TBI were also more likely to have a history of anxiety ($p=.01$) and PTSD ($p=.026$), but were no more likely to exhibit depression or alcohol/substance abuse. There were no differences in dementia rating scale scores.

Conclusions: Among middle- to older-age Veterans presenting with cognitive difficulties, those with an incidentally discovered history of TBI tended to be younger, potentially suggesting that TBI could

influence the age at which cognitive difficulties emerge. Those with a history of TBI were also more likely to have histories of mood and anxiety disorders, suggesting psychiatric factors may play a role in the interaction between cognitive aging and TBI.

1 Abstract presented at the Annual Meeting of the Associated Professional Sleep Societies, Minneapolis, MN, May 2014:

1. Sleep Disturbance and Neuropsychiatric Functioning in Veterans with Mild to Moderate Traumatic Brain Injury (mTBI) Compared with non-mTBI Veterans: (Henry Orff, Dawn M. Schiehser, Elizabeth Twamley, Amy J. Jak, Sean Drummond, & Lisa Delano-Wood)

Objective: Many Veterans of Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) experience post-concussive symptoms associated with a history of mild to moderate traumatic brain injury (mTBI). Sleep complaints are highly prevalent in post-mTBI Veterans, however the degree and impact of impairment, relative to Veterans who have not experienced mTBI, is largely unknown.

Methods: Veterans enrolled for studies of mTBI at the VA San Diego Healthcare System received a comprehensive screening of sleep (Pittsburgh Sleep Quality Inventory-PSQI; Insomnia Severity Index-ISI; Epworth Sleepiness Scale-ESS; Multidimensional Fatigue Inventory-MFI), psychiatric symptoms, post-concussive symptoms, alcohol/substance use, and quality of life. Results were compared using independent samples t-tests and bivariate correlations to explore differences between Veterans with and without mTBI.

Results: 21 Veterans with a history of mTBI (18M; age=32 yrs; education=14 yrs) and 17 Veterans with no history of mTBI (14M; [3 with combat experience]; age=34 yrs; mean=14 yrs) were studied. Compared to the non-mTBI group, the mTBI group exhibited significantly greater sleep disturbance (PSQI; $p=.004$), more insomnia symptoms (ISI; $p=.018$), more daytime sleepiness (ESS; $p=.002$), and higher levels of fatigue (MFI; $p<.001$). The mTBI group also exhibited significantly elevated depressive, anxious, PTSD-related, and post-concussive/neurobehavioral symptoms (all $ps<.001$), however, the groups did not differ on alcohol/substance abuse or quality of life measures. *PSQI Global scores were significantly correlated with lower quality of life and higher PTSD symptom severity in both groups. Additionally, PSQI Global scores were correlated with higher levels of post-concussive symptoms, anxiety symptom severity, and fatigue severity in mTBI Veterans.*

Conclusion: Veterans with mTBI exhibit increased levels of sleep disturbance relative to Veterans who have not experienced mTBI. Poor sleep also appears to be associated with greater neuropsychiatric impairment in these individuals. Future research should attempt to examine the causal relationships between mTBI, sleep disturbance, and neuropsychiatric functioning in Veterans with mTBI.

The following are 3 abstracts presented at the International Neuropsychological Society, Honolulu, HI, 2013:

1. Fornix Integrity is Related to Cognition but not Postconcussive Symptoms in Chronic Military Traumatic Brain Injury: A Quantitative Tractography Study: (Lisa Delano-Wood, Scott F. Sorg, Norman Luc, Dawn M. Schiehser, Elisa B. Lanni, Mark W. Jacobson, Daniel A. Nation, Amy J. Jak, Karen L. Hanson, Lawrence R. Frank, Mary Jane Meloy, Dean C. Delis, James B. Lohr, & Mark W. Bondi)

Objective: White matter (WM) changes have been reported in mild TBI, although few diffusion tensor imaging (DTI) tractography studies of military personnel exist in the literature. This study investigated the fornix, a WM limbic structure that is particularly vulnerable to TBI-related diffuse axonal injury.

Given this structure's connectivity and cholinergic input to the medial temporal lobe (MTL), we investigated associations between fornix microstructural integrity and cognition in both blast-related and mechanical blunt force mTBI.

Participants and Methods: Seventy-three military veterans (mTBI: $n = 53$; NC: $n = 20$) were administered 3T DTI scans (61 directions) and a comprehensive neuropsychological evaluation. White matter tracking was employed by seeding ROIs in bilateral contiguous slices on a registered T1 image and mean DTI values were derived from individual fractional anisotropic (FA) and mean diffusivity (MD) maps.

Results: The mTBI group performed significantly more poorly than NCs across several neuropsychological domains including attention/working memory, executive functioning, visual and verbal memory, and fine motor dexterity. Independent samples t-tests demonstrated that the mTBI group differed significantly from NCs on fornix FA ($t = 3.00(71)$, $t = 3.00_{[df=71]}$, $p = .004$) as well as fornix MD ($t = -2.10_{[df=71]}$, $p = .038$), but not on fornix volume ($p = .22$). Moreover, fornix DT indices positively correlated with performance on attention/working memory, executive functioning, and fine motor dexterity. Finally, mTBI subgroup analysis of blast, blunt, and NCs subgroups significantly differed on fornix MD ($F = 3.47(75) = .036$), fornix AD ($F = 4.25(75)$, $= .018$), and trend with fornix RD ($F = 2.74(75) = .07$).

