UNIVERSITY OF CALIFORNIA SAN DIEGO

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Markers of Mild Traumatic Brain Injury: Integration of In Vivo Myelin Imaging, Neuropsychological Measures of Processing Speed, and Subjective Post-concussive Symptoms

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy

in

Clinical Psychology

by

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The Dissertation of Sarah M. Jurick is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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Peer-reviewed articles

Jurick, S. M., Weissberger, G. H., Clark, L. R., Wierenga, C. W., Chang, Y-L., Schiehser, D. M., Han, D. S., Dev, S. I., Jak, A. J., & Bondi, M. W. (2017). Faulty adaptation to repeated face-name pairs in mild cognitive impairment. *Archives of Clinical Neuropsychology.* Advance online publication. doi: https://doi.org/10.1093/arclin/acx056

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Cook, N. E., Terry, D. P., **Jurick, S. M.,** Maxwell, B., Berkner, P. D., & Iverson, G. L. Return to school and sports following concussion in student athletes with attention-deficit/hyperactivity disorder.

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PEER-REVIEWED PRESENTATIONS

Jurick, S. M., Terry, D. P., Cook, N. E., Maxwell, B., Mannix, R., Zafonte, D. O., Berkner, D. O., Iverson, G. L. Association between multiple concussions and return to school and sports in high school and college athletes. Poster presented at the 46th annual International Neuropsychological Society Conference in Washington, D.C.

Jurick, S. M., Crocker, L. D., Keller, A. V., Hoffman, S. N., Thomas, K. R., Boyd, B., Rodgers, C., Twamley, E. W., & Jak, A.J. Can trauma-focused treatment improve poor neuropsychological performance validity in Veterans with PTSD and history of mTBI? Poster presented at the 46th annual International Neuropsychological Society Conference in Washington, D.C.

Crocker, L. D., **Jurick, S. M.,** Thomas, K., Keller, A. V., Sanderson-Cimino, M., Boyd, B., Rodgers, C., Norman, S. B., Lang, A.J., Twamley, E. W., & Jak, A. J. Do TBI injury

characteristics affect PTSD treatment in Veterans with PTSD and a history of TBI? Poster presented at the 46th annual International Neuropsychological Society Conference in Washington, D.C.

Keller, A. V., Crocker, L. D., **Jurick, S. M.,** Sanderson-Cimino, M., Hoffman, S. N., Merritt, V. C., Twamley, E. W., & Jak, A. J. The interactive effects of traumatic brain injury burden and cognitive functioning on suicidal ideation in Veterans. Poster presented at the 46th annual International Neuropsychological Society Conference in Washington, D.C.

Hoffman, S. N., Herbert, M. S., Crocker, L. D., DeFord, N. E., Keller, A. V., **Jurick, S. M.,** Sanderson-Cimino, M., Lee, M., Vasudevan, R. S., & Jak, A. J. The role of pain catastrophizing in cognitive functioning among Veterans with history of mild traumatic brain injury. Poster presented at the 46th annual International Neuropsychological Society Conference in Washington, D.C.

Vasudevan, R. S., Herbert, M. S., **Jurick, S. M.,** DeFord, N. E., Keller, A. V., Hoffman, S. N., Lee, M., Sanderson-Cimino, M., & Jak, A. J. Examination of symptom over-reporting and self-reported pain and depression in Iraq and Afghanistan Veterans with mild traumatic brain injury. Poster presented at the 46th annual International Neuropsychological Society Conference in Washington, D.C.

Crocker, L. D., **Jurick, S. M.,** Keller, A. V., Sanderson-Cimino, M., Thomas, K. R., Boyd, B., Rodgers, C. S., & Twamley, E. W. Worse baseline executive functioning is associated with dropout and poorer response to trauma-focused treatment. Presented at the International Society for Traumatic Stress Studies Conference.

Jurick, S. M., Crocker, L. D., Sanderson-Cimino, M., Keller, A. V., Hoffman, S. N., Rauch, A. A., Trenova, L. S., Boyd, B., Schiehser, D., Aupperle, R., Twamley, E. W., Rodgers, C. S., & Jak, A. J. (2017) Contributions to executive dysfunction in Operation Enduring Freedom/Operation Iraqi Freedom Veterans with post-traumatic stress disorder and traumatic brain injury history. Poster presented at the 45th annual International Neuropsychological Society Conference in New Orleans, LA.

Hoffman, S. N., **Jurick, S. M.,** Crocker, L. D., Steele, N. J., Keller, A. V., Rauch, A. A., DeFord, N. E., Sanderson-Cimino, M., & Jak, A. J. (2017). Patterns of performance and symptom validity tests in Iraq and Afghanistan Veterans with mild traumatic brain Injury History. Poster presented at the 45th annual International Neuropsychological Society Conference in New Orleans, LA.

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Keller, A. V., Crocker, L. D., **Jurick, S. M.,** Bomyea, J., DeFord, N. E., Hays, C. C., Twamley, E. W., & Jak, A.J. (2017). The role of cognitive functioning in suicidal ideation in Veterans with a history of mild traumatic brain injury and comorbid psychiatric conditions. Poster presented at the 45th annual International Neuropsychological Society Conference in New Orleans, LA.

Rauch, A. A., Hoffman, S. N., **Jurick, S. M.,** Keller, A. V., Sanderson-Cimino, M., Johnson, C., Trenova, L., Crocker, L., Boyd, B. L., & Jak, A. J. (2016). Examination of social relations and working memory in Iraq and Afghanistan Veterans with a history of mild to moderate TBI and PTSD. Poster presented at the 2016 American Psychological Association Annual Convention, Denver, CO.

Keller, A. V., **Jurick, S. M.,** DeFord, N. E., Sanderson-Cimino, M. E., Crocker, L. D., Rauch, A. A., Hoffman, S. N., Trenova, L. S., Boyd, B. L., Jak, A. J. (2016). Depressive symptom clusters and cognitive functioning in OEF/OIF Veterans with comorbid PTSD/TBI. Poster presented at the 2016 American Psychological Association Annual Convention, Denver, CO.

Jurick, S. M., Sanderson, M., Crocker, L. D., Johnson, C., Trenova, L. S., Keller, A. V., Rauch, A. A. & Jak, A. J. (2016). Examination of cut scores on the validity subscale of the Neurobehavioral Symptom Inventory in Iraq and Afghanistan Veterans with a history of mild to moderate traumatic brain injury. Poster presented at the 44th International Neuropsychological Society Conference and the 11th Annual Lewis L. Judd Young Investigators Symposium.

Crocker, L. D., **Jurick, S. M.,** Hays, C. C., & Jak, A. J. (2016). The role of depression and PTSD symptoms in cognitive functioning in Veterans with a history of mild traumatic brain injury. Poster presented at the 44th International Neuropsychological Society Conference.

Sanderson-Cimino, M., **Jurick, S. M.,** Crocker, L. D., Keller, A. V., Rauch, A., Johnson, C., & Jak, A. J. (2016). Use of the TOMM response consistency indices in Veterans with a history of mild traumatic brain injury and post traumatic stress disorder. Poster presented at the 44th International Neuropsychological Society Conference.

Crocker, L. D., **Jurick, S. M.**, Boyd, B., Rodgers, C. S., Twamley, E. W., Schiehser, D. M., & Jak, A. J. (2015). Treatment of Veterans with comorbid PTSD and TBI using a hybrid approach. Paper presented at the Anxiety and Depression Conference, April 2015.

Weissberger, G.H., Gollan, T. H., Bondi, M. W., Mizrahi, R., **Jurick, S. M.**, & Salmon, D. P. (2015). Longitudinal semantic fluency performance in Hispanic older adults in the early stages of Alzheimer's disease. Poster presented at the 43rd International Neuropsychological Society Conference.

Jurick, S. M., Sanderson-Cimino, M., Trenova, L. S., Boyd, B. L., Schiehser, D. M., Delano-Wood, L., Aupperle, R., Twamley. E. W., Rodgers, C. S. & Jak, A. J. (2015). Mental health treatment reduces post-concussive symptoms and symptom overreporting in Iraq

and Afghanistan Veterans. Poster presented at the 43rd International Neuropsychological Society Conference.

Ewald, I. J., Bangen, K. J., Clark, L. R., Nation, D. A., Wierenga, C. E., Weissberger, G. H., **Jurick, S. M.**, Dev, S. I., Sanderson-Cimino, M. E., and Bondi, M. W. (2014). Reduced cerebral blood flow predicts subsequent cognitive decline in older adults: An arterial spin labeling MRI study. Poster presented at the 42nd International Neuropsychological Society Conference.

Clark, L. R., Weissberger, G. H., **Jurick, S. M.,** Chang, Y-L., Schiehser, D. M., Wierenga, C. W., Han, D. S., Gravano, J. T., Dev, S. I. and Bondi, M. W. (2014). Faulty adaptation to repeated face-name pairs in mild cognitive impairment. Poster presented at the 42nd International Neuropsychological Society Conference.

Jurick, S. M., Rosen, J. W, and Jak, A. J. (2014). The factor structure of the NSI in a treatment seeking cohort of Veterans. Poster presented at the 42nd International Neuropsychological Society Conference.

Jurick, S. M., Hays, C. C., Orff, H. J., Twamley, E. W., and Jak, A. J. (2014). Post-concussive symptom over-reporting in Iraq and Afghanistan Veterans. Poster presented at the 42nd International Neuropsychological Society Conference.

Jurick, S. M., Colon, C., Orff, H. J., Hays, C. C., Gregory, A., Twamley, E. W., and Jak, A.J. (2013). Cognitive profiles of mild to moderate Traumatic Brain Injury in Iraq and Afghanistan veterans. Poster presented at the 41st International Neuropsychological Society Conference.

Clark, L. R., Delano-Wood, L. M., Libon, D. J., **Jurick, S. M.**, Lanni, E. B., and Bondi, M.W. (2012). Distinct neuropsychological profiles of Mild Cognitive Impairment: Effects of MCI classification scheme on empirically derived subgroups. Poster presented at the International Conference on Alzheimer's Disease.

Clark, L. R., Wierenga, C. E., Dev, S. D., Shin, D., **Jurick, S**. **M.**, Rissman, R., Liu, T. T., and Bondi, M. W. (2012). Differential effects of aging and APOE genotype on cerebral blood flow at rest. Poster presented at the 40th International Neuropsychological Society Conference.

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ABSTRACT OF THE DISSERTATION

Markers of Mild Traumatic Brain Injury: Integration of In Vivo Myelin Imaging, Neuropsychological Measures of Processing Speed, and Subjective Post-concussive Symptoms

by

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Doctor of Philosophy in Clinical Psychology

University of California San Diego, 2018
San Diego State University, 2018

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Rationale: A subset of Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) Veterans who incur a mild traumatic brain injury (mTBI) experience persisting post-concussive symptoms (PCS) and objective cognitive deficits (e.g., slowed processing speed). However, these symptoms are not unique to mTBI; overlapping symptoms and similar cognitive deficits are also observed in post-traumatic stress disorder (PTSD), depression, and after deployment and blast exposure not resulting in mTBI, all of which are common for OEF/OIF Veterans. Although advanced neuroimaging techniques have improved our understanding of white matter changes after mTBI, measuring myelin integrity has the potential to be a sensitive

and specific measure of slowed processing speed and PCS related to mTBI, and to help disentangle these symptoms from conditions with overlapping features.

Design: Utilizing a novel neuroimaging method, multicomponent-driven equilibrium single-pulse observation of T1 and T2 (mcDESPOT), the present study aimed to assess the relationship between myelin integrity and 1) injury variables (i.e., number of TBIs, loss of consciousness and post-traumatic amnesia, blast-related TBI), 2) cognitive variables including objective tests of working memory/attention that require speeded processing and simple measures of processing and motor speed (n = 4), and 3) subjective PCS in OEF/OIF combat Veterans with and without TBI history. This cross-sectional study assessed 57 OEF/OIF Veterans with history of mTBI (n = 31), history of moderate TBI (n = 4), or without history of TBI (n = 22). Across the entire sample, the prevalence of PTSD was 52.6%. Groups did not significantly differ with regard to presence/severity of current PTSD or depression, self-reported alcohol use (current substance use disorder was exclusionary), or demographic variables. Myelin integrity was measured using mcDESPOT's myelin water fraction (MWF) across multiple regions-of-interest (ROIs) in fronto-striatal and fronto-limbic circuits, and callosal fibers. Veterans were administered a comprehensive battery of neuropsychological tests including measures of simple and complex processing speed as well as PCS. Using partial correlations and multiple linear regression, relationships between myelin integrity and 1) injury variables, 2) cognition, and 3) subjective persistent PCS in the context of PTSD and depression were assessed.

Results: There were no differences between the combat comparison (CC), mTBI, or moderate TBI (modTBI) groups with respect to myelin integrity or cognitive performance. However, PTSD was significantly and positively associated with MWF. Injury variables demonstrated inconsistent relationships with myelin integrity, such that number of TBIs and

blast-related mTBI were positively associated with MWF, although the majority of these relationships did not survive Bonferroni correction and/or remain significant once controlling for PTSD. Significant and positive relationships were observed between MWF and objective cognitive measures (most notably a measure of speeded attention and processing) across multiple ROIs, when controlling for psychiatric diagnoses and/or symptoms. Furthermore, the relationship between MWF and cognition was significant within the mTBI, but not the CC group. Finally, no significant relationships were observed between MWF and PCS after controlling for psychiatric symptoms and/or diagnoses.

Conclusions: Given the prevalence of TBI and psychiatric comorbidities in OEF/OIF Veterans, the identification of reliable and objective biomarkers of brain damage after mTBI would provide the foundation for more accurate diagnosis of nonspecific symptoms, prognosis, and therapeutic opportunities. Results suggest that assessing myelin integrity using mcDESPOT may be a useful tool in delineating nonspecific reports of cognitive difficulties occurring after TBI in the context of commonly comorbid psychiatric disorders.

I. INTRODUCTION

Of the nearly than 400,000 traumatic brain injuries (TBI) diagnosed since the inception of Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF), approximately 82% are classified as mild (Defense and Brain Injury Center, 2017; Helmick et al., 2015). Mild TBI (mTBI) is characterized by a relatively brief loss of consciousness (LOC) and period of post-traumatic amnesia (PTA) compared to moderate and severe TBI, as well as anticipation of a complete recovery of any post-concussive symptoms (PCS) or objective cognitive impairment (e.g., memory, attention/working memory, processing speed deficits) for the large majority of people (95-97%) within days to weeks post-injury (Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005; McCrea, 2008; Schretlen & Shapiro, 2003). Nevertheless, self-report of persistent PCS and subtle objective cognitive difficulties have been observed months to years following mTBI (Lew, Tun, & Cifu, 2009; Vanderploeg, Curtiss, & Belanger, 2005), especially if multiple TBIs were incurred (Belanger, Spiegel, & Vanderploeg, 2010; Spira, Lathan, Bleiberg, & Tsao, 2014). For example, one study found that 67% OEF/OIF Veterans reported three or more PCS persisting longer than three months following mTBI (Lew et al., 2009).

Nearly 90% of OEF/OIF Veterans with history of TBI also carry a psychiatric diagnosis, most commonly post-traumatic stress disorder (PTSD) and/or depression which share many of the same somatic, cognitive, and affective features as PCS (Taylor et al., 2012). Further, various factors such as deployment, combat intensity, and blast exposure are also associated with PCS and/or objective cognitive impairment, even when a TBI did not occur (Franke, Czarnota, Ketchum, & Walker, 2014; Neipert et al., 2014; Vasterling & Proctor, 2011; Vasterling et al., 2006). Thus, cognitive impairments and persistent PCS, which are non-specific to mTBI (e.g., difficulty making decisions, slowed thinking, fatigue, irritability, frustration), are thought to be

more related to factors such as emotional distress, physical injuries, and/or iatrogenic consequences rather than the mTBI itself (Meares et al., 2011; Polusny et al., 2011; Roth & Spencer, 2013; Vanderploeg & Belanger, 2013; Vanderploeg et al., 2012).

The non-specific nature of PCS (Iverson, 2005), taken together with other factors commonly present in OEF/OIF Veterans such as frequent lack of documentation regarding details of their injuries (Pape et al., 2013), sustaining multiple mTBIs (Galarneau, Woodruff, Dye, Mohrle, & Wade, 2008), and high rates of pain and substance abuse (Calhoun, Elter, Jones, Kudler, & Straits-Tröster, 2008; Cifu, Scholten, & Campbell, 2013; Hawkins, Lapham, Kivlahan, & Bradley, 2010), have further complicated the study of mTBI sequelae in OEF/OIF Veterans. Nonetheless, history of mTBI is related to poorer mental health, physical health, and negative psychosocial outcomes such as self-reported disability, underemployment, low income, and marital problems (Gill et al., 2014; Vanderploeg, Curtiss, Luis, & Salazar, 2007; Zumstein et al., 2011). Further, the median annual cost per patient at the Veterans Health Administration is nearly four times higher for OEF/OIF Veterans with TBI history than those without (Taylor et al., 2012). The high rates and costs associated with TBI in OEF/OIF Veterans (Stroupe et al., 2012), taken together with emerging evidence that repeated concussions or even subconcussive blows to the head may be a risk factor for chronic traumatic encephalopathy (Baugh et al., 2012; McKee & Robinson, 2014), suggest that even a small percentage of individuals with protracted recovery represent a major public health concern.

Advanced neuroimaging techniques such as diffusion tensor imaging (DTI) have detected evidence of long-lasting changes in white matter tracts critical for processing speed (PS) required for attention and working memory after mTBI (Eierud et al., 2014; Hayes, Bigler, & Verfaellie, 2016). However, DTI has yielded inconsistent results in those with mTBI, and has not been able

to add diagnostic clarification regarding the etiology of cognitive deficits or PCS following mTBI (Toth, 2015). A recently developed neuroimaging method, multicomponent-driven equilibrium single-pulse observation of T1 and T2 (mcDESPOT) (Deoni, 2011; Deoni, Rutt, Arun, Pierpaoli, & Jones, 2008), holds promise as a useful technique to study myelin integrity after mTBI, which may be responsible for the slowed processing speed that results from shearing of axons resultant from mTBI. Examining myelin integrity after mTBI using mcDESPOT, as well as its relationships with deployment and injury variables, PCS, and speeded attention and processing has the potential to aid in the identification of an objective biomarker of myelin damage associated with persistent symptoms after mTBI and would provide foundation for more accurate injury severity grading, prognosis, and therapeutic opportunities.

Cognition in OEF/OIF Veterans

Since 2001, over two million military service members have been deployed in support of OEF/OIF (Bass & Golding, 2012). Cognitive impairment has been observed after deployment in at least a small subset of OEF/OIF (Vasterling et al., 2006; Vincent et al., 2012) and other era service members and Veterans (Chao, Abadjian, Hlavin, Meyerhoff, & Weiner, 2011; Hom, Haley, & Kurt, 1997), and has the potential to impact social and occupational functioning (Kalechstein, Newton, & Van Gorp, 2003; Machamer, Temkin, Fraser, Doctor, & Dikmen, 2005; Papero, Howe, & Reiss, 1992) and overall quality of life (Martindale et al., 2016). Risk factors for cognitive impairment during deployment include chemical warfare, environmental pollutants, physical and psychological stress, and TBI (Karr, Areshenkoff, Duggan, & Garcia-Barrera, 2014; Vasterling & Proctor, 2011). Interestingly, improved simple reaction time has been observed acutely after deployment even when accounting for deployment-related head injury, psychological stress, and depression (Vasterling et al., 2006), possibly due to altered

physiological responses following repeated exposure to life-threatening situations. It is likely that any acute gains or losses in neuropsychological functioning related to general deployment factors are transient but deficits may persistent in the context of TBI (Haran et al., 2013; Roebuck-Spencer et al., 2012), psychological distress (Lewis & Bowles, 2014), or when there is an interaction between the two (Combs et al., 2015; Nelson, Yoash-Gantz, Pickett, & Campbell, 2009), although these findings have not been universally replicated (Brenner et al., 2009; Ettenhofer & Abeles, 2009; Troyanskaya et al., 2015).

