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# PTSD and TBI Comorbidity

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It has long been recognized that in the context of certain life events, brain impingement from head injury and symptoms of traumatic stress go hand-in-hand. The co-occurrence of brain injury and traumatic stress was thrust into the forefront during World War I, when the use of high explosives led to a phenomenon that became known as "shell shock." Although there was much debate regarding the origin of shell shock, some military physicians described shell shock primarily as a *mental* effect of war (Smith & Pear, 1918).

Fast forward 100 years and traumatic brain injury (TBI) and posttraumatic stress disorder (PTSD) become the signature injuries of the latest military conflicts in the middle east and western Asia, this time due to the prevalence of improvised explosive devices. Among military personnel serving in the Iraq and Afghanistan wars, rates of TBI are as high as 23%, with the majority of mild severity, and with high rates of PTSD comorbidity. In this cohort, mild TBI (mTBI) is associated with chronic health problems such as headaches, more missed workdays and healthcare utilization than soldiers with other types of injuries (Hoge et al., 2008).

Despite the advances in TBI and PTSD knowledge since WWI, the debates appear to be very much the same. Are postdeployment symptoms in military Veterans due to TBI or PTSD? Can these conditions be dissociated? Is chronic postconcussive syndrome (PCS) entirely attributable to mental health effects? There are no shortage of controversies surrounding the pathology of concussion in both military and civilian contexts. Findings such as those reported by Shively and colleagues (2016), in which they claim to have found a specific brain pathology related to high explosives, have fueled debates regarding the nature of blast-related injuries. After media outlets proclaimed that the mystery of shell shock may now have been solved (National Geographic, 2016), others have pleaded for caution in presuming a distinct blast pathology (Stewart & Smith, 2016). Further attention to mental health in the context of TBI has arisen from high profile suicide cases in the National Football League (NFL), raising questions regarding the negative long-term consequences of these injuries. Even more recently, greater attention has been applied to concussion/trauma comorbidity in intimate partner violence which has largely been overshadowed by the military and sports contexts (Valera et al., 2019).

Unlike 100 years ago, we now have a range of tools to study PTSD and TBI that can surmount the invisible nature of these injuries. Researchers have applied *in-vivo* neuroimaging techniques, utilized neuropathological staining methods, and created animal models of injury to examine their comorbidity. In this context, this guide to the literature focuses on current knowledge of TBI and PTSD comorbidity, with an emphasis on neurobiological biomarkers and behavioral outcomes. We discuss the top questions in the field and conclude by citing references that have been key in understanding the differences and similarities between these two disorders.

This report focuses primarily on mild TBI/concussion, as mild injuries are thought to represent at least 75% of all TBIs (Centers for Disease Control and Prevention, 2003). Although there is some movement to distinguish mTBI from concussion, currently there is no clear distinction in pathological findings, and inciting injuries are biomechanically similar. Therefore, for the purpose of this review, concussion and mTBI will be used interchangeably. The generally accepted definition of mild TBI/concussion is that it occurs following an external force to the head and results in alterations in mental state such as confusion, disorientation, feeling dazed, and/or loss-of-consciousness less than 30 minutes, and/or loss of memory lasting less than 24 hours.

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## Are TBI and PTSD Dissociable?

The self-reported symptoms of PTSD and mTBI overlap substantially. Difficulty with concentration, irritability and anger, sleep disturbance, and fatigue are key features in both PTSD and acute mTBI (Stein & McAllister, 2009). The overlap in symptoms has made differential diagnosis a challenging endeavor, with the clinician often having to decide whether the reported alterations in consciousness, including feelings of confusion and memory loss directly after an event, may be attributable to emotional trauma rather than concussion. The entanglement of symptoms has further led to questions regarding the etiology of chronic PCS, which involves a constellation of behavioral, cognitive, and physical disturbance symptoms. Although PCS has traditionally been characterized as an outcome of the acute effects of concussion, ongoing PCS symptoms have been attributed to mental health and motivational factors (Lange et al., 2013). Thus, from a purely behavioral standpoint, dissociating PTSD and TBI stands to be a difficult prospect.

However, there is increasing evidence that neuropathologically, the two disorders can be dissociated. Traumatic axonal injury (TAI) is the primary neuropathology associated with mTBI and has been demonstrated in post-mortem brain tissue using immunostaining methods (Blumbergs et al., 1995). TAI reflects a variety of interrelated primary and secondary pathological events that occur progressively and may lead to axonal disconnection over time. The severity of axonal injury is often tied to the duration of loss-of-consciousness and other markers of severity of injury. In mTBI, TAI can injure small clusters of axons in any given area which are exceedingly difficult to visualize and detect without specialized imaging techniques. Diffusion tensor imaging (DTI) has shown promise in detecting these subtle white matter abnormalities in mTBI, especially when the head injury is accompanied by loss-of-consciousness. A growing number of studies have shown diffusely distributed white matter abnormalities following both blunt and blast-related mTBI (Miller et al., 2016; Kinnunen et al., 2011).