2. Iowa Gambling Task Impairment is Associated with Executive Dysfunction in Veterans with Chronic Mild to Moderate Traumatic Brain Injury:

(Norman Luc, Daniel A. Nation, Scott F. Sorg, Dawn M. Schiehser, Karen L. Hanson, Mark W. Bondi, Elisa B. Lanni, Amy J. Jak, Adelina Matevosyan, Russell T. Kim, Mark W. Jacobson, & Lisa Delano-Wood)

Objective: The Iowa Gambling Task (IGT) has been widely employed to examine risk-related decision-making performance across several clinical populations; however, few studies have investigated performance on this task in the context of traumatic brain injury (TBI). Given that decision-making likely plays an important role in long-term functional outcome following neurotrauma, the current study compared IGT performance between OEF/OIF veterans with a history of chronic mild to moderate TBI and normal control (NC) participants. We hypothesized that mTBI patients would demonstrate deficits in decision-making and that IGT performance would be related to other measures of executive functioning.

Participants and Methods: Forty-seven demographically-matched participants (TBI: $n=26$; NC $n=21$; mean age = 32.7; mean months since TBI = 80.7) were administered a comprehensive neuropsychological battery which included a computerized version of the IGT. Participants were divided into impaired and unimpaired performance on IGT based on a T-score cutoff corresponding to > 1 standard deviation below the mean ($T \leq 39$).

Results: TBI participants were significantly more likely to exhibit impairment on the IGT total score relative to the NC group (% Impaired: TBI = 20.7%; NC = 0%; $p = .02$). Repeated measures ANOVA indicated a significant group by block interaction ($p = .04$), whereby the TBI group performed significantly worse than NCs on block 4 ($p = .03$) and were more likely to exhibit impairment on 2 or more blocks (% Impaired: TBI = 19.2%; NC = 0%). Collapsed across group, IGT performance was negatively related to executive functioning (DKEFS Trails Switching [$r = -.36$, $p = .02$], WCST Perseverative Responses [$r = -.35$, $p = .02$], and Set Losses [$r = -.30$, $p = .049$]).

Conclusions: Findings indicate that mild to moderate military TBI is associated with subtle impairment in reward-related decision-making and suggest that the IGT may be a sensitive index of this aspect of executive dysfunction in military chronic TBI.

3. Processing Speed and Memory Deficits in Veterans with Mild to Moderate TBI: Associations with Anterior White Matter Integrity:

(Scott F. Sorg, Lisa Delano-Wood, Dawn M. Schiehser, Norman Luc, Elisa B. Lanni, Amy J. Jak, Karen L. Hanson, Mary Jane Meloy, Daniel A. Nation, Mark W. Jacobson, Lawrence R. Frank, James B. Lohr, & Mark W. Bondi) *Objective:* High rates of mild to moderate traumatic brain injuries (TBI) are reported in veterans of the Iraq and Afghanistan wars. The long-term neuropsychological outcome of these injuries and their relationship with cerebral white matter microstructure is unclear. Using diffusion tensor imaging (DTI) tractography, this study investigated the effects of TBI on a sample of veterans in terms of cognition and white matter integrity.

Participants and Methods: Thirty-eight veterans with TBI and 17 veteran normal control (NC) participants completed neuropsychological and psychiatric testing with adequate effort and underwent a DTI scan an average of 4 years following their TBI event(s). Fractional anisotropy (FA), a measure of white matter integrity, was extracted from 7 white matter tracts.

Results: TBI participants had higher depression and PTSD scores than the control group and completed fewer years of education. Controlling for age, education, depression, and PTSD symptoms, ANCOVA revealed that TBI participants performed worse than NCs on a memory composite ($p=.02$, $\eta^2=.11$) and on a test of psychomotor processing speed ($p=.02$, $\eta^2=.11$), whereas the two groups did not differ on an executive function composite ($p=.37$, $\eta^2=.02$) or on a measure of attention ($p=.56$, $\eta^2=.01$). The TBI group evidenced lower FA in the left cingulum bundle ($p=.01$, $\eta^2=.13$) and in the genu of the corpus callosum ($p=.03$, $\eta^2=.09$). Partial correlations adjusting for age and education showed significant positive associations between psychomotor processing speed and FA in the left cingulum ($r=.38$, $p=.04$), genu ($r=.50$, $p<.01$) and body of the corpus callosum ($r=.52$, $p<.01$), and left posterior internal capsule ($r=.45$, $p=.01$).

Conclusions: Results suggest that the cognitive consequences of TBI may be enduring in veterans, and may be associated with poorer performance in memory and processing speed. Findings further suggest that slowed processing speed may be a consequence of TBI-related damage to anterior white matter pathways.