TBI. Approximately 15-23% of OEF/OIF Veterans screen positive for TBI history in the Department of Defense (DOD) and Veterans Affairs (VA) systems (Evans et al., 2013; Hoge et al., 2008; Sayer, Nelson, & Nugent, 2011; Terrio et al., 2009). The large number of Veterans returning with TBIs may be due to advances in body armor and increased survival rates after severe bodily injuries as compared to previous wars (Warden, 2006). Only about 1% of TBIs incurred meet criteria for severe TBI, 1.4% are penetrating injuries, and the vast majority are mild (82.4%), defined as a confused or disoriented state which lasts less than 24 hours and loss of consciousness that lasts up to 30 minutes with no findings on traditional neuroimaging (Defense and Brain Injury Center, 2015; VA/DoD, 2016).

Deficits in processing speed, attention/working memory, executive functioning, and episodic memory have been detected acutely after mTBI (Landre, Poppe, Davis, Schmaus, & Hobbs, 2006; Luethcke, Bryan, Morrow, & Isler, 2011; McAllister & Arciniegas, 2002), and resolve for the majority of people within three months post-injury (Dikmen, Machamer, Winn, & Temkin, 1995; Schretlen & Shapiro, 2003). The prevalence and extent to which these deficits persist past the window of expected recovery after mTBI is unclear. One meta-analysis demonstrated moderate to large effect sizes for persistent neuropsychological impairment in

clinic-based and litigation samples but no residual neuropsychological impairment in prospective or unselected samples three months post-injury (Belanger et al., 2005). Persisting neuropsychological impairment has also been observed in OEF/OIF military service members and Veterans (Karr, Areshenkoff, Duggan, et al., 2014; Peskind et al., 2011), although a number of studies have failed to find any evidence of lasting cognitive impairment after mTBI (Ivins, Kane, & Schwab, 2009; Neipert et al., 2014; Troyanskaya et al., 2015). There is some evidence that multiple mTBIs results in longer lasting cognitive impairment than a single mTBI (Belanger et al., 2010), but this finding is also not universal (Iverson, 2006). A recent systematic review of eleven meta-analyses indicated that although the majority of studies reported complete recovery by 90 days, the strongest effects of cognition were within the domain of executive functioning and various factors such as multiple mTBIs may contribute to persistent cognitive symptoms (Karr, Areshenkoff, & Garcia-Barrera, 2014). However, Karr, Areshenkoff, and Garcia-Barrera (2014) did encourage caution while interpreting their results due to methodological flaws inherent to meta-analyses (e.g., heterogeneous samples, publication bias, and sampling bias), and meta-analyses have been demonstrated to obscure sub-group or individual effects that may be present (Iverson, 2010; Pertab, James, & Bigler, 2009; Rohling, Larrabee, & Millis, 2012). Within the domain of executive functioning, tests of complex attention/working memory or set-shifting which require speeded processing are likely the most commonly impaired post-acutely after a single (Crawford, Knight, & Alsop, 2007; Demery, Larson, Dixit, Bauer, & Perlstein, 2010; Rohling et al., 2011; Stuss et al., 1985) or multiple mTBIs (Karr, Garcia-Barrera, & Areshenkoff, 2014; Moser & Schatz, 2002; Wall et al., 2006).

Although the reasons for persistent neurocognitive impairment after mTBI are likely multifactorial, there is evidence that they have at least some dose-response relationships with

injury variables (e.g., greater neurocognitive impairment after multiple mTBIs, and after LOC as opposed to just an alteration of consciousness [AOC]), especially within the domains of processing speed and speeded tests of executive functioning (Dams-O'Connor et al., 2013; Kalkstein et al., 2016; Kontos et al., 2013; Sorg et al., 2014; Spira et al., 2014). However, psychiatric factors are also strongly associated with neuropsychological functioning in this population (Barker-Collo et al., 2015; Lewis & Bowles, 2014; Verfaellie, Lafleche, Spiro III, & Bousquet, 2014), and injury variables appear to be more related to subjective cognitive complaints rather than objective cognitive performance (Drag, Spencer, Walker, Pangilinan, & Bieliauskas, 2012). Although there is some accruing concern that repetitive subconcussive blows may increase the risk for neuropsychological impairment or other neurofunctional changes, there is limited evidence to support that in the literature to date (Belanger, Vanderploeg, & McAllister, 2015; Brokaw et al., 2017; Kuzminski et al., 2018; Mainwaring, Ferdinand Pennock, Mylabathula & Alavie, 2018; Reynolds et al., 2017). However, given the high number of blast exposures and mTBIs OEF/OIF Veterans report (Karr, Areshenkoff, Duggan, et al., 2014), it is an important area of research to explore.

Blast exposure. The most common cause of any physical injury in the recent conflicts in Iraq and Afghanistan are explosions (Gondusky & Reiter, 2005; Owens, Kragh, Macaitis, Svoboda, & Wenke, 2007). The majority (70-72%) of OEF/OIF Veterans report that blast was the primary injury source of their mTBI, and 86.9% reported exposure to two or more blasts during combat deployment (Hoge et al., 2008; Wilk et al., 2010). In fact, recent studies indicate that on average, OEF/OIF Veterans report over 13 mTBIs (Matthews, Spadoni, Lohr, Strigo, & Simmons, 2012; Nelson et al., 2012; Peskind et al., 2011; Petrie et al., 2014) and/or blast exposures (Fortier et al., 2014). Blast injuries can be caused by rocket shells, grenades, and most

commonly, improvised explosive devices (IEDs; Campbell & O'Hanlon, 2008). Damage to the brain may be caused by a change in atmospheric pressure from the blast overpressurization wave (i.e., primary blast injury), rapidly propelled objects such as shrapnel (i.e., secondary blast injury), or as a result of the force of the overpressurization wave propelling the body into a solid object or the ground (i.e., tertiary blast injury; Elder & Cristian, 2009). Miscellaneous causes of injury (e.g., structures falling, exposure to toxins or radiation, or burns) are considered quaternary blast injuries (Pennardt & Lavonas, 2009). Although the mechanisms by which primary blast injury causes brain tissue damage are still not entirely understood, it has been posited that damage to the cerebral vasculature is caused by arterial air emboli (Dennis & Kochanek, 2007) or a surge in arterial or venous pressure in blood vessels of the brain (Cernak, Wang, Jiang, Bian, & Savic, 2001a). Another possibility is that the rapid acceleration of the blast wave causes a collision of the brain into the skull, similar to what is observed in a coup and contre-coup injury (Dennis & Kochanek, 2007). Because white matter has different physicochemical properties than gray matter (e.g., tissue density and distribution, energy consumption rates), it is affected differently by blasts (Chafi, Karami, & Ziejewski, 2010). In fact, junctions between differing biological materials are disproportionately damaged in blast injuries (Cernak & Noble-Haeusslein, 2010; Chavko et al., 2011; Ganpule, Alai, Plougonven, & Chandra, 2013; Nakagawa et al., 2011). Although the type of helmets used by OEF/OIF Veterans help protect against blunt forces, a simulation study demonstrated that they may not provide any more protection from blast forces than the skull alone (Nyein et al., 2010).

Animal models have provided useful information regarding the pathophysiology of injury incurred via blast exposure. For example, studies using rats have demonstrated that a primary blast injury can cause abnormalities of neurons, glia, and myelin, as well as behavioral changes

(Cernak et al., 2001a; Cernak, Wang, Jiang, Bian, & Savic, 2001b; Säljö, Bao, Haglid, & Hansson, 2000). Furthermore, these changes have been observed even at lower blast pressures (Moochhala, Md, Lu, Teng, & Greengrass, 2004) and are more pronounced after repeated injuries (Ahlers et al., 2012). Because factors such as head size, head shape, skull thickness, and elasticity cause primary blast injury to affect primates differently than rodents (Agoston & Kamnaksh, 2015), blast models have also been applied to non-human primates such as monkeys and have demonstrated similar results (Lu et al., 2012). Rat models have also shown that blast injury increases vulnerability to PTSD (Elder et al., 2012), although this may be a transient effect (Kwon et al., 2011). Recent public attention has focused on the idea that multiple blast exposures without AOC can cause brain dysfunction, though there is limited empirical data supporting this hypothesis (Howe, 2009).

Animal studies have provided evidence that primary blast waves can impact the brain, however, extrapolations from animal research to humans is limited by anatomical and methodological differences between the two (Bauman et al., 2009; Sips, Mulder, Koolstra, & van Eijden, 2008). Although there is some theoretical (Ling, Bandak, Armonda, Grant, & Ecklund, 2009) and empirical evidence in animals (Begonia et al., 2014) to suggest that blast and non-blast mTBI may differentially impact the central nervous system, evidence for structural differences between blast versus non-blast mTBI mechanisms is mixed (Goldstein et al., 2012; Jorge et al., 2012; Yeh et al., 2014), though a number of studies have shown differences between the two using functional neuroimaging (Fischer et al., 2014; Mendez et al., 2013; Newsome et al., 2015). Behaviorally, the vast majority of human studies suggest that cognitive impairment does not differ based on mechanism of injury (Belanger, Kretzmer, Yoash-Gantz, Pickett, & Tupler, 2009; Cooper, Chau, Armistead-Jehle, Vanderploeg, & Bowles, 2012; Lange et al., 2012;

Luethcke et al., 2011). However, there is at least some evidence that blast mTBI in combination with blunt force mechanisms confers additional risk for visual memory and reaction time deficits than mTBI via blunt force mechanisms alone (Kontos et al., 2013), and that Veterans with a history of exposure to blasts at close range have poorer verbal memory than those with non-close-range blast exposure regardless of whether a concussion was incurred (Grande et al., 2018). Additionally, there is some evidence that certain physical (e.g., headaches, tinnitus) and psychological (e.g., post-traumatic stress) symptoms may be more prevalent when mTBI is related to blast rather than non-blast mechanisms (Belanger et al., 2009; Wilk et al., 2010). In fact, PTSD may be associated with white matter alterations (Bazarian et al., 2013), PCS (Schneiderman, Braver, & Kang, 2008), and cognitive impairment (Storzbach et al., 2015) to a greater extent than blast mTBI itself.

Stress exposure and PTSD. PTSD occurs after exposure to a psychologically traumatic event (e.g., actual or threatened death, serious injury, sexual violence), and is characterized by intrusive re-experiencing of the event, negative alterations in mood and thought, hypervigilance, and avoidance of stimuli associated with the traumatic event (American Psychiatric Association, 2013). PTSD is estimated to occur in 12-30% of OEF/OIF service members and Veterans (Higgins et al., 2014; Hoge et al., 2004; Seal et al., 2009; Thomas et al., 2010), although prevalence estimates vary widely based on the methodology used to assess PTSD in each study (Sundin, Fear, Iversen, Rona, & Wessely, 2010). In a recent study by Lippa et al. (2015), history of military mTBI increased odds of a PTSD diagnosis by 300% and depressive disorders, pain, and sleep disturbance by at least 140% (Lippa et al., 2015). In fact, PTSD is the most common psychiatric comorbidity of mTBI (Carlson et al., 2011; Chapman & Diaz-Arrastia, 2014; French, Iverson, Lange, & Bryant, 2011) and has been shown to mediate the relationship between TBI

and poor functional outcomes (Hoge et al., 2008; Ragsdale, Neer, Beidel, Frueh, & Stout, 2013). PTSD has been associated with a number of structural and functional abnormalities in various regions within the frontal and temporal lobes (Li et al., 2016a; Sussman, Pang, Jetly, Dunkley, & Taylor, 2016; Zhang et al., 2016), as well as objective cognitive difficulties in the domains of memory, executive functioning, attention, and speed of processing (Aupperle, Melrose, Stein, & Paulus, 2012; Scott et al., 2014). It is possible that PTSD accounts for cognitive test performance to a greater degree than mTBI (Drag et al., 2012; Neipert et al., 2014; Shandera-Ochsner et al., 2013; Storzbach et al., 2015), with some studies finding PTSD and mTBI to have independent or synergistic negative effects on cognition (Combs et al., 2015; Dolan et al., 2012; Nelson et al., 2012), and others not (Soble, Spanierman, & Fitzgerald Smith, 2013; Vasterling et al., 2012).

The mechanisms by which PTSD and mTBI interact to cause poor functional outcomes are not entirely clear, but it has been proposed that mTBI may cause further damage to already abnormal circuits that regulate fear via the prefrontal cortex (Bryant, 2011; Vasterling, Verfaellie, & Sullivan, 2009). It is also possible that mTBI depletes cognitive resources to handles stressors (Bryant, 2011). Interestingly, even chronic stress that does not reach the level of PTSD has been associated with neurocognitive deficits and functional brain changes (van Wingen et al., 2012; Vasterling & Proctor, 2011). Regardless of whether PTSD confers additional risk for impaired cognition in the context of mTBI, the common comorbidity of PTSD and history of mTBI have caused issues with diagnostic accuracy of persistent PCS. This is especially relevant in Veterans who are seeking treatment months to years after mTBI in which details regarding the injury may be incomplete or incorrect, as LOC or altered mental state can occur as a result of dissociation in the context of emotional trauma (Bremner et al., 1992). Within OEF/OIF Veterans, depression is also highly comorbid with PTSD (Walker, Franke,

McDonald, Sima, & Keyser-Marcus, 2015), and the combination of mTBI history, PTSD, and depression may be the most clinically impairing (Haagsma et al., 2015; Seal et al., 2016).

Depression. Depression is a mood disorder characterized by somatic, affective, and cognitive symptoms (American Psychiatric Association, 2013). Within individuals with depression, cognitive impairment has been identified in the domains of inhibition and working memory (Gohier et al., 2009), verbal fluency (Henry & Crawford, 2005), learning and memory (Porter, Gallagher, Thompson, & Young, 2003), processing speed (Tsourtos, Thompson, & Stough, 2002), and executive functioning (Snyder, 2013). A diagnosis of PTSD and history of mTBI have both been shown to confer additional risk for depression (Guskiewicz et al., 2007; Rapoport, 2012; Walker et al., 2015). History of mTBI and depression results in additional risk for poor neuropsychological performance (Levin et al., 2001); structural (Isaac et al., 2015; Maller et al., 2014; Matthews et al., 2011) and functional (Banks et al., 2016) brain changes may underlie these cognitive symptoms. As with PTSD, cognitive impairments and other symptoms of depression have significant overlap with those observed after mTBI, and its presence can also cause difficulty determining the etiology of persistent symptoms in those with history of mTBI (Iverson, 2006).

Other factors related to cognition. Other factors such as sleep problems, pain, and substance abuse are also highly prevalent in OEF/OIF Veterans with and without mTBI history (Bryan, 2013; Gilbert, Kark, Gehrman, & Bogdanova, 2015; Lippa et al., 2015; Stojanovic et al., 2016) and are associated with objective cognitive changes (Daniel & Woods, 2014; Hart, Wade, & Martelli, 2003; Moriarty, McGuire, & Finn, 2011), or at least subjective cognitive complaints (Orff, Drummond, Nowakowski, & Perlis, 2007). Threats to adequate performance on neuropsychological tests also need to be considered during neuropsychological evaluations

(Nelson et al., 2010), especially in mTBI cases where there are high rates of performance validity test failure (Jak et al., 2015). Although relationships between objective cognitive performance and subjective PCS are inconsistent at best (Drag et al., 2012; Lewis & Bowles, 2014; Schiehser et al., 2011), Veterans have been shown to report greater persistent PCS after mTBI than civilians (Bolzenius, Roskos, Salminen, Paul, & Bucholz, 2015), and persistent PCS are predictive of poorer quality of life (Schiehser et al., 2015).

Self-reported PCS. Cognitive, affective, vestibular, and somatic PCS (e.g., headache, dizziness, fatigue, difficulty concentrating) are common and expected acutely after mTBI and typically resolve within 1 to 2 months for the vast majority of individuals (Yang, Tu, Hua, & Huang, 2007). However, a portion of civilians, military service members, and Veterans continue to report PCS past the expected window of recovery (Carroll et al., 2004; Dretsch, Silverberg, & Iverson, 2015; Lew et al., 2009). Prevalence estimates of persistent PCS vary widely, with anywhere from 7.5 to 67% of OEF/OIF Veterans reporting at least three PCS more than three months post-injury (Lew et al., 2009; Morissette et al., 2011; Schneiderman et al., 2008; Terrio et al., 2009). With regard to specific symptoms, a recent study reported that after controlling for socio-demographic and comorbid behavioral health conditions, vestibular symptoms (dizziness, balance problems, and coordination difficulties) are reported with the greatest frequency in OEF/OIF Veterans with mTBI history compared to those without mTBI history (Baldassarre et al., 2015). However, another study that did not control for these factors found that vestibular symptoms were reported the least, with affective symptoms (fatigue, sleep problems, anxiety, sadness, irritability) reported most frequently and cognitive (concentration, forgetfulness, decision-making, slowed thinking) and somatic (headaches, nausea, vision problems, light sensitivity, noise sensitivity, numbness, and change in taste and smell) symptoms moderately

endorsed (Soble et al., 2014). Factors associated with persistent reporting of PCS include many of the same factors that also contribute to neuropsychological deficits after mTBI such as pre- and post-injury psychological symptoms and characteristics (Cooper et al., 2011; Greiffenstein & Baker, 2001; Lee, Garber, & Zamorski, 2015; Nelson et al., 2016; Schneiderman et al., 2008; Seal et al., 2016), history of deployment (Soble et al., 2014), combat stress (Cooper et al., 2011), secondary gain (Binder & Rohling, 1996; Paniak et al., 2002), and possible iatrogenic and expectation effects (Gunstad & Suhr, 2004; Roth & Spencer, 2013; Vanderploeg & Belanger, 2013). Although some have suggested that psychiatric factors such as PTSD account for persistent PCS reporting almost entirely (Schneiderman et al., 2008), others have found that mTBI and PTSD contribute independently to PCS reporting and thus the effects of mTBI and PTSD may be additive (Vanderploeg, Belanger, & Curtiss, 2009).

Although demographic (e.g., age, gender), and injury variables (e.g., presence and duration of LOC and PTA) have shown weak associations with persistent PCS (Petrie et al., 2014), these findings are inconsistent and largely disappear when psychiatric symptoms are accounted for (Drag et al., 2012; Thornhill et al., 2000; Waldron-Perrine, Hennrick, Spencer, Pangilinan, & Bieliauskas, 2014). History of multiple mTBIs has been associated with greater reporting of persistent PCS (Spira et al., 2014), with headache remaining a significant symptom even when controlling for psychiatric factors (Wilk, Herrell, Wynn, Riviere, & Hoge, 2012). However, even for those with history of multiple mTBIs, symptoms of post-traumatic stress mediate the association between mTBI and PCS (Dretsch et al., 2015). Similar to objective cognitive performance, whether self-reported PCS is greater in those with blast-related mTBI compared to non-blast mechanisms remains equivocal (Belanger et al., 2011; Mendez et al., 2013). However, those with a history of blast-related mTBI do report greater sensory symptoms

than those with history of blast exposure but no mTBI (Callahan et al., 2018), and greater post-traumatic stress symptoms than those with a history of mTBI from non-blast mechanisms (Lippa, Pastorek, Benge, & Thornton, 2010). Given the non-specificity of persistent PCS and cognitive declines after mTBI, advanced neuroimaging techniques that can detect microstructural white matter changes have potential to aid diagnosis and provide information about etiology and prognosis for this population.

White matter imaging in mTBI

Neuroimaging has the potential to add clarity in determining the etiology of persistent symptoms in OEF/OIF Veterans with a history of mTBI which can be challenging given the frequency with which mental health disorders (e.g., PTSD, depression, and substance abuse) are comorbid with mTBI. Additionally, neuroimaging may aid in improving prognostic information provided to patients as there is often incomplete or inaccurate historical data used as predictors of outcome in this population (e.g., duration of LOC, PTA, and Glasgow Coma Scale) especially when injuries were sustained in combat. Finally, neuroimaging has the potential to detect existing vulnerabilities to mTBI effects, inform rehabilitation strategies and pharmacological interventions, and expand the understanding of the potential late effects of trauma, blast exposure and mTBI via blast mechanisms, as well as dose-response relationships with injury variables (Wilde et al., 2015).

White matter is particularly vulnerable to disruption from rapid acceleration and deceleration forces and secondary neurometabolic cascades after TBI (Büki & Povlishock, 2006; Park, Bell, & Baker, 2008), and can occur even after mild forms of neurotrauma (Bigler, 2001; Oppenheimer, 1968). TBI has long been characterized as a disorder of white matter (Johnson, Stewart, & Smith, 2013; Peerless & Rewcastle, 1967; Smith, Meaney, & Shull, 2003; Strich,

1956), and abnormalities in white matter connecting specific neural networks likely underlie cognitive changes (Hayes et al., 2016). Historically TBI was thought to cause structural damage to the axon at the time of injury, however, more recently it is becoming clear that axonal swelling and secondary axotomy, termed traumatic axonal injury (TAI), is common after mTBI (Hurley, McGowan, Arfanakis, & Taber, 2009) and can continue to occur days to months after injury in humans (Blumbergs et al., 1995). Because most mTBIs are non-hemorrhagic, conventional neuroimaging modalities (e.g., computerized tomography and structural magnetic resonance imaging) are not sensitive to detect small clusters of damaged axons that result from TAI (Taber & Hurley, 2013). Advanced neuroimaging techniques such as DTI have shown promise in detecting subtle changes in white matter integrity (WMI) even post-acutely after TBI (Fakhran, Yaeger, & Alhilali, 2013; Geary, Kraus, Pliskin, & Little, 2010; Lipton et al., 2008), and have improved our understanding of the pathophysiology of mTBI (Hulkower, Poliak, Rosenbaum, Zimmerman, & Lipton, 2013; Shenton et al., 2012). However, various issues such as inconsistent findings in individuals with mTBI, inconsistent relationships to injury, cognitive, and emotional symptoms, and difficulty interpreting DTI measures have limited its utility in the present population (Laule et al., 2006; Wright et al., 2016).

DTI. DTI is a non-invasive technique that is sensitive to diffusion of water molecules (Jones, 2008). When there is damage to an axon and/or myelin, water movement is less restricted because the membrane has become leaky, sheared, or has broken down. DTI studies have most consistently reported reduced WMI in long white matter tracts that connect the anterior and posterior regions of the brain including the corpus callosum and other frontal association pathways (e.g., cingulum bundle, anterior corona radiata, uncinate fasciculus, superior longitudinal fasciculus) acutely and chronically after mTBI in civilian, military, and Veteran

samples (Chong & Schwedt, 2018; Eierud et al., 2014; Shenton et al., 2012). However, not all studies have found differences even acutely after mTBI (Davenport, Lim, & Sponheim, 2015b; Levin et al., 2010; Zhang et al., 2010). Two of the most frequently used DTI metrics to quantify white matter pathology are the apparent diffusion coefficient (ADC), and fractional anisotropy (FA). Other metrics include mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD). FA is likely the most commonly used DTI metric and describes the degree to which the displacement of water is directionally dependent. Values can range from zero (diffusion is isotropic or unrestricted) to one (diffusion is restricted and occurs only along one axis), with higher values indicating strong anisotropy and subsequently more intact microstructure, although abnormally high values may be indicative of inflammation (Bramlett & Dietrich, 2015). However, both decreased (Lipton et al., 2009; Miles et al., 2008; Niogi et al., 2008) and increased (Bazarian et al., 2007; Lo, Shifteh, Gold, Bello, & Lipton, 2009; Mayer, Mannell, Ling, Gasparovic, & Yeo, 2011) FA has been observed when comparing control to groups with history of mTBI. Although there is some evidence to suggest that increased FA is more frequent in acute samples whereas reduced FA is a more chronic response (Chong & Schwedt, 2018; Eierud et al., 2014), the biological meaning of change in FA remains unclear as it may reflect neuroinflammatory reactions within white matter (Assaf & Pasternak, 2008), myelin content and/or axonal diameter, density, or configuration (e.g., crossing fibers; Beaulieu, 2002; Shenton et al., 2012).

Pathologically high ADC and MD indicate that water has been impeded in the tissue of interest suggesting decreased neuronal integrity, whereas pathologically low values suggest cellular edema or inflammation. AD reflects diffusion of water along the longitudinal axis of the tensor, and has been interpreted to indicate structural damage of the axon, albeit with some

controversy (Hayes et al., 2016). RD reflects diffusion of water along the two non-primary axes, and is the DTI metric most closely associated with myelin integrity (Johansen-Berg & Behrens, 2013). Similar to FA, RD has also shown inconsistencies with both decreased (Chu et al., 2010; Mayer et al., 2010; Wilde et al., 2008) and increased (Kumar et al., 2009; Mac Donald et al., 2011; Taber et al., 2015) RD values in groups with mTBI history compared to control groups. Myelin breakdown may occur post-acutely after mTBI, which could explain RD changes found in chronic samples of mTBI (Niogi & Mukherjee, 2010; Sorg et al., 2014). However, RD is also susceptible to crossing fibers and partial volume effects from low FA, warranting caution in interpretation (Taber et al., 2015).

DTI: Blast-related mTBI. Blast-related mTBI typically co-occurs with other mechanisms (i.e., blunt injury as a result of secondary or tertiary blast mechanisms), thus the majority of DTI studies have included Veterans with a history of mTBI via blast or mixed mechanisms (Hayes et al., 2016). However, case studies that have examined primary blast injury have observed similar white matter abnormalities as seen in civilians with blunt force mTBI history (Hayes, Morey, & Tupler, 2012; Warden et al., 2009). More recently, a small study detected evidence of selective white matter damage to the cerebellum in three of four U.S. military service members with a history of primary blast mTBI (Mac Donald et al., 2013), and another study failed to detect differences in FA between OEF/OIF Veterans with mTBI as a result of primary blast versus a combination of primary and tertiary mechanisms (Hayes, Miller, Lafleche, Salat, & Verfaellie, 2015). Of the studies that have employed DTI in Veterans with history of mTBI due to blast and mixed mechanisms, there do appear to be significant differences in WMI compared to control groups even in the chronic stages after mTBI using a variety of analytic approaches including voxel-based, region-of-interest (ROI), and tractography (Davenport, Lim, Armstrong, &

Sponheim, 2012; Jorge et al., 2012; Mac Donald et al., 2011; Morey et al., 2013). Finally, a recent DTI study detected altered FA and RD in blast-exposed OEF/OIF Veterans with and without mTBI symptoms (e.g., alteration of consciousness) at the time of injury (Taber et al., 2015). Taber and colleagues hypothesized that in blunt force trauma, injury to the reticular activating system is the likely cause of alteration of consciousness, whereas in blast injury cortical regions that do not result in alteration of consciousness may be implicated.

DTI: Relationships with psychiatric variables. Several studies have found strong relationships between DTI-derived WMI in the cingulum, uncinate fasciculus, and thalamic radiations and psychiatric symptoms such as post-traumatic stress, depression, and alcohol misuse in OEF/OIF Veterans with history of mTBI related to blast or mixed mechanisms (Bazarian et al., 2013; Davenport et al., 2015b; Isaac et al., 2015; Lepage et al., 2017; Maksimovskiy et al., 2014; Matthews et al., 2011). Furthermore, a relatively large study of OEF/OIF Veterans that employed generalized FA, a generalization of the FA measure that incorporates high angular resolution diffusion imaging data, found strong relationships between PTSD and WMI, while history of mTBI was associated with fewer abnormal MD regions (Davenport et al., 2015b). However, other studies have failed to find relationships between WMI measured by DTI and symptoms of PTSD and depression (Davenport et al., 2012; Dretsch et al., 2017; Matthews et al., 2012; Morey et al., 2013). Bazarian and colleagues (2013) asserted that exposure to blast mechanisms may increase vulnerability to PTSD, suggesting that an interaction between injury variables and psychiatric symptoms is taking place in these individuals. This hypothesis is further supported by Hayes et al. (2015), who did not find significant relationships between PTSD and white matter abnormalities, but did find that PTSD symptom severity mediated the relationship between LOC and reduced FA.

DTI: Relationships with injury variables. Although DTI measures have been associated with injury variables in OEF/OIF Veterans such as decreased WMI in those with LOC compared to AOC only (Hayes et al., 2015; Jorge et al., 2012; Matthews et al., 2012), longer duration of LOC (Morey et al., 2013), longer duration of PTA (Jorge et al., 2012) and after multiple mTBIs (Petrie et al., 2014), these findings are not entirely consistent. For example, one study of OEF/OIF Veterans failed to find decreased white matter integrity measured using DTI in those with a history of mTBI prior to deployment or multiple blasts after controlling for multiple comparisons (Davenport et al., 2012). Although the animal literature has provided fairly robust evidence for increased severity of white matter damage after repeated head injury from blast or other mechanisms (Bennett, Mac Donald, & Brody, 2012; Donovan et al., 2014; Ng et al., 2014), further study in OEF/OIF Veterans is warranted.

DTI: Relationships with cognitive variables. A meta-analysis conducted by Hulkower and colleagues (2013) found considerable heterogeneity in the neuropsychological domains and measures used across studies, as well as inconsistent relationship between DTI and neuropsychological measures. Of those studies in OEF/OIF Veterans with history of mTBI that have directly compared DTI measures to neuropsychological outcome measures, several have found associations between DTI measures and neurocognitive measures of memory (Hayes et al., 2015; Levin et al., 2010), and to a greater degree executive function (Jorge et al., 2012; Sorg et al., 2014; Taber et al., 2015). However, very few of these studies controlled for symptoms of PTSD, depression, or neuropsychological performance validity which limits the interpretability of these results. Sorg and colleagues (2014) excluded those with poor performance validity, and found that a subgroup of OEF/OIF Veterans with history of mTBI and impaired executive functioning (impaired performance on a test of novel problem solving, a timed test of verbal

category switching, or a timed test of visual set-shifting) demonstrated significantly lower WMI within prefrontal, commissural, and posterior association tracts compared to OEF/OIF Veterans with mTBI history and no executive functioning deficits and healthy controls. These results remained significant after controlling for both PTSD and depression. The findings by Sorg and colleagues are consistent with the civilian literature that has demonstrated associations between lower white matter integrity and performances on simple and complex timed attention/working memory tasks (Lipton et al., 2009; Miles et al., 2008; Niogi et al., 2008). Additionally, Sorg and colleagues found higher RD in their reduced executive functioning group compared to the group with intact executive functioning and a comparison group, suggesting that compromised myelin integrity may contribute to reduced overall white matter integrity in the frontal white matter, corpus callosum, and posterior cingulum.

DTI: Relationships with PCS. Several studies of OEF/OIF Veterans, military service members, and civilians have demonstrated positive associations between the number of persistent self-reported PCS and decreased FA (Levin et al., 2010), especially for physical PCS, even when controlling for post-traumatic stress (Miller, Hayes, Lafleche, Salat, & Verfaellie, 2016). Others have either failed to find significant relationships (Petrie et al., 2014) or demonstrated that the relationships between white matter integrity and PCS are strongest for those with PTSD (Davenport et al., 2015b). Further, persistent PCS may be more strongly related to underlying personality characteristics rather than underlying white matter pathology related to mTBI (Davenport, Lim, & Sponheim, 2015a), however, these authors raised the possibility that current imaging techniques are insensitive to brain damage incurred as a result of mTBI. The civilian literature results have been similarly mixed with one study demonstrating associations between persistent PCS and reduced FA in various regions including the junction of the ventral

striatum, genu of the internal capsule, optic chiasm, left cingulum bundle, and left thalamus (Yeh et al., 2014), and others failing to find differences in FA and ADC between groups with persistent PCS after mTBI and those without (Lange, Iverson, Brubacher, Mädler, & Heran, 2012; Wäljas et al., 2015). However, it is possible that these negative findings are related to study design, as correlational designs may have more power than group designs (Hayes et al., 2016). Additionally, there is some evidence that the less frequently used measures such as MD and RD may have stronger relationships with persistent PCS (Lange et al., 2015), suggesting that myelin integrity may play a role.

In summary, although DTI has been helpful in expanding our knowledge of WMI after mTBI, several issues limit the interpretability of the current literature including difficulties interpreting DTI measures such as FA and RD, conflicting relationships with injury variables, cognition, and PCS, and equivocal results in the presence of psychiatric comorbidities common after mTBI. However, given the positive FA and particularly RD findings, the possible role of myelin integrity in persistent PCS complaints and objective measures of working memory/attention that require speeded processing warrants further study.

Myelin. Despite accounting for a major component of white matter, the role of myelin pathology is understudied in TBI but likely plays a significant role in the pathophysiology of mTBI (Armstrong, Mierzwa, Marion, & Sullivan, 2016; Mierzwa, Marion, Sullivan, McDaniel, & Armstrong, 2015; Wright et al., 2016). Myelin is the fatty covering of axons in the brain composed of a lipid layer surrounded by two layers of protein that border the axon that allows rapid transmission of information by saltatory conduction (Raine, 1984). Myelin damage, especially in the corpus callosum, may ensue from the neurometabolic cascade that occurs after diffuse shear tissue strains both acutely and chronically after TBI (Benarroch, 2009; Johnson et

al., 2013) and likely causes reciprocal damage to the axon (Shi et al., 2015; Tsunoda & Fujinami, 2002). Further, it may be impacted by oxidative stress resulting from cerebral hypoperfusion known to occur following mTBI (Flygt, Djupsjö, Lenne, & Marklund, 2013; Miyamoto et al., 2013).

Rat models indicate that TBI induces widespread myelin and oligodendrocyte loss within the corpus callosum and external capsule as a result of axonal damage days to weeks after injury (Flygt et al., 2013; Lotocki et al., 2011). This myelin loss likely compromises the integrity of the axon, which may be the mechanism affecting neuronal signaling and subsequently cognitive function after mTBI (Kinnunen et al., 2010; Sharp et al., 2011). Disruption of the myelin sheath has been observed even after minor damage to the axon caused by stretch injuries to the optic nerve in guinea pigs (Maxwell, Domleo, McColl, Jafari, & Graham, 2003; Maxwell, Kosanlavit, McCreath, Reid, & Graham, 1999). Apoptotic oligodendrocyte loss after mild to moderate TBI induced in the rat brain has also been observed in various white matter regions including the internal and external capsules, corpus callosum, and fimbria, possibly due to loss of trophic support from the axon (Conti, Raghupathi, Trojanowski, & McIntosh, 1998; Lotocki et al., 2011; Raghupathi et al., 2002). Furthermore, rat models have demonstrated loss of myelin staining in the rat brain in association with progressive white matter atrophy up to one year post-injury suggesting that this damage may help account for persisting symptoms after the expected window of recovery from mTBI (Bramlett & Dietrich, 2002). Rat models have also been able to mimic repetitive and blast-related mTBI, and have demonstrated changes in cognitive tasks and in myelin integrity of the corpus callous and cingulum months post-injury, and to an even greater degree after repetitive blast-related mTBI (Cernak et al., 2001b; Donovan et al., 2014; Mierzwa et al., 2015; Rubovitch et al., 2011).

Although there is a growing awareness of the role of myelin in disorders that affect cognition (Fields, 2008), few studies have evaluated myelin damage directly after TBI in humans. One study of patients with head injuries that survived 5 hours to 10 days revealed apoptotic oligodendroglia in white matter using staining techniques to characterize lesions and their time course. Histochemical analysis of diffuse axonal injury (DAI) has revealed both acute myelin damage (Ng, Mahaliyana, & Poon, 1994) as well as damage to long white matter tracts (Adams et al., 1989) in humans. A limited number of studies have attempted to use magnetic transfer ratio (MTR) to estimate myelin composition (Hofman, Verhey, Wilmink, Rozendaal, & Jolles, 2002; McGowan et al., 2000) including Petrie et al. (2014) who utilized macromolecular protein fraction (MPF) mapping to quantify myelin composition integrity based on the magnetic transfer effect and found reduced MPF in OEF/OIF Veterans with a history of repetitive blast-related mTBI versus Veterans with no history of blast exposure in various brain regions (e.g., external capsule, longitudinal fasciculus, precuneus, frontal gyri, anterior cingulate). Although MPF may be a more specific measure of myelin compared to MTR, whether these measures reflect neuropathological changes in myelin composition remains to be determined. Given that myelin integrity is directly related to axonal conduction velocity (Waxman, 1977), targeting sensitive and specific in vivo imaging of myelin holds promise as a specific metric of the slowed processing that is commonly observed in those with a history of TBI, as well as a potential marker of change and a target for interventions.

A novel, myelin-selective MRI technique. A novel imaging method, multicomponent-driven equilibrium single-pulse observation of T1 and T2 (mcDESPOT; Deoni, 2011; Deoni et al., 2008) has recently been developed to calculate myelin volume in vivo. mcDESPOT uses multicomponent analysis of relaxation data (MCR) and decomposes the magnetic resonance

(MR) signal into three water compartments: free water (intra- and extra-axonal space), trapped water (between bilayers of the myelin sheath), and the CSF or free water pool and the T1 and T2 of that pool. Each compartment contributes a unique MR signal and results in the myelin water fraction (MWF), whereas DTI acquisition only provides information on the directional preference of water diffusion. mcDESPOT has been shown to be more sensitive and specific to myelin growth and degeneration than standard DTI (Mädler, Drabycz, Kolind, Whittall, & MacKay, 2008). It also corresponds highly with gold standard histological measurements in which lower MWF is associated with lower myelin content, distinguishes between myelin and inflammation, and has good longitudinal and across-site/platform repeatability (Gareau, Rutt, Karlik, & Mitchell, 2000; Laule et al., 2006; Stanisz, Webb, Munro, Pun, & Midha, 2004; Stewart, Mackay, Whittall, Moore, & Paty, 1993; Webb, Munro, Midha, & Stanisz, 2003) making it particularly well-suited for future use as a clinical tool.

mcDESPOT has been successfully used to detect decreased myelin in clinical populations with multiple sclerosis, a disorder that primarily affects myelin, and lower MWF has been associated with worse performance on a timed test of motor dexterity and worse scores on a clinical rating scale of MS disability severity (Kolind et al., 2012; Kolind et al., 2015). MWF corresponds with language abilities and processing speed in healthy infants and toddlers (Chevalier et al., 2015; O'Muircheartaigh et al., 2014), a stage of exponential development of myelin, and decreased MWF has been detected in infants at genetic risk for Alzheimer's disease (Dean et al., 2014). Furthermore, in a study of healthy young adults, lower WMF in the parahippocampal cingulum was associated with lower physical activity, but no relationships were identified between physical activity and DTI measures (Bracht et al., 2016).

Although cognitive and motor slowing is also observed in mood and anxiety disorders (Scott et al., 2014; Tsourtos et al., 2002), a recent study found lower FA but no differences in RD or AD in Veterans with depression in the context of TBI (Isaac et al., 2015), suggesting that myelin changes are not significantly contributing to these white matter alterations. Taken together with other evidence that myelin damage occurs more commonly after neurological conditions such as ischemic stroke (Alexander, Lee, Lazar, & Field, 2007), and MS (Roosendaal et al., 2009) myelin damage would be anticipated only from TBI and would not be the expected mechanism for mental health driven cognitive changes, although further research is warranted.

Given histological and animal data that suggest those with mTBI history have more myelin breakdown than those without, taken together with the limitations of conventional DTI metrics, mcDESPOT may be a particularly useful technique to study WMI in TBI. The first report using myelin water imaging to study mTBI was recently published, albeit using a different pulse sequence, and found reduced MWF at two weeks post-injury in concussed athletes (n = 10), relative to pre-injury scans, in several regions including the corpus callosum, posterior thalamic radiation, corona radiata, superior longitudinal fasciculus, and internal capsule (Wright et al., 2016). MWF values were recovered to pre-TBI values at two-month follow up. This study involved a small sample of collegiate athletes after a single concussive event and did not evaluate relationships between MWF and demographic, injury, or neurocognitive variables. Nor did it examine MWF values into the chronic phase following mTBI. Notably, findings from animal models show myelin changes in closed-skull impacts in mice up to 6-weeks post-injury (Mierzwa et al., 2015). Further, animal and human studies suggest that blast and repetitive mTBI may confer additional myelin damage than single mTBIs that are due to non-blast mechanisms (Cernak et al., 2001b; Donovan et al., 2014; Petrie et al., 2014; Rubovitch et al., 2011). Given the

small number of studies and seemingly discrepant findings across studies, additional myelin-specific studies with larger samples and consideration of exposure to blast and multiple mTBIs are warranted.

Purpose of the Current Study

The study and clinical management of mTBI sequelae has been hampered in OEF/OIF war Veterans due to various factors specific to this population such as the frequent lack of documentation regarding injury details, common exposure to multiple mTBIs, and high rates of comorbid PTSD, depression, pain and substance abuse. The identification of objective biomarkers of brain damage associated with persistent cognitive symptoms in mTBI could provide the foundation for more accurate injury severity grading, prognosis, and therapeutic opportunities. White matter tracts critical for processing speed, attention, and working memory are particularly vulnerable to disruption after mTBI. Speeded processing is of particular importance because it affects performance on higher order cognitive tasks vital for everyday functioning (Kail & Salthouse, 1994), and is associated with reduced employment and relationship difficulties (Dams O'Connor et al., 2013). Advanced white matter imaging techniques such as DTI have greatly improved our ability to measure WMI and our understanding of the pathophysiology of mTBI, but have notable limitations; DTI has demonstrated inconsistent results in those with history of mTBI compared to control groups and has also had limited use in demonstrating dose-response relationships with injury and cognitive variables. White matter and myelin imaging have shown some dose-response relationships with injury variables and changes after blast exposure, particularly within fronto-striatal and fronto-limbic circuits, and callosal fibers. Although white matter changes have been detected in those with psychiatric diagnoses such as PTSD and depression, myelin specifically may be more

affected by neurological damage such as in mTBI. Furthermore, although difficulties in speeded attention and working memory are hallmarks of both TBI and psychiatric disorder, white matter damage has been implicated in underlying the slowed processing observed after mTBI, therefore the relationship between myelin integrity and speeded attention and working memory would only be expected in those with history of TBI, not psychiatric disorders. However, a recent study demonstrated that those with history of mTBI and comorbid PTSD had reduced WMI as measured by DTI, and lower scores on measures of mental flexibility, processing speed, encoding, and retrieval compared to those with history of mTBI only, suggesting that psychiatric diagnoses may interact with underlying neuropathology to cause poorer functional outcome (Lopez et al., 2017). Specific relationships between slowed processing and persistent PCS and myelin are theoretically expected but need to be scientifically explored.

Given the high rates of mTBI and psychiatric comorbidities in OEF/OIF Veterans, taken together with the nonspecific nature of PCS and cognitive difficulties following TBI, diagnosis and subsequent treatment of persistent symptoms after TBI has become a costly problem both financially and in its devastating effects on quality of life, distress, and everyday functioning in returning Veterans. Traditional imaging modalities have limitations in their diagnostic and prognostic abilities, and growing evidence suggests that targeting myelin in vivo has the potential to capture neurological rather than psychiatric symptoms following TBI. Therefore, the purpose of this study was to target in vivo imaging of myelin to determine its effectiveness as a biological marker of mTBI. Given the importance of correlating an objective measure of cognitive functioning with neuroimaging data to determine its utility as a biomarker associated with functional outcome in mTBI (Belanger, Vanderploeg, Curtiss, & Warden, 2014), the present study also examined the relationship of myelin integrity and objective and subjective

measures of functioning after mTBI. To our knowledge, this study was the first to utilize mcDESPOT in Veterans with a history of TBI and a combat comparison group (CC).

Aim 1: Quantify any dose-response relationships between mcDESPOT MWF and TBI injury variables in OEF/OIF combat Veterans.

Hypothesis 1a. It was hypothesized that across the entire sample, mcDESPOT MWF in the ROIs would be negatively related to history of LOC and PTA, and number of mTBIs.

Hypothesis 1b: It was hypothesized that any significant relationships between mcDESPOT MWF and injury variables would remain significant when controlling for PTSD and depression.

Aim 2: Explore the relationship between mcDESPOT MWF and objective cognitive performance in OEF/OIF combat Veterans.

Hypothesis 1a: It was predicted that across the mTBI and CC groups, lower MWF across ROIs would be related to poorer performance on a test of working memory/complex attention, and simple measures of processing and motor speed.

Hypothesis 2b: It was predicted that MWF across ROIs would interact with emotional distress (PTSD, depression) to predict poorer performance on a test of complex attention/working memory and simple measures of processing and motor speed. Specifically, among those Veterans with higher levels of emotional distress, those with lower MWF would have poorer performance than those with higher MWF.

Aim 3: Explore the relationship between mcDESPOT MWF and subjective PCS in OEF/OIF combat Veterans.

Hypothesis 3a: It was predicted that across the mTBI and CC groups, lower MWF across ROIs would be significantly related to higher levels of self-reported PCS.

Hypothesis 3b: It was predicted that lower MWF across ROIs would continue to be associated with physical and cognitive PCS (vestibular, somatic, cognitive) after controlling for emotional distress.

Chapters I-IV, in part, are currently being reviewed for publication of the material. Jurick, S.M., Hoffman, S. N., Keller, A. V., Evangelista, N. D., DeFord, N. E., Sanderson-Cimino, M., Bangen, K., Delano-Wood, Deoni, S., & Jak, A. J. The dissertation author was the primary investigator and author of this material.

II. METHODS

Participants

Participants included three groups of OEF/OIF combat Veterans, with history of mTBI (mTBI), moderate TBI (modTBI), and a combat comparison group (CC) without history of mTBI. The small group of Veterans with moderate TBI were incorporated in the present study to further explore relationships between myelin integrity and variables of interest in the presence of a larger range of severity and to aid in 'proof of concept' of mcDESPOT given it has only been used in one published study of TBI to date. Participants were recruited from various clinics within the Veterans Affairs San Diego Healthcare System (VASDHS) including TBI Polytrauma, Primary Care, Physical Medicine and Rehabilitation, the OEF/OIF/OND Transition Center, as well as various Veterans centers at local community colleges and universities. Interested participants underwent preliminary screening on the phone to determine that they met basic inclusion criteria (e.g., demographics, diagnoses). If the phone screening suggested they met basic criteria, they were scheduled for an in-person appointment at which they participated in the informed consent process followed by initial assessments that confirmed their study eligibility.

Eligible participants were required to be OEF/OIF war era Veterans with a history of combat exposure defined as a score of greater than one on the Deployment Risk and Resiliency Inventory, Version 2, Section D (DRRI-D-2; Vogt et al., 2013), right-handed, and between the ages of 18-50 years at the time of the study enrollment. For the present study, mild and moderate TBI were based on the VA/DoD 2016 practice guidelines (Management of Concussion/mTBI Working Group, 2016). Specifically, mTBI was defined as an injury event followed by loss of consciousness less than or equal to 30 minutes or alteration of consciousness up to 24 hours and

post-traumatic amnesia up to 24 hours. Moderate TBI was defined by an injury event followed by loss of consciousness greater than 30 minutes but less than 24 hours, alteration of consciousness greater than 24 hours, and post-traumatic amnesia greater than 1 day but less than 7 days. In both TBI groups, the injury event had to have occurred greater than three months prior to study enrollment. Exclusion criteria included active substance dependence, suicidal intent or attempt within the previous month, current psychotic disorder, neurological conditions including dementia, contraindications to MRI (e.g. ferrous metal in the body, claustrophobia, pacemaker, etc.), and history of severe TBI. Individuals were not excluded for depression or PTSD diagnoses due to the high rate of comorbidities in this population.

Procedure

Once inclusion and exclusion criteria were verified, participants underwent a comprehensive evaluation of neuropsychological, emotional, and behavioral functioning. The in-person clinical assessment lasted approximately four hours and the MRI scanning procedures lasted approximately 1.5 hours. These were scheduled on separate days to minimize participant fatigue. The majority of neuroimaging scans were performed within a month of neuropsychological assessment. One participant was scanned 64 days after neuropsychological assessment due to scheduling conflicts. Trained research assistants administered all assessment and neuroimaging procedures.

After undergoing MRI safety screening, participants underwent neuroimaging at the University of California, San Diego Center for Functional MRI (CFMRI). CFMRI houses two research-dedicated 3 Tesla (3T) General Electric (GE) Signa Infinity MRI scanners with eight- and thirty-two channel head coils.

mcDESPOT imaging: mcDESPOT data was collected using the multi-component relaxation time imaging method comprising a series of spoiled gradient recalled echo (SPGR) and T2/T1-weighted balanced steady-state free precession (SSFP) data acquired over a range of flip angles. Whole-brain, sagittal data was acquired with the following parameters: 22 cm^2 x 16 cm FOV; 128 x 128 matrix; 3/4 partial Fourier acquisition and the following sequence-specific parameters: SPGR: TR/TE = 5.3/2.5 ms; flip angles = (3, 4,5,6,7,9,12 & 17)°; receiver bandwidth (BW) = ±22.3 kHz. SSFP: TE/TR=1.6/3.2ms; flip angles = (12,16,21,27,33,40,51 & 68)°; BW = ±50 kHz. An inversion-recovery prepared SPGR (IR-SPGR) scan was acquired to allow correction for transmit magnetic field (B_1) inhomogeneities; and the SSFP data was acquired with two phase-cycling patterns to permit correction for main magnetic field (B_0) off-resonance effects.

Measures

The following measures were selected from a larger battery of tests to address the hypotheses of the present study.

Psychological/Psychosocial Assessment. The Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) is a short (15-20 minute) diagnostic structured interview that covers 17 Diagnostic and Statistical Manual (DSM-5; American Psychiatric Association, 2013) psychiatric disorders and is designed to allow administration by non-specialized interviewers. One to two screening questions rule out diagnoses when answered negatively and affirmative answers lead to further dichotomous probes. Kappa coefficient, sensitivity, specificity, inter-rater and test-retest reliability are all very strong. The MINI was used to rule out exclusionary psychiatric conditions and identify mental health comorbidities. The PTSD Checklist-5 (PCL-5) is a 20-item self-report measure of the DSM-5 symptoms of PTSD takes

approximately five minutes to complete and was used to assess self-reported PTSD symptoms (Weathers et al., 2013). Respondents rate how much they were "bothered by that problem in the past month" in relation to PTSD symptoms. Items are rated on a 5-point scale ranging from 0 ("not at all") to 4 ("extremely"). The Center for Epidemiologic Studies Depression Scale (CES-D) Patient Health Questionnaire-9 (PHQ-9) is a short self-report measure that is validated to assess depression after a TBI (Kroenke, Spitzer, & Williams, 2001) and was used to assess depressive symptoms. The Alcohol Use Disorders Identification Test (AUDIT) is a 10-item screen for risky drinking behavior in Veterans that has been validated for non-VA and general populations (Bush, Kivlahan, McDonell, Fihn, & Bradley, 1998). The AUDIT was used to assess the level of alcohol use in the present sample. Although not primary aims, given the high comorbidity of sleep and pain complaints in the population of interest, the Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality and disturbances over a 1-month interval (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) and the Patient-Reported Outcome Measurement Information System (PROMIS) pain behavior item bank was used to assess pain level (Revicki et al., 2009).

TBI interview. The Structured Interview for Potential Concussion Event Mapping is a structured interview that allows for diagnosis based on the VA/DoD 2016 criteria (Walker et al., 2015). It was used to obtain standardized data to confirm mTBI history as well as information on number of TBIs, and time since TBI.

Premorbid functioning: The Wide Range Achievement Test-4 (WRAT-4) was used as a test of premorbid verbal intellectual abilities as single-word reading ability has been shown to be resilient to brain dysfunction (Wilkinson & Robertson, 2006).

Processing Speed: Speeded processing of attention/working memory was assessed using the Paced Auditory Serial Addition Test (PASAT), an auditory test of processing speed that is well-validated as an extremely sensitive test of processing speed after mTBI (Gronwall & Wrightson, 1974; Tombaugh, 2006). The PASAT requires participants to add the last two digits heard and recite the sum after each digit that is presented. Three trials were given for the present study, with increasingly fast interstimulus intervals (3 seconds, 2.4 seconds, and 2 seconds, respectively).

Simple processing speed was assessed using the Wechsler Adult Intelligence Scale – Fourth Edition (WAIS-IV) Symbol Search and Coding subtests (Wechsler, 2008). These are tests of processing speed that involve numbers and symbols, take approximately two minutes each to administer, have strong psychometric properties, and are sensitive to the effects of TBI (Wilde et al., 2010). The raw scores from the two subtests based on speed of completion were used as outcome measures.

Motor speed was assessed using the Delis-Kaplan Executive Function System (D-KEFS) Trail-Making Motor Sequencing task completion time, which requires participants to trace a dotted line as quickly as possible (Delis, Kaplan, & Kramer, 2001). A raw score of the completion time was used as an outcome measure.

Other Cognitive Measures: To determine whether relationships between myelin integrity and cognition were specific to speeded processing and attention, tests from various other cognitive domains were included in the present study. Visual memory was assessed using the Brief Visuospatial Memory Test -- Revised (BVMT-R; Benedict, 1997), which has an immediate and delayed recall score. Verbal memory was assessed with the California Verbal Learning Test – Second Edition (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000). Immediate

and delayed recall raw scores were used as outcome measures. The digit span total raw score of the WAIS-IV was used to measure simple attention without time constraints. The Trail-Making Number-Letter Switching total completion time from D-KEFS was included for a measure of set shifting, and the D-KEFS Color-Word Inhibition subtest was used as a measure of inhibition.

Performance Validity: Inadequate performance validity was considered <45 on Trial 2 of the Test of Memory Malingering, a 50-item recognition test validated in OEF/OIF Veterans with mTBI (Proto et al., 2014; Tombaugh & Tombaugh, 1996). Veterans were excluded from all analyses using cognitive data if they had inadequate performance validity, but were included in all other analyses.

PCS: PCS was measured using the Neurobehavioral Symptom Inventory (NSI) which is a 22-item self-report measure that takes approximately 10 minutes to administer (Cicerone & Kalmar, 1995). A four-factor model of somatic, vestibular, cognitive, and affective symptoms has been identified in OEF/OIF Veterans with a history of mTBI; thus, clusters of PCS were also examined (Caplan et al., 2015).

Data Analyses

Imaging Processing

mcDESPOT Data: FSL was used for post-processing of mcDESPOT images. BET was used to remove non-brain voxels from analyses. Intrasubject linear co-registration of scans to a chosen mcDESPOT target image (e.g., SPGR α=18°) into MNI-152 space was performed using FMRIB's Linear Image Registration Tool (FLIRT) and registered images were processed with the mcDESPOT fitting code, which estimates the three-compartment model parameters. ROIs was identified using the ICBM-DTI-81 stereotaxic white matter parcellation map, which includes white matter tract labels that were created by hand segmentation of a standard-space average of

diffusion MRI tensor maps from 81 participants (Mori et al., 2008). FSL's Automated Segmentation Tool (FAST) was used to create white matter masks that were applied to the ROI masks to ensure that only white matter voxels were included. All resulting white matter ROIs were visually inspected with reference to landmarks and coordinates identified by the white matter parcellation map as well as white matter anatomical atlases. mcDESPOT myelin water fraction volume maps were multiplied by the binary parcellation maps to obtain average values for each ROI (corpus callosum, cingulate, internal capsule, corona radiata; see Figures 1-3). ROIs were chosen based on DTI studies (Chong & Schwedt, 2018; Eierud et al., 2014; Shenton et al., 2012) indicating that these are the most commonly impacted white matter regions following TBI and the one study conducted using MWF in a sports concussion sample (Wright et al., 2016). An annual software upgrade from DV24 to DV25 supplied by General Electric took place during the study. A total of 18 participants in the sample were scanned before and a total of 39 participants were scanned after this upgrade occurred. The software upgrade was coded as a dummy variable (1 = before upgrade, 2= after upgrade) and included as a covariate in all analyses.

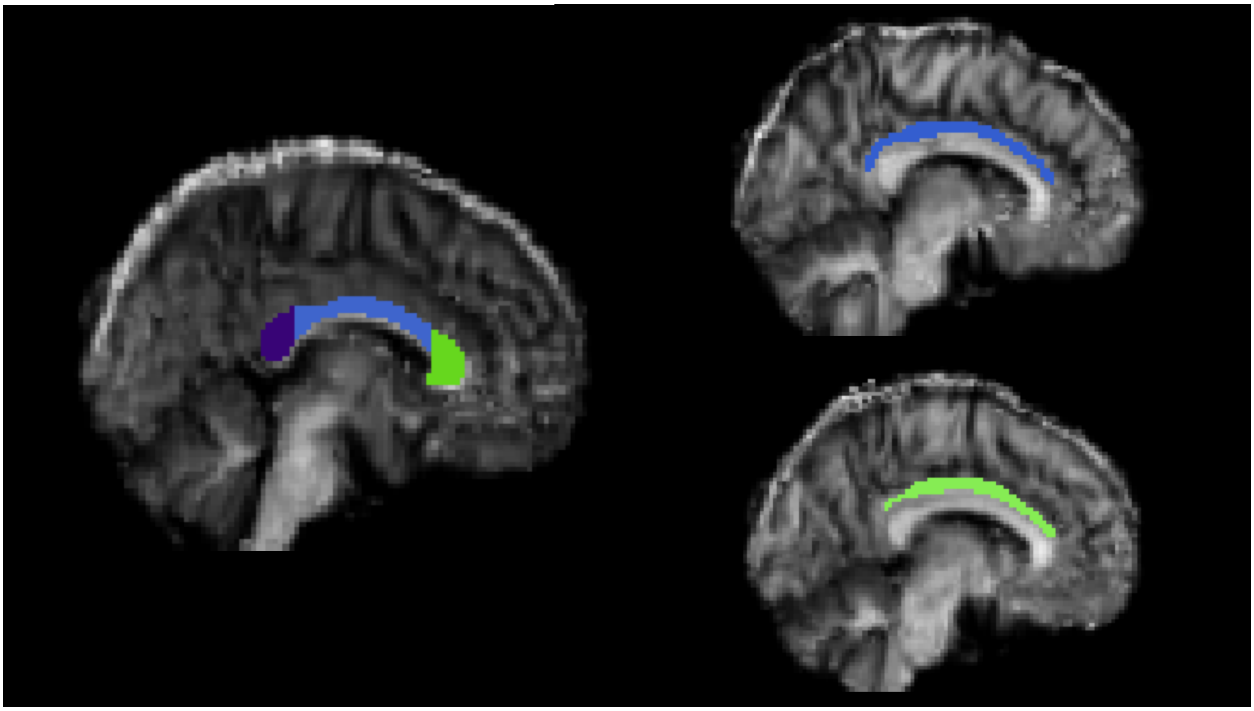

Figure 1. Regions-of-interest in the corpus callosum and cingulate. On the left side of the figure is the splenium, body, and genu of corpus callosum (left to right), right cingulum (top right), and left cingulum (bottom right) depicted on a combat comparison myelin water fraction image.

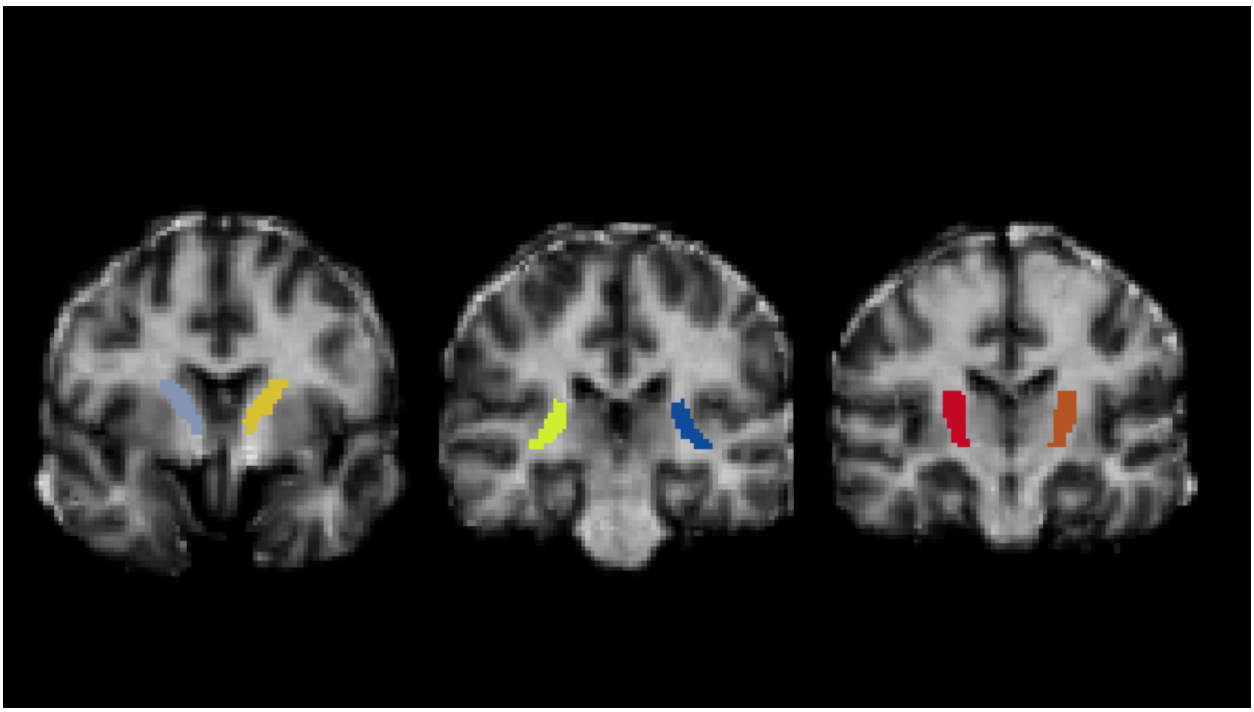

Figure 2. Regions-of-interest in the internal capsule. From left to right: the right and left anterior, retrolenticular, and posterior limbs of the internal capsule depicted on a combat comparison myelin water fraction image.

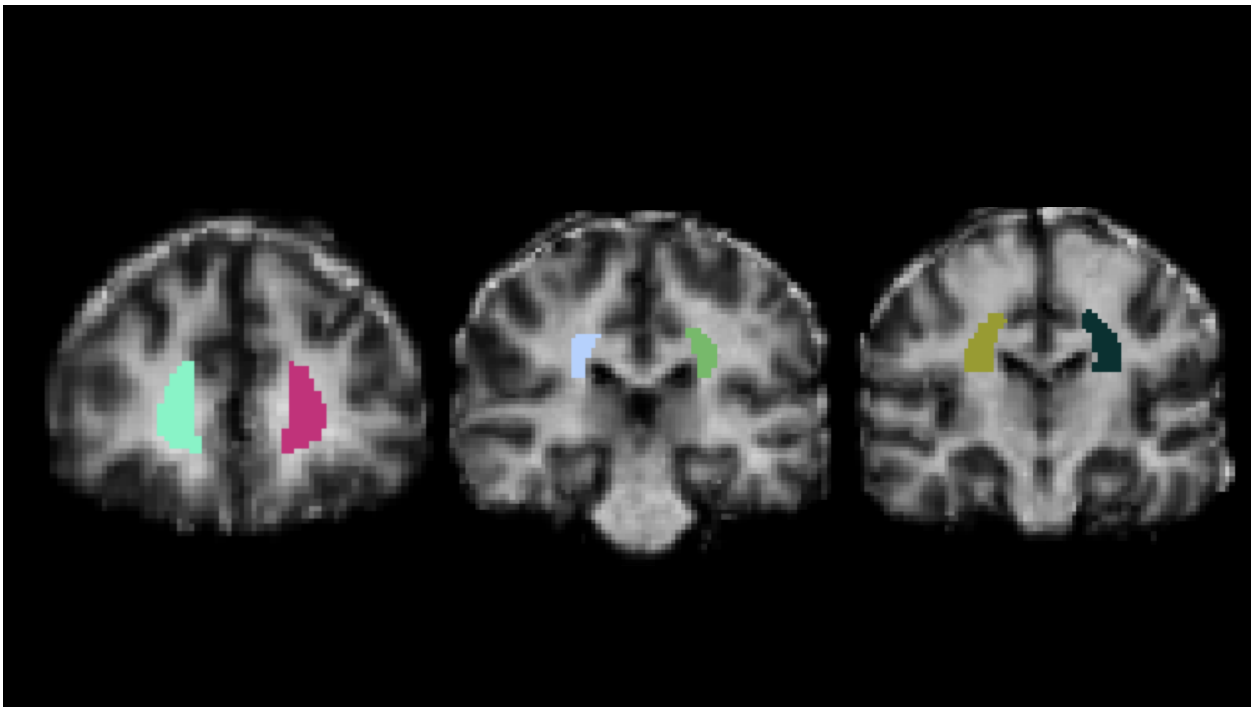

Figure 3. Regions-of-interest in the corona radiata. From left to right: right and left anterior, posterior, and superior limbs of the corona radiata (left to right) depicted on a combat comparison myelin water fraction image.

Examination of statistical assumptions and outliers was conducted prior to all analyses and transformations (e.g., square root, log) were conducted as needed. All analyses were performed using Statistical Package for Social Sciences (SPSS) 23.0. Relationships between demographic variables (e.g., age, education, and gender) and all outcome variables were assessed, and any significant variables were controlled for in subsequent analyses. Multiple compairsons were corrected for by applying a family-wise Bonferroni corrected *p*-value of .017 (.05/3) for the three sets of aims. Previous studies using DTI, MTI, and myelin water imaging observed medium to large effect sizes when evaluating relationships between white matter/myelin and mTBI injury variables in those with a history of mTBI, and cognition and disability severity in those with MS and healthy infants and toddlers (Chevalier et al., 2015; Jorge et al., 2012; Levin et al., 2010; Petrie et al., 2014). Thus, power analyses using the G*Power program (Faul, Erdfelder, Lang, & Buchner, 2007) indicate that there is 84% chance of

detecting a medium effect size ($f^2 = 0.15$), and a 95% chance of detecting a large effect size ($f^2 = 0.35$) given a sample size of 40 Veterans.

Hypothesis testing.

Hypothesis 1. *It was hypothesized that lower MWF across ROIs would be associated with history of LOC, PTA, and greater number of mTBIs. Further, it was predicted that any significant associations would remain after controlling for PTSD and depression.*

A series of linear regressions for each ROI were conducted to examine the relationships between MWF and injury variables (LOC, PTA, and number of TBIs). MWF in each ROI was used as the outcome measure and regressions were conducted in CC and mTBI groups, and then within the mTBI and modTBI groups. In the CC group, all injury variables were coded as "0" and included in analyses to increase power to detect effects and range of severity. Any demographic variables that were found to be significantly related to MWF in each ROI were included in the regressions. After these regressions were conducted, PTSD and depression (symptom report and diagnosis) were entered in separate regressions.

Hypothesis 2. *It was hypothesized that lower MWF across ROIs would be associated with poorer performance on a neuropsychological test of complex attention/working memory, and simple measures of motor and processing speed. Further, it was predicted that MWF would interact with PTSD and depression such that those with lower MWF and higher PTSD and depression symptoms would have worse performance.*

Across the mTBI and CC groups (excluding those with poor performance validity), a series of partial correlations for each ROI were conducted to examine the relationships between MWF and all cognitive measures (controlling for group and any demographic or psychiatric variables associated with the ROI). Significant partial correlations between MWF in each ROI

were then submitted to regressions conducted across the mTBI and CC groups. Any demographic or psychiatric variables that were found to be significantly related to MWF were entered into separate regressions for each significant cognitive variable. PTSD and depression, as well as the MWF-by-emotional distress terms were then entered into separate regressions.

Hypothesis 3. *It was hypothesized that lower MWF across ROIs would be associated with higher PCS. Further, it was predicted that MWF would be associationed with somatic, cognitive, and vestibular PCS after controlling for PTSD and depression symptoms.*

Across the entire sample, a series of partial correlations for each ROI were conducted to examine the relationships between MWF and PCS total score as well as all symptom clusters (vestibular, somatic, cognitive, and emotional symptoms. Group (mTBI versus CC) and any demographic or psychiatric variables associated with the ROI were included in the partial correlations.

Chapters I-IV, in part, are currently being reviewed for publication of the material. Jurick, S.M., Hoffman, S. N., Keller, A. V., Evangelista, N. D., DeFord, N. E., Sanderson-Cimino, M., Bangen, K., Delano-Wood, Deoni, S., & Jak, A. J. The dissertation author was the primary investigator and author of this material.

III. Results

Sample Characteristics

The final sample was 57 OEF/OIF Veterans (22 CC, 31 mTBI, 4 modTBI), whose demongraphic characteristics are presented in Table 1. The three groups did not differ with regard to demographic variables including age ($F(2, 54) = 1.47$, p = .240), gender ($\chi^2(2) = 0.72$, p = .698), years of education ($F(2, 54) = 2.32$, p = .108), ethnicity ($\chi^2(2) = 2.95$, p=.229), premorbid intelligence ($F(2, 54)=0.69$, p = .507) as measured by WRAT-4 Reading scores,

number of controlled detonations ($F(2, 54) = 2.32$, $p = .067$), blast exposures ($F(2, 54) = 3.81$, $p = .604$), or whole brain volume ($F(2, 54) = 0.43$, $p = .654$). Nearly all variables were normally distributed (skewnwess and kurtosis values below 2) and did not possess outliers (within 3 standard deviations from the mean). However, the number of blast exposures was not normally distributed and included outliers (greater than 3 standard deviations from mean), findings were replicated using the non-parametric Kruskal-Wallis *H* test ($\chi^2(2) = 2.36$, $p = .307$) and the square root transformed variable that did not include outliers ($F(2, 54) = 0.95$, $p = .395$) When $n < 5$ in a cell, Fisher's exact test was employed to confirm the results of the chi-square tests (all above findings remained nonsignificant).

Table 1. Sample Characteristics

Variable	CC	mTBI	modTBI	Sig.
Age [*M (SD)*]	33.55 (6.22)	32.35 (5.44)	37.50 (6.25)	
Gender [% Female]	13.6	9.7	0	
Ethnicity [% Hispanic/Latino]	47.6	33.3	0	
Education [*M (SD)*]	15.18 (1.40)	14.61 (1.71)	16.25 (1.26)	
Reading [*M (SD)*]	104.86 (10.56)	101.61 (9.95)	102.50 (4.20)	
Combat Exposure [*M (SD)*]	37.77 (12.11)	39.61 (16.60)	63.00 (20.77)	†‡
Controlled Detonations [*M (SD)*]	7.59 (20.97)	23.61 (36.23)	42.75 (45.59)	
Blast Exposures [*M (SD)*]	1.82 (1.87)	2.26 (3.27)	3.25 (1.89)	
PTSD Symptoms [*M (SD)*]	25.14 (17.79)	28.26 (17.56)	43.00 (22.14)	
PTSD %	59.1	48.4	50	
Depression Symptoms [*M (SD)*]	8.50 (7.85)	10.16 (6.11)	11.00 (5.94)	
Lifetime Depression %	59.1	83.9	100	◊
Current Depression %	27.3	29	50	
PCS [*M (SD)*]	16.18 (12.25)	28.81 (15.22)	32.75 (15.06)	◊‡
Vestibular	0.86 (1.32)	3.13 (2.50)	3.50 (3.11)	◊
Somatic	2.95 (2.72)	6.97 (4.82)	6.25 (4.35)	◊
Cognitive	3.95 (3.11)	6.13 (3.67)	8.25 (2.22)	◊‡
Emotional	6.95 (5.21)	10.10 (5.41)	11.25 (5.50)	◊
Alcohol Use [*M (SD)*]	4.36 (4.69)	4.65 (3.91)	4.50 (1.91)	
Sleep Quality [*M (SD)*]	9.14 (4.22)	11.74 (3.91)	13.00 (4.76)	◊
Pain [*M (SD)*]	7.32 (3.03)	9.16 (2.24)	7.50 (4.20)	◊
Whole Brain Volume [*M (SD)*]	1156320.41 (87612.79)	1171728.97 (94133.87)	1129571.75 (147890.16)	

Note. CC = Combat comparison group; mTBI = History of mild TBI group; modTBI = History of mod TBI group; Reading refers to WRAT-4 Reading score (age-corrected Standard Score); Combat Exposure refers to degree of exposure to wartime stressors as measured by the DRRI-2; Symptoms of post-traumatic stress disorder (PTSD) as measured by the PCL-5; Symptoms of depression as measured by the PHQ-9; PCS = Post-concussive Symptoms as measured by the NSI including symptom clusters; Alcohol use as measured by the AUDIT; Sleep quality as measured by the PSQI; Pain as measured by the PROMIS. ◊ = CC differs from mTBI at $p<.05$; † = mTBI differs from modTBI at $p<.05$; ‡ = CC differs from modTBI at $p<.05$.

Groups did not significantly differ in their symptom report of PTSD ($F(2, 54) = 1.68$, p = .195), depression ($F(2, 54) = 0.47$, p = .626), alcohol use (F (2, 54) = .033, p = .968), or current diagnoses of PTSD ($\chi^2(2) = 0.44$, p = .801) or depression ($\chi^2(2) = 0.86$, p = .652) assessed by psychiatric interview (MINI). Because the alcohol use self-report scores as measured by the AUDIT were not normally distributed and included one slight outlier, findings were replicated using the Kruskal-Wallis *H* test ($\chi^2(2) = 1.37$, p = .504) and the log transformed variable that did

not include outliers (F (2, 54) = 0.46, p = .636). The percentage of lifetime depression was higher in the mTBI group (84%) compared to the CC group (59%; $\chi^2(1) = 4.07$, p = .044).

Group differences emerged for DRRI-D-2 ($F(2, 54) = 6.23$, p = .004), and follow-up independent samples t-tests revealed that the modTBI group reported a greater degree of exposure to wartime stressors than the mTBI group ($t(33) = -2.59$ $p = .014$) and CC group ($t(24) = -3.98$ $p = .001$). Groups differed with regard to self-reported sleep quality (F(2, 54) = 3.23, p = .047) as measured by the PSQI in which the mTBI group reported worse sleep quality than the CC group (t(51) = -2.31, p = .025). Groups differed with regard to self-reported pain level as measured by the PROMIS (F(2, 54) = 3.18, p = .049), although groups exhibited unequal variances on this variable therefore Welch ANOVA was employed and was nonsignificant (F (2, 8) = 7.74, p = .119). However, follow up independent-samples t-tests revealed that the mTBI group did report higher pain levels than the CC group (t(51) = -2.55, p = .014).

Groups also differed on the NSI ($F(2, 54) = 5.92$, p = .005), in which the modTBI group ($t(24) = -2.41$ $p = .024$) and mTBI group ($t(51) = -3.22$, $p = .002$) reported higher PCS compared to the CC group. Regarding PCS clusters, groups differed on cognitive PCS ($F(2, 54) = 4.12$, p = .022) in which the modTBI group ($t(24) = -2.62$ $p = .015$) and the mTBI group ($t(51) = -2.26$ $p = .028$) reported more cognitive PCS than the CC group. When including the entire sample (CC, mTBI, and modTBI groups), groups did not differ on emotional PCS ($F(2, 54) = 2.62$, p = .082), However, a follow-up independent samples *t*-test revealed that the mTBI group reported more emotional PCS than the CC group when the modTBI group was removed (t(51) = -2.11, p = .039). The groups exhibited unequal variances on the vestibular and somatic NSI subscales, therefore, Welch ANOVA was employed and determined group differences in vestibular ($F(2, 8) = 9.17$, p = .009) and somatic ($F(2, 8) = 7.26$, p = .015) PCS reporting. The mTBI group reported

higher vestibular ($t(47.69) = -4.28$ $p < .001$) and somatic ($t(48.88) = -3.85$ $p < .001$) PCS than the CC group.

Within the mTBI and CC groups, MWF across all ROIs was significantly different between pre- and post-scanner upgrade (all p's < .001). When ANCOVA was employed to control for scanner upgrade (a dichotomous variable coded as 1 for pre-scanner upgrade and 2 for post-scanner upgrade), MWF was significantly and positively related to age in the body and splenium of the corpus callosum, and all other ROIs (all ROIs within the internal capsule, corona radiata, and cingulum; all p's < .05). Gender was significantly related to MWF in the left anterior ($F(2, 50) = 4.50$, p = .039) and posterior (F(2, 50) = 4.51, p = .039) IC, as well as the left superior CR (F(2, 50) = 4.13, p = .048). In all cases, females exhibited lower MWF. Neither WRAT reading score or years of education were significantly related to MWF in any ROI (all p's > .05).

Veterans with current PTSD had higher values of MWF in the body ($F(2, 50) = 4.88$, p = .032) and splenium ($F(2, 50) = 4.96$, p = .030) of the corpus callosum, right ($F(2, 50) = 7.16$, p = .010) and left ($F(2, 50) = 7.39$, p = .009) anterior limb of the IC, right ($F(2, 50) = 4.98$, p = .030) and left ($F(2, 50) = 5.33$, p = .025) posterior limb of the IC, right ($F(2, 50) = 7.38$, p = .009) and left ($F(2, 50) = 4.98$, p = .030) retrolenticular part of the IC, right ($F(2, 50) = 5.25$, p = .026) and left ($F(2, 50) = 5.79$, p = .020) anterior CR, right ($F(2, 50) = 5.24$, p = .026) and left ($F(2, 50) = 5.92$, p = .019) superior CR, right ($F(2, 50) = 5.91$, p = .019) and left ($F(2, 50) = 5.15$, p = .028) posterior CR. A partial correlation was observed for MWF values in the right retrolenticular part of the internal capsule in which greater self-reported symptoms of PTSD were associated with higher MWF values ($r = .28$, p = .046). Neither self-reported symptoms of depression nor depression diagnoses were associated with MWF values (all p's > .05). Thus, scanner upgrade

was controlled for in all analyses, and age, gender, and PTSD were included in all analyses in which they were associated with the outcome variable. When evaluating these relationships within the TBI groups only (mTBI and modTBI groups), there were no significant associations between MWF and demographic or psychiatric variables (all p's > .05).

As shown in Table 2, there were no group differences in MWF when using ANCOVA to control for scanner upgrade (all p's > .05). These nonsignificant findings were replicated when including associated covariates in the model (e.g., age, gender, PTSD). These findings were again replicated when the modTBI group was excluded (all p's > .05).

Table 2. Estimated Marginal Means of MWF

Variable	CC	mTBI	modTBI
Genu of the corpus callosum	0.155	0.153	0.148
Body of the corpus callosum	0.147	0.146	0.146
Splenium of the corpus callosum	0.158	0.159	0.157
R Anterior Limb of the IC	0.150	0.149	0.154
L Anterior Limb of the IC	0.156	0.156	0.159
R Posterior Limb of the IC	0.161	0.161	0.165
L Posterior Limb of the IC	0.165	0.165	0.169
R Retrolenticular Limb of the IC	0.166	0.172	0.168
L Retrolenticular Limb of the IC	0.171	0.172	0.169
R Anterior CR	0.175	0.175	0.172
L Anterior CR	0.177	0.177	0.176
R Superior CR	0.166	0.166	0.171
L Superior CR	0.169	0.170	0.173
R Posterior CR	0.160	0.161	0.163
L Posterior CR	0.165	0.165	0.167
R Cingulum	0.134	0.133	0.126
L Cingulum	0.128	0.130	0.124

Note. Estimated marginal means were derived from ANCOVAs controlling for scanner upgrade. No significant differences emerged (all p's > .05). CC = Combat comparison group; mTBI = History of mild TBI group; modTBI = History of mod TBI group; MWF = Myelin Water Fraction; CC = Combat comparison group; mTBI = History of mild TBI group; modTBI = History of mod TBI group; R = Right; L = Left; IC = Internal Capsule; CR = Corona Radiata.

TBI Injury Characteristics

TBI injury characteristics for the mTBI and modTBI groups are shown in Table 3. In the mTBI sample, Veterans reported an average of 6.65 years since their most recent TBI (range: 8 months to 21 years), and over half (55%) reported history of greater than 2 mTBIs. The majority of the mTBI group reported history of LOC (65%) and PTA (68%), and 39% reported blast-related mTBI. Of those Veterans who were able to estimate the duration of LOC and PTA during their worst injury, the average duration of LOC was 4.91 minutes (range .03-25 minutes) and the average duration of PTA was 25.88 minutes (range .17-240 minutes). Within the modTBI group, Veterans reported an average of 8.91 years since their most recent TBI (range 5.13-12.08), and all reported greater than 2 TBIs and history of blast-related mTBI. Duration of LOC, PTA and number of TBIs were not normally distributed. When square root and log tranformations were performed, number of TBIs normalized but duration of LOC and PTA did not. Thus, presence of LOC and PTA were used instead of duration for all analyses, as well as the square root of number of TBIs.

Table 3. Injury Characteristics in TBI groups

Variable	mTBI	modTBI
Years Since TBI [*M (range)*]	6.65 (.70-20.98)	8.91 (6.96)
Number of TBIs [*M (range)*]	2.97 (1-11)	3.75 (3-5)
Number of blast-related TBIs [*M (range)*]	0.94 (0-8)	1.25 (1-2)
History of blast-related TBI [% Yes]	38.7	100
Longest duration of LOC in minutes [*M (range)*]	3.17 (0-25.00)	390.00 (150.00-720.00)
History of LOC [% Yes]	64.5	100
Longest duration of PTA in minutes [*M (range)*]	18.36 (0-240)	300*
History of PTA [% Yes]	67.7	100

Note. mTBI = History of mild TBI group; modTBI = History of mod TBI group; LOC = loss of consciousness; PTA = post-traumatic amnesia; *only one Veteran with history of moderate TBI reported duration of PTA.

There were no significant associations between MWF and presence of LOC or PTA, or number of TBIs across the mTBI and CC groups when controlling for scanner and upgrade and any demographic variables that were associated with the outcome variable (all p's > .05). These relationships remained nonsignificant (p > .05) when controlling for PTSD.

To determine whether relationships existed within the TBI groups, regressions were employed across the mTBI and modTBI groups. There were no significant associations between MWF and presence of LOC or PTA whether or not PTSD was included in the model (all p's > .05). When number of TBIs was regressed onto MWF, the full model including scanner upgrade was significant for the left anterior CR ($F(2, 32) = 21.10$, $p < .001$; see Table 4 for complete statistics). Number of TBIs was positively associated with MWF, although this failed to reach significance after Bonferonni correction at .017 (p = .039; see Table 4 for complete statistics). When PTSD was included in the model, the relationship between MWF in the left anterior CR was again significant at p < .05, but did not survive Bonferonni correction (p = .047). Similiarly, MWF in the left posterior CR ($F(2, 32) = 23.90$, $p < .001$) was significantly associated with number of TBIs, although this relationship also failed to reach significance after Bonferonni correction (p = .043), and when PTSD was included in the model (p = .052). (See Figure 4)

Table 4. Association between MWF and Number of TBIs across TBI groups

L ACR	**β**	**t**	***p*-value**	**L PCR**	**β**	**t**	***p*-value**
Model 1							
Number of TBIs	0.25	2.15	0.039*	Number of TBIs	0.24	2.11	0.043*
Model 2							
PTSD	0.06	0.54	0.59	PTSD	0.09	0.77	0.45
Number of TBIs	0.25	2.07	0.047*	Number of TBIs	0.23	2.03	0.052

Note: TBI groups include the mTBI and modTBI groups; Regressions included scanner upgrade in all models; MWF = myelin water fraction; L = left; ACR = anterior corona radiata; PCR = posterior corona radiata; β = standardized coefficient; t = t-statistic. *$p<.05$

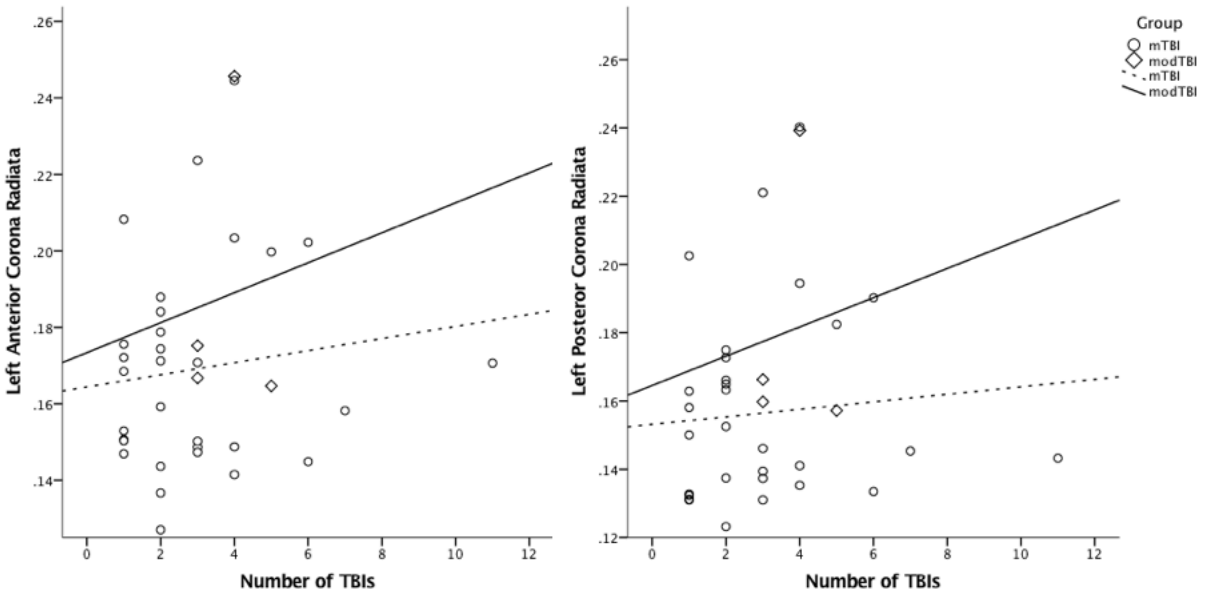

Figure 4. Relationships between lifetime number of TBIs and myelin water fraction in the left anterior and posterior corona radiata. mTBI = group with history of mild traumatic brain injury; modTBI = group with history of moderate traumatic brain injury.

Exploratory Relationships with Injury Variables

Exploratory analyses were conducted to assess possible associations between MWF and blast-related mTBI, number of blast exposures (whether or not they resulted in mTBI), deployment, and time since injury. Across the mTBI and CC groups, full models were significant and indicated that presence of blast-related mTBI was positively associated with MWF in the right ($F(3, 49) = 19.23$, $p < .001$) and left ($F(3, 49) = 20.40$, $p < .001$) anterior CR and left posterior corona radiata ($F(3, 49) = 23.37$, $p < .001$), although these relationships failed to reach significance after Bonferonni correction at .017. When controlling for PTSD, the relationship between MWF in the right anterior CR and blast-related mTBI was no longer significant ($p > .05$). Relationships between the presence of blast-related mTBI remained significant at $p < .05$, when controlling for PTSD but not after Bonferonni correction, in the left anterior CR ($F(4, 48)$

= 16.37, p < .001) and left posterior corona radiata ($F(4, 8) = 18.70$, p < .001). Refer to Table 5 for full statistics of the significant models.

Table 5. Association between MWF and blast-related mTBI across mTBI and CC groups

R ACR	**β**	**t**	***p*-value**	**L ACR**	**β**	**t**	***p*-value**
Model 1							
Age	0.20	1.99	0.053	Age	0.19	1.98	0.054
History of Blast	0.21	2.09	0.042*	History of Blast	0.24	2.40	0.020*
Model 2							
Age	0.16	1.61	0.12	Age	0.15	1.58	0.120
PTSD	0.16	1.62	0.11	PTSD	0.17	1.71	0.093
History of Blast	0.19	1.86	0.069	History of Blast	0.21	2.17	0.035*
L PCR							
Model 1							
Age	0.18	1.90	0.064				
History of Blast	0.22	2.31	0.025*				
Model 2							
Age	0.14	1.52	0.135				
PTSD	0.15	1.59	0.119				
History of Blast	0.20	2.09	0.042*				

Note: mTBI = mild traumatic brain injury; CC = combat comparison group; Regressions included scanner upgrade in all models; MWF = myelin water fraction; L = left; R = right; ACR = anterior corona radiata; PCR = posterior corona radiata; β = standardized coefficient; t = t-statistic. *$p<.05$

Across the modTBI and mTBI groups, blast-related mTBI was positively associated with MWF in the right anterior limb of the IC ($F(2, 32) = 18.77$, p < .001), left anterior limb of the IC ($F(2, 32) = 19.32$, p < .001), right anterior CR ($F(2, 32) = 19.39$, p < .001), left anterior CR ($F(2, 32) = 23.02$, p < .001), left superior CR ($F(2, 32) = 22.46$, p < .001), right posterior CR ($F(2, 32) = 24.26$, p < .001), and left posterior CR ($F(2, 32) = 25.81$, p < .001). However, only the association between blast-related mTBI and MWF in the left anterior CR survived Bonferonni correction (p < .017). When controlling for PTSD, relationships between blast-related mTBI and MWF in the right and left anterior limb of the IC and left anterior and posterior CR remained significant at p < .05, but not after Bonferroni correction. Refer to Table 6 for full statistics for significant models.

Table 6. Association between MWF and blast-related mTBI across TBI groups

R ALIC	**β**	**t**	***p*-value**	**L ALIC**	**β**	**t**	***p*-value**
Model 1							
History of Blast	0.26	2.19	0.036*	History of Blast	0.29	2.44	0.020*
Model 2							
PTSD	-0.01	-0.04	0.97	PTSD	0.02	0.13	0.90
History of Blast	0.26	2.10	0.044*	History of Blast	0.29	2.29	0.029*
R ACR				**L ACR**			
Model 1							
History of Blast	0.25	2.13	0.041*	History of Blast	0.29	2.55	0.016**
Model 2							
PTSD	0.01	0.04	0.97	PTSD	0.01	0.11	0.92
History of Blast	0.25	2.01	0.053	History of Blast	0.29	2.40	0.023*
L SCR				**R PCR**			
Model 1							
History of Blast	0.25	2.20	0.035*	History of Blast	0.24	2.15	0.039*
Model 2							
PTSD	0.06	0.46	0.65	PTSD	0.03	0.22	0.83
History of Blast	0.24	1.99	0.056	History of Blast	0.23	1.99	0.056
L PCR							
Model 1							
History of Blast	0.27	2.49	0.018*				
Model 2							
PTSD	0.04	0.36	0.72				
History of Blast	0.26	2.28	0.030*				

Note: TBI groups include the mTBI and modTBI groups; Regressions included scanner upgrade in all models; MWF = myelin water fraction; L = left; R = right; ALIC = anterior limb of the internal capsule; ACR = anterior corona radiata; SCR = superior corona radiata; PCR = posterior corona radiata; β = standardized coefficient; t = t-statistic. **p<.05; **p <.017*

Within the mTBI group, partial correlations controlling for scanner upgrade and associated demographic variables revealed significant and negative associations between time since injury and MWF in the splenium of the corpus callosum ($r = -.42$, $p = .025$), left retrolenticular part of the IC ($r = -.44$, $p = .019$), and left posterior CR ($r = -.38$, $p = .04$), but no other ROIs (all p's > .05). When controlling for PTSD as well as associated demographic variables, significant relationships remained significant at $p < .05$. No significant relationships emerged when the partial correlations were performed across the modTBI and mTBI groups (all p's > .05).

No significant relationships were observed between MWF and deployment burden as measured by DRRI-D-2 scores or controlled detonations across all groups (all p's > .05). Number of blast exposures (regardless of whether TBI occurred) was significantly and positively associated with MWF across the TBI groups (modTBI and mTBI) within the right anterior limb of the IC ($r = .34$, $p = .048$), although this relationship did not remain signficant once controlling for PTSD ($r = .35$, $p = .051$). There were no significant relationships between number of blast exposures and MWF in any ROIs across the mTBI and CC groups (p's > .05).

Cognitive Variables

Three Veterans within the mTBI and CC groups failed performance validity and thus were excluded from all analyses using cognitive data. Those who failed PVT did not differ on demographic, injury, or psychiatric variables (p's > .05), with the exception of years of education in which Veterans who passed performance validity had fewer years of education than those who did not ($F(1, 51) = 4.38$, $p = .041$). Nearly all cognitive variables were normally distributed and did not have outliers, with the exception of Color-Word Inhibition, which was not normally distributed and Trail-Making motor speed, which was not normally distributed and included a slight outlier. All analyses conducted with these variables were replicated using the log transformed and windsorized variables when applicable.

The mTBI and CC groups did not differ with regard to any cognitive variables except for the PASAT 2-second trial in which the mTBI group performed more poorly than the CC group ($p = .038$; see Table 7). Significant partial correlations at $p < .05$ (controlling for PTSD, group, and associated demographic variables) were observed for PASAT 3-second and MWF in the genu ($r = .41$, $p = .004$), body ($r = .38$, $p = .010$), and splenium of corpus callosum ($r = .38$, $p = .010$), right ($r = .41$, $p = .004$) and left ($r = .35$, $p = .017$) anterior limb of the IC, right ($r = .40$, p

= .006) and left (r = .32, p = .030) posterior limb of the IC, left retrolenticular part of the IC (r = .32, p = .032), right (r = .41, p = .004) and left (r = .38, p = .010) anterior CR, right (r = .39, p = .007) and left (r = .31, p = .036) superior CR, right (r = .38, p = .010) and left (r = .35, p = .017) posterior CR, and right (r = .40, p = .006) and left (r = .36, p = .015) cingulum. Significant partial correlations were also observed between PASAT 2.4-second and MWF in the genu (r = .39, p = .008) and body (r = .29, p = .047) of the corpus callosum, right (r = .34, p = .022) and left (r = .32, p = .033) anterior limb of the IC, right posterior limb of the IC (r = .31, p = .035), right (r = .35, p = .016) and left (r = .33, p = .025) anterior CR, right superior CR (r = .30, p = .041), and right (r = .34, p = .021) and left cingulum (r = .31, p = .036). PASAT 2-second was significantly correlated with MWF in the genu (r = .32, p = .028) of the corpus callosum, right (r = .32, p = .032) and left (r = .30, p = .032) anterior CR, and right cingulum (r = .049). Significant partial correlations were also observed for MWF in the right anterior CR (r = .30, p = .045) and right superior CR (r = .31, p = .035) and CVLT-II short delay recall. In all correlations, lower MWF was related to lower cognitive performance. There were no significant parital correlations between MWF and symbol search, coding, motor speed, number-letter switching, color-word inhibition, BVMT-R immediate or delayed recall, CVLT-II long delay recall, or digit span total.

Table 7. Cognitive Variables

Variable	CC	mTBI	Sig.
PASAT 3-second trial [*M (SD)*]	40.38 (6.56)	36.31 (7.61)	0.054
PASAT 2.4-second trial [*M (SD)*]	34.62 (8.81)	31.66 (7.67)	0.211
PASAT 2-second trial [*M (SD)*]	32.67 (8.55)	27.66 (7.75)	0.036*
Symbol Search [*M (SD)*]	37.14 (6.50)	33.66 (8.96)	0.136
Coding [*M (SD)*]	72.71 (12.42)	68.21 (15.62)	0.279
Digit Span total [*M (SD)*]	28.52 (4.84)	27.79 (5.58)	0.632
Trail-Making Motor Speed [*M (SD)*]	20.38 (7.16)	21.59 (10.14)	0.643
Trail-Making Switching [*M (SD)*]	64.67 (19.24)	73.38 (19.11)	0.119
Color-Word Inhibition [*M (SD)*]	47.00 (8.43)	52.00 (14.03)	0.153
Visual Memory Immediate [*M (SD)*]	25.90 (5.37)	25.86 (4.93)	0.977
Visual Memory Delay [*M (SD)*]	9.71 (1.88)	9.55 (1.62)	0.744
Verbal Memory Immediate [*M (SD)*]	12.29 (2.81)	11.57 (2.28)	0.332
Verbal Memory Delay [*M (SD)*]	12.52 (2.68)	11.82 (2.37)	0.337

Note. CC = Combat comparison group; mTBI = History of mild TBI group; PASAT = Paced Auditory Serial Addition Test; Symbol Search, Coding, and Digit Span total refer to Wechsler Adult Intelligence Scale – Fourth Edition processing speed measures; Trail-Making and Color-Word refer to Delis Kaplan Executive Functioning Systems subtests; Visual Memory refers to California Verbal Learning Test – Second Edition; Verbal Memory refers to Brief Visuospatial Memory Test – Revised. * = CC differs from mTBI at $p < .05$.

Significant partial correlations were then submitted to regressions. Full models including scanner upgrade, age, PTSD, and group (mTBI versus CC) revealed positive associations significant after Bonferroni correction (p's ≤ .017) between MWF and PASAT 3-second in the genu ($F(4, 45) = 14.69$, $p < .001$), body ($F(5, 44) = 14.70$, $p < .001$), and splenium of the corpus callosum ($F(5, 44) = 17.21$, $p < .001$), right ($F(5, 44) = 14.62$, $p < .001$) and left ($F(6, 43) = 12.27$, $p < .001$) anterior limb of the IC, right posterior limb of the IC ($F(5, 44) = 16.76$, $p < .001$), right ($F(5, 44) = 14.23$, $p < .001$) and left ($F(5, 44) = 13.87$, $p < .001$) anterior CR, right ($F(5, 44) = 16.60$, $p < .001$) and left ($F(6, 43) = 12.17$, $p < .001$) superior CR, right ($F(5, 44) = 17.50$, $p < .001$) and left ($F(5, 44) = 15.33$, $p < .001$) posterior CR, and right ($F(5, 44) = 14.93$, $p < .001$) and left ($F(5, 44) = 14.65$, $p < .001$) cingulum, and PASAT 2.4-second in the genu of the corpus callosum ($F(4, 45) = 14.69$, $p < .001$) and right anterior CR ($F(5, 44) = 13.00$, $p < .001$). For full statistics, sees Table 8-11.The following findings were significant at $p < .05$ but did not

survive Bonferoni correction: MWF and PASAT 3-second in the left posterior limb of the IC ($F(6, 43) = 13.13$, $p < .001$), left retrolenticular part of the IC ($F(5, 44) = 16.52$, $p < .001$), left superior CR ($F(5, 44) = 13.92$, $p < .001$), PASAT 2.4-second in the body of the corpus callosum ($F(5, 44) = 13.25$, $p < .001$), right ($F(5, 44) = 13.12$, $p < .001$) and left ($F(5, 44) = 11.77$, $p < .001$) anterior limb of the IC, right posterior limb of the IC ($F(5, 44) = 15.03$, $p < .001$), left anterior CR ($F(5, 44) = 13.02$, $p <.001$), right superior CR ($F(5, 44) = 14.88$, $p < .001$), right ($F(5, 44) = 13.82$, $p < .001$) and left ($F(5, 44) = 13.89$, $p < .001$) cingulum, PASAT 2-second in the genu of the corpus callosum ($F(4, 45) = 12.71$, $p < .001$), right ($F(5, 44) = 12.42$, $p < .001$) and left ($F(5, 44) = 12.49$) anterior CR, and right cingulum ($F(5, 44) = 13.06$, $p <.001$), and CVLT-II short delay free recall and MWF in the right superior CR ($F(5, 43) = 14.30$, $p < .001$) and right anterior CR. Significant relationships were also observed between CVLT-II short delay free recall and MWF in the right superior CR ($F(4, 45) = 14.30$, $p < .001$) and anterior CR ($F(5, 43) = 11.58$, $p < .001$).

Table 8. Association between MWF and PASAT 3-second total score

Genu of corpus callosum	**β**	**t**	***p*-value**	**Body of corpus callosum**	**β**	**t**	***p*-value**
				Age	0.17	1.78	0.082
mTBI	0.08	0.69	0.50	mTBI	0.10	0.94	0.36
PTSD	0.27	2.67	0.010**	PTSD	0.27	2.73	0.009**
PASAT 3-second	0.33	3.06	0.004**	PASAT 3-second	0.27	2.71	0.010**
Splenium of corpus callosum				**R ALIC**			
Age	0.18	1.96	0.057	Age	0.22	2.26	0.029*
mTBI	0.12	1.21	0.23	mTBI	0.11	1.06	0.29
PTSD	0.26	2.75	.009**	PTSD	0.32	3.27	.002**
PASAT 3-second	0.26	2.68	.010**	PASAT 3-second	0.30	3.01	.004**
L ALIC				**L PLIC**			
Age	0.17	1.71	0.094	Age	0.14	1.48	0.15
Gender	-0.14	-1.41	0.17	Gender	-0.14	-1.46	0.15
TBI	0.09	0.79	0.43	TBI	0.08	0.76	0.45
PTSD	0.32	3.23	0.002**	PTSD	0.27	2.85	0.007**
PASAT 3-second	0.26	2.48	0.017**	PASAT 3-second	0.23	2.24	0.030*
R PLIC				**L RLIC**			
Age	0.18	1.99	0.053	Age	0.19	2.08	0.043*
TBI	0.11	1.05	0.30	TBI	0.11	1.05	0.30
PTSD	0.27	2.89	0.006**	PTSD	0.23	2.49	0.017**
PASAT 3-second	0.28	2.88	0.006**	PASAT 3-second	0.22	2.21	0.032*
R ACR				**L ACR**			
Age	0.17	1.76	0.085	Age	0.16	1.68	0.10
TBI	0.11	1.02	0.31	TBI	0.11	1.05	0.30
PTSD	0.29	2.94	0.005**	PTSD	0.29	2.92	0.005**
PASAT 3-second	0.31	3.01	0.004**	PASAT 3-second	0.28	2.70	0.010**
R SCR				**L SCR**			
				Gender	-0.14	-1.39	0.17
Age	0.17	1.80	0.079	Age	0.12	1.24	0.22
TBI	0.11	1.12	0.27	TBI	0.08	0.78	0.44
PTSD	0.28	2.93	0.005**	PTSD	0.29	2.92	0.006**
PASAT 3-second	0.27	2.82	0.007**	PASAT 3-second	0.22	2.17	0.036*
R PCR				**L PCR**			
Age	0.15	1.71	0.095	Age	0.15	1.59	0.12
TBI	0.13	1.27	0.21	TBI	0.12	1.11	0.27
PTSD	0.28	3.03	0.004**	PTSD	0.26	2.73	0.009**
PASAT 3-second	0.26	2.69	0.010**	PASAT 3-second	0.25	2.48	0.017**
R Cingulum				**L Cingulum**			
Age	0.21	2.21	0.032*	Age	0.23	2.35	0.023
TBI	0.09	0.87	0.39	TBI	0.15	1.41	0.17
PTSD	0.22	2.27	0.028*	PTSD	0.23	2.39	0.021*
PASAT 3-second	0.29	2.87	0.006**	PASAT 3-second	0.25	2.52	0.015**

Note: mTBI = mild traumatic brain injury; CC = combat comparison; PASAT refers to Paced Auditory Serial Addition Test 3-second trial total score; Regressions included scanner upgrade in all models; MWF = myelin water fraction; L = left; R = right; CC = corpus callosum; ALIC = anterior limb of the internal capsule; PLIC = posterior limb of the internal capsule; RLIC = retrolenticular limb of the internal capsule; ACR = anterior corona radiata; PCR = posterior corona radiata; SCR = superior corona radiata; β = standardized coefficient; t = t-statistic. *$p<.05$; **$p<.017$

Table 9. Association between MWF and PASAT 2.4-second total

Genu of corpus callosum	**β**	**t**	***p*-value**	**Body of corpus callosum**	**β**	**t**	***p*-value**
				Age	0.14	1.35	0.19
mTBI	0.07	0.58	0.566	mTBI	0.08	0.75	0.46
PTSD	0.26	2.56	0.014**	PTSD	0.26	2.55	0.014**
PASAT 2.4-second	0.29	2.80	0.008**	PASAT 2.4-second	0.21	2.04	0.047*
R ALIC				**L ALIC**			
				Gender	-0.17	-1.71	0.10
Age	0.18	1.73	0.092	Age	0.12	1.20	0.24
mTBI	0.10	0.87	0.39	mTBI	0.07	0.65	0.52
PTSD	0.31	3.08	.004**	PTSD	0.32	3.18	.003**
PASAT 2.4-second	0.25	2.38	.022*	PASAT 2.4-second	0.23	2.21	.033*
R PLIC				**R ACR**			
Age	0.15	1.52	0.14	Age	0.13	1.24	0.22
TBI	0.09	0.85	0.40	TBI	0.09	0.86	0.40
PTSD	0.26	2.69	0.010**	PTSD	0.29	2.81	0.007**
PASAT 2.4-second	0.22	2.18	0.035*	PASAT 2.4-second	0.26	2.50	0.016**
L ACR				**R SCR**			
Age	0.12	1.19	0.24	Age	0.13	1.35	0.18
TBI	0.10	0.92	0.37	TBI	0.10	0.91	0.37
PTSD	0.29	2.83	0.007**	PTSD	0.27	2.73	0.009**
PASAT 2.4-second	0.24	2.32	0.025*	PASAT 2.4-second	0.21	2.10	0.041*
R Cingulum				**L Cingulum**			
Age	0.17	1.68	0.10	Age	0.19	1.86	0.069
TBI	0.08	0.72	0.48	TBI	0.14	1.28	0.21
PTSD	0.22	2.18	0.035*	PTSD	0.23	2.32	0.025*
PASAT 2.4-second	0.25	2.40	0.021*	PASAT 2.4-second	0.22	2.17	0.036*

Note: mTBI = mild traumatic brain injury; CC = combat comparison; PASAT refers to Paced Auditory Serial Addition Test 2.4-second trial total score; Regressions included scanner upgrade in all models; MWF = myelin water fraction; L = left; R = right; CC = corpus callosum; ALIC = anterior limb of the internal capsule; PLIC = posterior limb of the internal capsule; ACR = anterior corona radiata; SCR = superior corona radiata; β = standardized coefficient; t = t-statistic. **p<.05; **p <.017*

Table 10. Association between MWF and PASAT 2-second total

Genu of corpus callosum	**β**	**t**	***p*-value**	**R Cingulum**	**β**	**t**	***p*-value**
				Age	0.14	1.35	0.19
mTBI	0.09	0.72	0.48	mTBI	0.08	0.75	0.46
PTSD	0.27	2.50	0.016**	PTSD	0.26	2.55	0.014**
PASAT 2-second	0.25	2.28	0.028*	PASAT 2-second	0.21	2.04	0.047*
R ACR				**L ACR**			
Age	0.13	1.26	0.22	Age	0.13	1.21	0.23
mTBI	0.12	1.03	0.31	mTBI	0.12	1.07	0.29
PTSD	0.30	2.80	.008**	PTSD	0.30	2.82	.007**
PASAT 2-second	0.25	2.21	0.032*	PASAT 2-second	0.23	2.05	0.046*

Note: mTBI = mild traumatic brain injury; CC = combat comparison; PASAT refers to Paced Auditory Serial Addition Test 2-second trial total score; Regressions included scanner upgrade in all models; MWF = myelin water fraction; L = left; R = right; CC = corpus callosum; ACR = anterior corona radiata; β = standardized coefficient; t = t-statistic. **p<.05; **p <.017*

Table 11. Association between MWF and Immediate Verbal Memory

R ACR				R SCR			
Age	0.22	2.10	0.041*	Age	0.21	2.15	0.037*
mTBI	0.09	0.82	0.42	mTBI	0.10	0.98	0.33
PTSD	0.25	2.44	.019*	PTSD	0.25	2.54	.015**
CVLT-II	0.21	2.06	0.045*	CVLT-II	0.21	2.17	0.035*

Note: mTBI = mild traumatic brain injury; CC = combat comparison; CVLT-II refers to CVLT-II Short Delay Free Recall Score; Regressions included scanner upgrade in all models; MWF = myelin water fraction; R = right; ACR = anterior corona radiata; SCR = anterior corona radiata; β = standardized coefficient; t = t-statistic. *$p<.05$; **$p<.017$*

When the significant partial correlations were explored within each group, significant correlations ($p < .05$) existed between MWF and PASAT 3-second in the genu ($r = .44$, $p = .023$), body ($r = .42$, $p = .034$), and splenium ($r = .40$, $p = .043$) of the corpus callosum, right ($r = .46$, $p = .017$) anterior limb of the IC, right posterior limb of the IC ($r = .43$, $p = .029$), right ($r = .48$, $p = .013$) and left ($r = .43$, $p = .029$) anterior CR, right superior CR ($r = .46$, $p = .017$), right posterior CR ($r = .42$, $p = .033$), and right ($r = .44$, $p = .026$) and left ($r = .43$, $p = .028$) cingulum in the mTBI group only. Also only within the mTBI group, there was a trend toward a relationship between MWF in the right anterior limb of the IC ($r = .39$, $p = .051$). Significant relationships were also observed between PASAT 2-second total score and MWF in the genu of the corpus callosum ($r = .45$, $p = .020$), right ($r = .50$, $p = .010$) and left ($r = .46$, $p = .018$) anterior CR, and right cingulum ($r = .40$, $p = .044$) in the mTBI group only. CVLT-II short delay recall in the right anterior CR ($r = .48$, $p = .015$) and right superior CR ($r = .45$, $p = .026$), also in the mTBI group only. There were no significant correlations (p's > .05) within the CC or mTBI groups for the other ROIs. No significant interactions between cognition and PTSD or depression diagnoses or symptoms were observed (all p's > .05). See Figures 5-9.

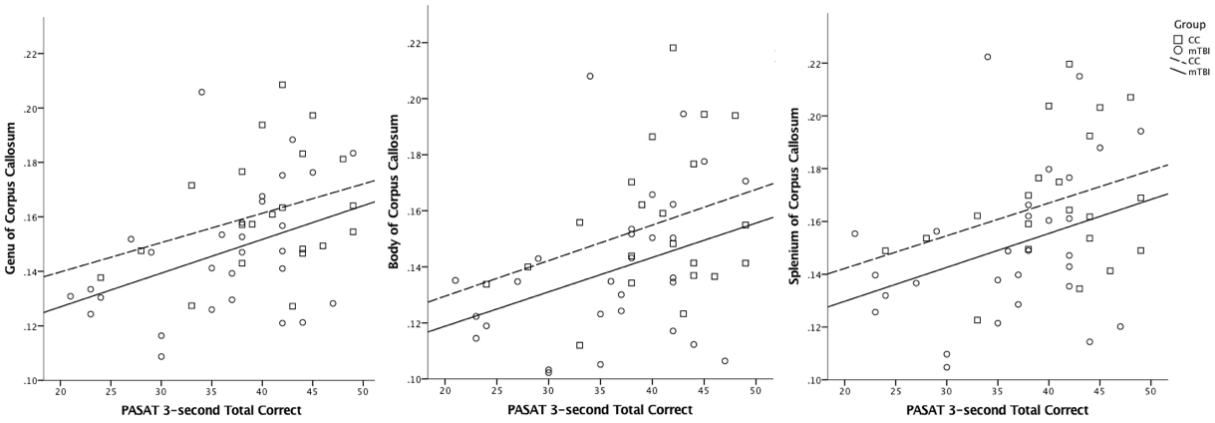

Figure 5. Relationships surviving Bonferroni correction between Paced Auditory Serial Addition Test (PASAT) 3-second total score and myelin water fraction in the corpus callosum. CC = combat comparison group; mTBI = group with history of mild traumatic brain injury.

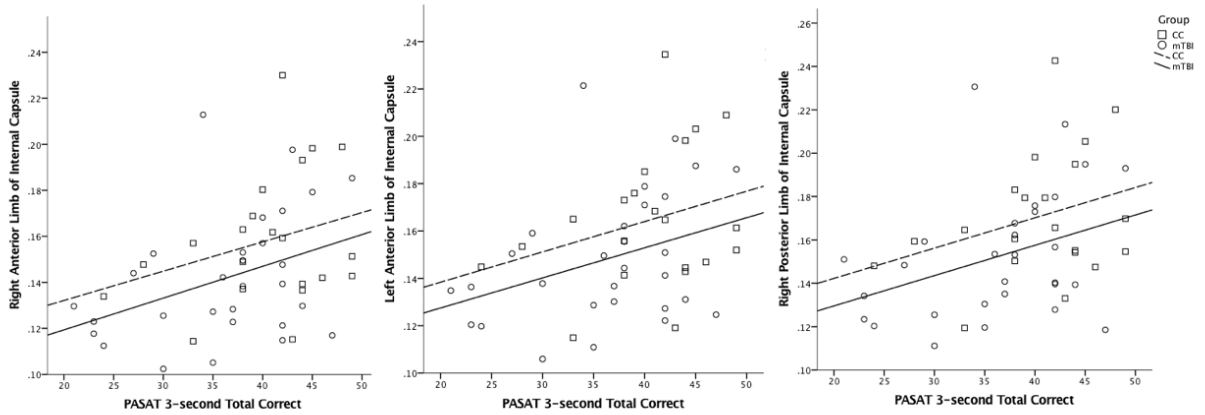

Figure 6. Relationships surviving Bonferroni correction between Paced Auditory Serial Addition Test (PASAT) 3-second total score and myelin water fraction in the internal capsule. CC = combat comparison group; mTBI = group with history of mild traumatic brain injury.

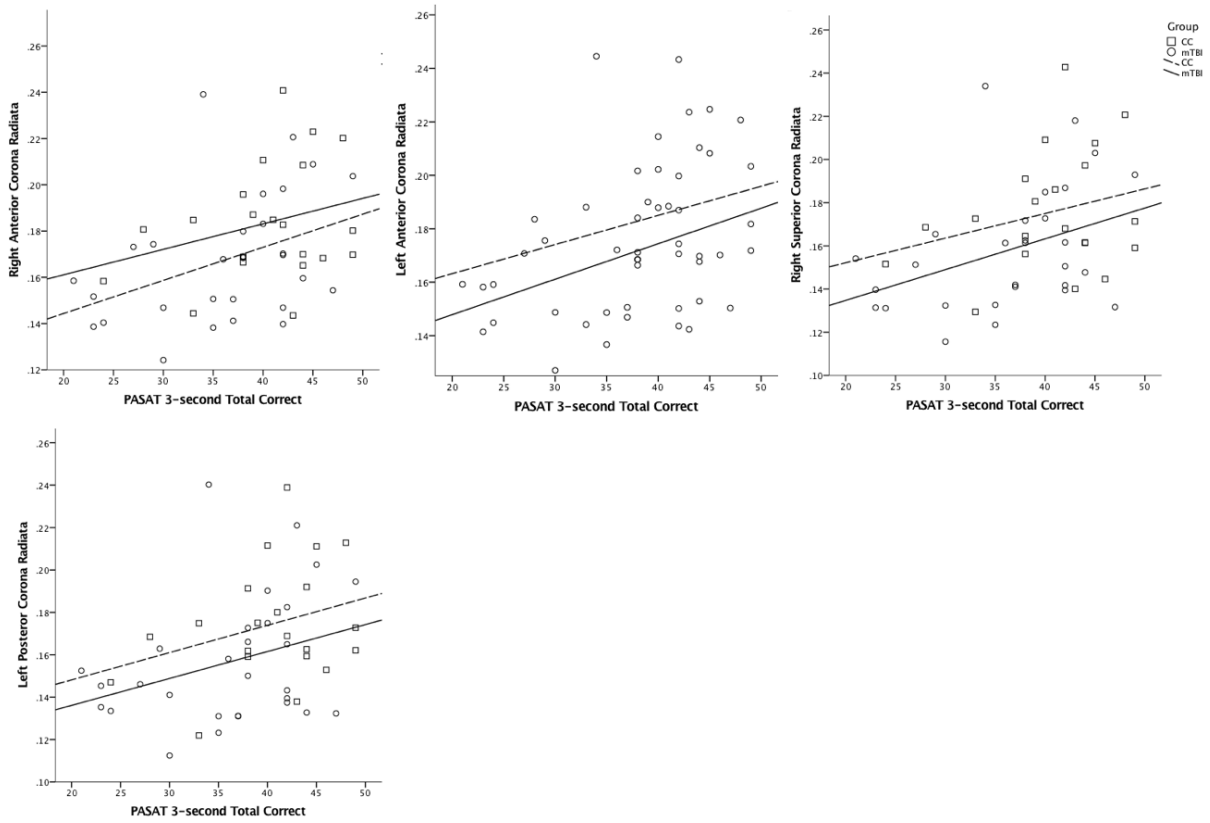

Figure 7. Relationships surviving Bonferroni correction between Paced Auditory Serial Addition Test (PASAT) 3-second total score and myelin water fraction in the corona radiata. CC = combat comparison group; mTBI = group with history of mild traumatic brain injury.

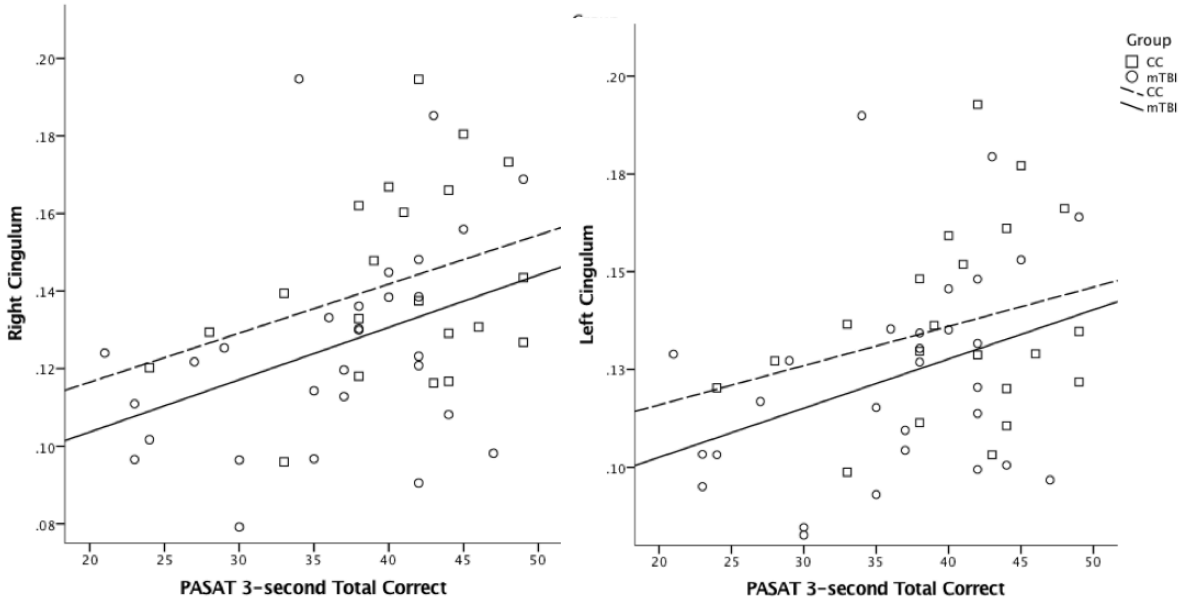

Figure 8. Relationships surviving Bonferroni correction between Paced Auditory Serial Addition Test (PASAT) 3-second total score and myelin water fraction in the cingulum. CC = combat comparison group; mTBI = group with history of mild traumatic brain injury.

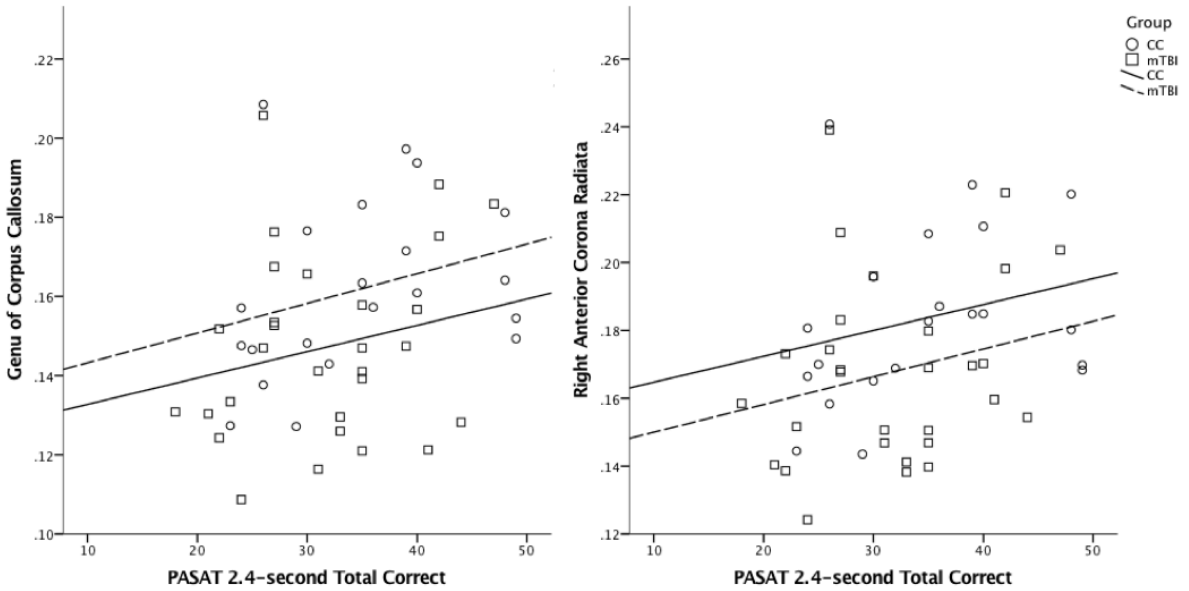

Figure 9. Relationships surviving Bonferroni correction between Paced Auditory Serial Addition Test (PASAT) 2.4-second total score and myelin water fraction in the genu of the corpus callosum and right anterior corona radiata. CC = combat comparison group; mTBI = group with history of mild traumatic brain injury.

Post-concussive Symptoms

Partial correlations controlling for scanner upgrade, group (CC versus mTBI), and associated demographic variables revealed no significant relationships between MWF and PCS (p's > .05). Regarding symptom clusters, no significant relationships emerged between MWF and vestibular, somatic, or cognitive PCS. Somatic symptoms were significantly and positively related to MWF in the splenium of the corpus callosum (r = .291, p = .04), right (r = .293, p = .039) and left (r = .295, p = .037) retrolenticular part of the IC, left anterior CR (r = .296, p = .037), right (r = .344, p = .014) and left (r = .339, p = .016) posterior CR. However, these relationship did not remain significant once controlling for PTSD or depression diagnosis or symptom report (all ps > .05). As exploratory analyses, partial correlations between MWF and pain, alcohol use, and sleep quality were conducted controlling for scanner upgrade and group (CC versus mTBI). All analyses were nonsignificant (p's > .05), whether or not controlling for PTSD.

Chapters I-IV, in part, are currently being reviewed for publication of the material. Jurick, S.M., Hoffman, S. N., Keller, A. V., Evangelista, N. D., DeFord, N. E., Sanderson-Cimino, M., Bangen, K., Delano-Wood, Deoni, S., & Jak, A. J. The dissertation author was the primary investigator and author of this material.

IV. DISCUSSION

The present study was designed to investigate utility of a novel, myelin-selective neuroimaging technique in OEF/OIF Veterans with combat history and other risk factors for cognitive difficulties (history of TBI, mental health diagnoses). There were no significant differences in myelin integrity as measured by mcDESPOT between OEF/OIF Veterans with or without history of TBI. However, those with PTSD showed higher MWF values than those without in multiple ROIs. Further, there was some evidence to support an association between myelin content/integrity and injury variables (e.g., number of TBIs, history of blast-related mTBI). Relationship between MWF and number of TBIs were in the opposite of the hypothesized direction (higher MWF values were associated with higher numbers of TBIs), although these findings did not survive Bonferonni correction. Presence of blast-related mTBI was associated with higher MWF values across mutliple ROIs, and may have been underlying the associations between and MWF and number of TBIs. With the exception of one sensitive measure of speeded attention, cognitive performance did not differ between Veterans with a history of mTBI and the combat comparison group. Consistent with our hypotheses, MWF values were associated with objective auditory processing speed scores such that worse performance on a speeded attention task was related to lower MWF. The relationship between cognition and MWF values was observed on a speeded measure of attention and working memory and one measure of immediate verbal memory, but was not present for other memory, executive functioning, attention, or simple processing or motor speed measures. The relationships between myelin content/integrity and cognitive performance were present when controlling for PTSD, and were stronger for those with history of mTBI compared to the combat

comparison group. Finally, although MWF values were associated with somatic symptoms of PCS, these relationships did not remain significant once controlling for PTSD.

Traumatic Brain Injury

There were no differences in myelin integrity between Veterans with and without history of mTBI. This finding is congruent with DTI studies that have failed to find evidence of decreased WMI in OEF/OIF Veterans and service members following mTBI in the absence of psychiatric comorbidities (Davenport et al., 2015b; Lepage et al., 2017; Levin et al., 2010). Differences in myelin integrity remained nonsigificant when Veterans with history of moderate TBI were included in analyses. It should be noted that the present sample of those with history of moderate TBI was small (n = 4), however, Levin and colleagues (2010) also failed to find differences in WMI in a sample of Veterans with history of mild and moderate TBI. Alternatively, differences in WMI measured using FA have been identified in those with history of mTBI (Lo, Shifteh, Gold, Bello, & Lipton, 2009; Jorge et al., 2012) and mild and moderate TBI (Sorg et al., 2016), compared to those without history of TBI. There are various possible explanations for the discrepant findings across studies including the size, composition, and clinical severity of the sample and comparison group, and neuroimaging methodology. For example, the present study used a combat comparison group, although there was no evidence in the present sample that the degree of combat exposure was associated with myelin integrity. It is also possible that the sample of Veterans with history of TBI captured in the present study was not experiencing the same degree of prolonged PCS as those used in the studies which found differences in WMI. However, the average PCS score within Veterans within the mTBI group in the present sample was within the 10-24th percentile of a sample of Florida National Guard service members with history of deployment and mTBI (Soble et al., 2014), suggesting that a

clinically-elevated group was captured. Self-reported PCS are strongly associated with presence and severity of comorbid mental health diagnoses (e.g., depression, PTSD), however, and thus it is difficult to determine the extent to which self-reported PCS are related to TBI versus other causes (Cooper et al., 2011; Greiffenstein & Baker, 2001; Lee et al., 2015; Nelson et al., 2016; Schneiderman et al., 2008; Seal et al., 2016).

Regarding myelin specifically, findings from animal models have shown myelin changes in closed-skull impacts in mice up to 6-weeks post-injury (Mierzwa et al., 2015). A study by Yeh and colleagues (2014) identified increased RD in Veterans with history of TBI suggesting possible dys- and de-ymelination, however, the sample was heterogenous (included several Veterans with history of moderate TBI and one Veteran with history of severe TBI) and included a large range of duration since injury (21 to 1,860 days). The only other known published study examining MWF following mTBI, while showing acute decrements in MWF following sports concussion, did not show persistent decrements in MWF (Wright et al., 2016). Thus, our findings of Veterans in the post-acute period following mTBI are largely consistent with the work of Wright and colleagues, showing limited persistent MWF changes distal from the mTBI event.

Comorbid Mental Health Conditions

Despite the nonsignificant findings with regard to TBI groups, positive relationships between myelin content/integrity and PTSD were identified in nearly all ROIs including the corpus callosum, internal capsule, and corona radiata. These regions overlap with other studies that have observed white matter differences (e.g., lower and higher FA in relation to comparison groups) associated with PTSD in the context of military TBI (Davenport et al., 2015b; Lepage et al., 2017; Yeh et al., 2014) as well as in civilians with no history of TBI (Li et al., 2016b). A recent longitudinal study revealed increased MD in a subacute phase after injury (10-20 days)

and decreased FA and increased MD in the chronic phase (1-6 months) in various regions including the corpus callosum in those who developed PTSD within six months of their TBI compared to healthy comparison subjects and those with history of mTBI who did not develop PTSD. To our knowledge, only one study has used an in vivo measure of myelin (the ratio of T1-weighted/T2-weighted MRI) to evaluate myelin content in PTSD and identified higher myelin content in the hippocampi of male Veterans with PTSD compared to trauma-exposed Veterans without PTSD (Chao, Tosun, Woodward, Kaufer, & Neylan, 2015). Chao and colleagues discussed their findings in the context of research in a rat model demonstrating that stress stimulates the production of oligodendroctyes (Chetty et al., 2014), as well as research demonstrating that excess myelin may have negative consequences such as inhibition of axon growth cones, inhibition of synapse formation, and reduced plasticity in the central nervous system; all of which are critical for learning and memory especially within the hippocampus and associated white matter tracts. Increased myelin content/integrity in Veterans with PTSD could also be related to preexisting vulnerabilites or overuse of frontal association pathways due to symptoms of anxiety (Spadoni, Huang, & Simmons, 2017).

Interestingly, the relationships between myelin content/integrity and mental health variables were specific to PTSD, and were not observed for depression, substance use, pain, or sleep, all of which commonly occur in this population and can complicate attribution of PCS following TBI (Bryan, 2013; Gilbert et al., 2015; Lippa et al., 2015; Stojanovic et al., 2016). Despite accumulating evidence suggesting that deficient myelin may be involved in depression (Jiang et al., 2018; Shail, 2017), there was no evidence of relationships between myelin content/integrity and depression in the present study. The null findings in depression but positive findings in PTSD may be due to the higher portion of those with current PTSD compared to

depression in the present sample (53% versus 30%, respectively), and thus greater power to detect effects. Given that suicidal intent or attempt within the previous month was exclusionary, the level of severity of depression in the present sample may be lower than what is observed in the overall combat Veteran population. Similarly, although pain, sleep disturbance, and substance use commonly occur in combat Veterans, the present study did not recruit Veterans to evaluate these variables and therefore future research should examine the relationship between myelin content/integrity and these variables in a more purposeful manner.

Relationships between Myelin and Injury Variables

Contrary to hypotheses, no significant dose-response relationships between injury variables (presence of LOC and PTA, number of TBIs) were observed after correcting for multiple comparisons. These findings diverge from previous studies demonstrating associations between WMI and injury variables such as LOC, PTA, and number of TBIs (Hayes et al., 2015; Jorge et al., 2012; Matthews et al., 2012), although these findings are not universal (Davenport et al., 2012), and may be stronger for acute injury (Wilde et al., 2016). Although nonsignificant after Bonferroni correction, higher MWF in the CR was associated with number of TBIs when evaluating these relationships across TBI groups only. The addition of PTSD to these models caused the relationship between myelin integrity and number of TBIs in the posterior CR to become nonsignificant, but remained significant within the anterior CR at $p < .05$. Additionally, presence of blast-related mTBI was associated with higher MWF in various regions including the anterior limb of the IC, and throughout the CR. The findings across CC and mTBI groups did not remain significant once controlling for PTSD and/or applying Bonferroni correction. That being said, findings pertaining to blast-related mTBI were more robust compared to number of TBIs (more regions of significance). Additionally, those with blast-related mTBI had higher numbers

of TBI than those without ($p < .05$), suggesting that the findings related to number of TBIs may be primarily driven by blast-related mTBI. Although myelin integrity in the anterior limb of the IC was significantly associated with number of blast exposures (with or without associated mTBI), this finding was only present across the TBI groups and did not hold when controlling for PTSD. Thus, contrary to prior studies that have employed DTI and functional connectivity studies (Robinson et al., 2014; Trotter, Robinson, Milberg, McGlinchey, & Salat, 2015), the present study did not find robust evidence of myelin changes after blast exposures that did not result in mTBI.

Although some studies have failed to find differences in WMI between those with TBI related to primary blast versus a combination of primary and tertiary mechanisms or no history of TBI (Hayes et al., 2015; Levin et al., 2010), a growing body of literature suggests that blast-related mTBI is associated with structural changes (Davenport et al., 2012). Furthermore, the biophysical differences between blast-related mTBI and blunt force trauma may result in varying spatial distribution of white matter damage and timing of pathological events (e.g., disruption of blood-brain barrier and cerebral vasospasm; Bauman et al., 2009; Cernak & Noble-Haeusslein, 2010, Ling et al., 2009), therby resulting in myelin alterations different from what has been observed in blunt force trauma such as in sports concussion (Wright and colleagues, 2015). Additionally, damage to white matter related to blast injury may be more marked in brainstem, cerebellar, and inferior-superiorly oriented fibers such as the CR (Mac Donald et al., 2011; Yeh et al., 2014), which corresponds to findings from the present study (blast-related mTBI was most robustly associated with MWF in the CR). Another possibility is that, consistent with studies with null findings related to blast mentioned above, there simply are not effects of primary blast on myelin integrity and that those with blast-related mTBI are more similar to the combat

comparisons. Lending further support to this hypothesis, the associations between myelin content/integrity and blast-related mTBI became less pronounced when controlling for PTSD, were elevated such as in Veterans with PTSD, and overlapped with the regions associated with PTSD. Finally, the majority of the analyses of blast-related TBI did not survive Bonferonni correction, further highlighting the need for future research of this topic with larger samples.

Cognition

Outside of one sensitive measure of speeded attention, cognitive performance did not differ between the CC and mTBI groups. This is consistent with the large body of literature demonstrating that cognitive deficits resolve for the majority of people within three months post-injury (Dikmen et al., 1995; Ivins, Kane, & Schwab, 2009; Neipert et al., 2014; Schretlen & Shapiro, 2003; Troyanskaya et al., 2015), and that multiple mTBIs may result in persisting cognitive difficulties most notably in the domain of executive functioning (Karr et al., 2014). The relationships between myelin integrity and cognition were positive and widespread (e.g., observed across all ROIs including the genu, body, and splenium of the corpus callosum, anterior and posterior limb of the IC, anterior, posterior, and superior CR, and left cingulum). These findings were most notable for a speeded measure attention and working memory, although one measure of immediate verbal memory was also positively associated with myelin integrity in the CR (although this finding did not survive Bonferroni correction). The PASAT task was complex and involved multiple components including rapidly and accurately processing auditory information, utilizing working memory and simple math to generate an accurate response, and generating motor output. The complexity of the task may explain the widespread findings within the corpus callosum which transports information across hemispheres, the corona radiata and

internal capsule which connect frontal and striatal regions, and the cingulum bundle which connects frontal and limbic circuits.

This is the first study to evaluate relationships between myelin integrity measured using mcDESPOT and objective cognitive measures in those with a history of mTBI. The significant relationships reported herein between an objective measure of speeded attention and MWF in the corpus callosum, CR, IC, and cingulum are consistent with studies in cognitively healthy adults that found myelin integrity predicts processing speed in similar regions including the anterior CR, superior CR, anterior limb of the IC, and genu and splenium of the corpus callosum (Chopra et al., 2017; Lu et al., 2013). MWF has also been shown to correspond to timed cognitive measures in clinical populations such as multiple sclerosis (Kolind et al., 2015), and other measures of white matter and myelin integrity have demonstrated associations with speeded attention and executive functioning tasks (Jorge et al., 2012; Sorg et al., 2014). Further, a recent study of cognitively intact older adults and those with mild cognitive impairment demonstrated associations between MWF in temporal, frontal, and periventricular normal-appearing white matter and episodic and semantic memory performance (Kavroulakis et al., 2017).

Interestingly, relationships between MWF and cognition remained significant once controlling for PTSD, were more prominent in the mTBI group, and were most robust in a speeded measure of attention that differentiated the CC and mTBI groups, giving promise to mcDESPOT as a potential biological marker of persistent cognitive changes after mTBI separate from what is observed in PTSD. Although DTI measures were not included in the present analyses, the relationship between DTI and objective cognitive measures has been inconsistent (Hulkower et al., 2013). Furthermore, neuropsychological performance has been demonstrated to have conflicting relationships with anisotropy over time. Specifically, cognitive performance has

been shown to be negatively correlated with anisotropy in acute phases and positively correlated with anisotropy in chronic phases (Eirud et al., 2014). Possible explanations for this puzzling inconsistency are that inflammation and secondary injury factors that contribute to elevated anisotropy in the acute phase do not contribute in the chronic phase, or that there is not a simple causal relationship between anisotropy and cognitive performance. These interesting findings observed using anisotropy may be related to what was observed in the present study (higher MWF in association with blast-related mTBI and number of TBIs as well as better cognitive performance). Contrary to hypotheses, there was no evidence of an interaction between emotional distress and TBI with respect to myelin integrity. In any case, the robust findings observed in the present study between objective neuropsychological measures and MWF are promising as a biomarker specific to cognitive performance following TBI.

PCS

As anticipated, the TBI group reported higher symptoms of PCS (including cognitive, vestibular, and somatic) than the CC group. Although somatic symptoms of PCS were significantly and positively related to MWF in the splenium of the corpus callosum and parts of the IC and CR, these relationships did not remain significant once controlling for PTSD. This is consistent with literature suggesting that persisting PCS have a psychogenic origin (Cooper et al., 2011; Hoge et al., 2008; Nelson et al., 2016; Schneiderman et al., 2008; Seal et al., 2016), as well as the variable findings between PCS and measures of WMI (Lange, Iverson, Brubacher, Mädler, & Heran, 2012; Petrie et al., 2014; Wäljas et al., 2015).

There is a growing body of research suggesting that persistent PCS, in addition to psychiatric variables, may be iatrogenic and/or related to coping styles and attribution of symptoms (Roth & Spencer, 2013; Belanger, Barwick, Kip, Kretzmer, & Vanderploeg, 2013).

Although analyses evluating this possibility were outside the scope of the present study, future research should address these questions in addition to any potential role of neuroimaging in further delineating these factors.

Limitations

One limitation of the present study is the cross-sectional data collection, which limits the ability to make causal inferences regarding findings. However, given the paucity of studies examining the experimental techniques used (i.e., cutting edge white matter imaging technique of mcDESPOT to examine mTBI), information gathered from the present cross-sectional investigation is likely to significantly impact this nascent area of research.

Although neuroimaging studies with much smaller samples have been published, the present sample size is small by traditional experimental design standards. There were also large number of variables within each regression especially when demographic variables were related to the outcome measure. However, a recent study suggested that only two subjects per variable is required for linear regression (Austin & Steyerberg, 2015), which is well within the ratio of the present study. Further, the number of a priori ROIs was limited due to the sample size; thus, it is possible that MWF differences were present in other ROIs that were not explored as part of the present study.

As mentioned in the literature review, blast exposure, levels of pain and amount of sleep likely contribute to neuropsychological performance and PCS reporting but were not within the specific aims of the current project. Although there were limited associations between myelin integrity and these variables in the present study, it is possible that they may have been contributing to variance in the neuropsychological and PCS measures. Finally, the high rate of performance validity failure within this population may have been present to a larger extent than

was captured by the PVT variable (Armistead-Jehle, 2010). Future research should evaluate whether using different cut scores and measures for performance validity impacts the relationship between cognition and myelin integrity in this population.

Summary and Future Directions

In summary, this project is, to our knowledge, the first investigation to explore a measure of *in vivo* myelin integrity in the chronic phase following mTBI, and the first to evaluate this technique in a Veteran sample. Although there were no significant group differences with regard to TBI groups, myelin content/integrity was elevated in Veterans with PTSD (but not depression, pain, sleep, or alcohol use) across many ROIs, suggesting that this technique nonetheless could be useful in differentiating TBI and common co-occurring psychiatric disorders in the combat Veteran population. Future research would benefit from including a larger sample of those with PTSD only (no history of TBI), and employing analyses to determine the diagnostic utility of mcDESPOT in this population.

Findings related to injury characteristics were variable, however, they appeared to be strongest for blast-related mTBI. Given the significant overlap between the regions implicated in blast-related mTBI and PTSD, taken together with the fact that the relationships between myelin content/integrity and blast-related mTBI were less robust when PTSD was included in the models, the presence or severity of PTSD may have contributed to findings relating to blast. In fact, studies have demonstrated that blast-related mTBI may leave Veterans more vulnerable to developing PTSD. Longitudinal studies are crucial to understanding the time course of these dynamic events, and would be helpful in this case to further delineate the complex relationships between myelin content/integrity, blast-related mTBI, and PTSD. Given that the present study did not find robust relationships between number of blast exposures that did not result in TBI and

myelin content/integrity, it appears as though forces sufficient to induce an event meeting criterion for TBI may play a role in this equation.

Finally, myelin integrity was significantly associated with objective measures of cognitive performance, but not self-reported PCS. The findings related to cognition were selective to a speeded measures of attention and working memory, and one test of immediate verbal memory. Interestingly, the findings remained once controlling for PTSD and were more robust in the mTBI group than in the combat comparison group. Although preliminary, taken together with the findings related to PTSD and blast, the present study provides support for the use of mcDESPOT in OEF/OIF combat Veterans with history of TBI and comorbid psychiatric conditions and is hopefully the first of many to examine these relationships.

Chapters I-IV, in part, are currently being reviewed for publication of the material. Jurick, S.M., Hoffman, S. N., Keller, A. V., Evangelista, N. D., DeFord, N. E., Sanderson-Cimino, M., Bangen, K., Delano-Wood, Deoni, S., & Jak, A. J. The dissertation author was the primary investigator and author of this material.

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