Whereas mTBI neuropathology appears to impact white matter, the case for PTSD-related white matter abnormalities is less robust. Studies that have examined mTBI and PTSD concurrently show that TBI accounts for greater variance in white matter abnormalities than PTSD (Hayes et al., 2015), and those with mTBI have greater white matter abnormalities than those with PTSD when directly compared (Klimova et al., 2019). These results suggest that the degree to which white matter is altered may dissociate the two disorders. In addition, when white matter changes are observed in PTSD alone, they often occur in subcortical tracts potentiating the medial prefrontal cortex and cingulum (Schuff et al., 2012). By contrast, white matter abnormalities in mTBI tend to be spatially distributed. PTSD is more consistently characterized by gray matter changes, both in structure and function. One of the more robust neurobiological findings in PTSD is decreased hippocampal volume (Bremner et al., 1995; Logue et al., 2018). Although smaller hippocampal volume has also been found in TBI, it is related more to moderate and severe cases than mild (Jorge et al., 2007). Decades of neuroimaging research have demonstrated that PTSD is not only associated with structural gray matter abnormalities, but also functional alterations in key regions including the medial prefrontal cortex and medial temporal lobe regions (Shin et al., 2004; Pitman et al., 2012) that comprise the default mode network (Miller et al., 2017). In a meta-analytic study that examined overlap of functional activity in mTBI and PTSD, only the middle prefrontal gyrus emerged in the results (Simmons & Matthews, 2012) and the activation was in opposing directions (i.e. greater activation in PTSD versus controls and less activation in mTBI). Thus, at the macro level of large-scale networks, human neuroimaging studies have yet to provide clear evidence for overlapping brain signatures in mTBI and PTSD.

New studies have provided clues regarding the etiology of PCS symptoms. Emerging data suggests that mTBI and PTSD are independently associated with PCS (Schneiderman et al., 2008). A recent neuroimaging study demonstrated that PCS symptoms may be mediated by white matter abnormalities for individuals with mTBI, but not for PTSD (Miller et al., 2016). In particular, this study showed that white matter abnormalities mediated the relationship between TBI and physical PCS symptoms, such as headaches and light sensitivity. These results are important because they demonstrate that TBI and PTSD can be dissociated neurally, and that chronic physical PCS symptoms may be rooted in the white matter pathology seen in mTBI.

## Does Having One Put You at Risk for the Other?

There is growing support for the notion that mTBI increases vulnerability for developing PTSD. However, the extent to which an individual can develop PTSD despite having TBI-related amnesia for the trauma event has been debated (Harvey et al., 2003). Some have suggested that individuals with amnesia are at low risk for developing PTSD due to lack of memory for the trauma event. Further work has questioned this notion by demonstrating significant rates of PTSD even among those with memory loss (Alway et al., 2016). Such findings suggest that individuals still retain “islands” of memories around the event, as well as memories prior to and following the trauma that are the subject of intrusive thoughts.

Epidemiological and prospective cohort studies have been critical in determining the risk of PTSD following mTBI. In one prospective cohort study examining the prevalence of new psychiatric disorders following mTBI, patients were more likely to develop PTSD if they had mTBI than if they did not (Bryant et al., 2010). In a study that followed Marines from a pre-deployment baseline to post-deployment, deployment-related mTBI was the strongest predicter of PTSD symptoms even after accounting for pre-deployment symptoms (Yurgil et al., 2014). Vasterling et al. (2017) supported these findings in another longitudinal prospective study, showing that mTBI was associated with more severe PTSD symptoms.

The mechanisms by which mTBI may confer greater risk for PTSD are yet unknown but are the focus of several lines of work. Psychological mechanisms posit that having an incomplete memory of the trauma due to mTBI may make it difficult for an individual to contextualize and integrate fragmented trauma memories into a coherent autobiographical narrative, although the importance of this ability is not known (Bryant, 2011). One idea gaining momentum is that mTBI impairs trauma recovery via disrupted fear extinction learning. A recent study showed that in military service members, those with deployment-related TBI showed greater startle responses during fear extinction learning than those without deployment-related TBI (Glenn et al., 2017). Although this study represents an important step forward in examining mechanisms in humans, mechanistic approaches are more precisely examined in animal models. After a mild head injury, rats show greater fear responses (Elder et al., 2012) and impaired

fear extinction learning relative to controls (Zhao et al., 2018). Elevations in amygdala protein stathmin 1 following mTBI has been posited as a potential mechanism for greater fear responses (Elder et al., 2016). Another set of findings suggests that defective brain-derived neurotrophic factor (BDNF) signaling in the prefrontal cortex following mTBI may stunt the long-term retention of extinction learning, leading to resurgence of fear (Corne et al., 2019).

Other mechanisms that may increase vulnerability to PTSD following TBI may be related to alterations in the hypothalamic-pituitary-adrenal (HPA) axis (Russell et al., 2018) that lead to reduced capacity for stress coping. Yet another emerging body of work outlines the role of inflammation and microglia in mediating neuropsychiatric symptoms following TBI. Microglia, the immune cells of the brain, respond to damaged cells and may upregulate a prolonged inflammatory response, which has been associated with depressive-like behaviors in rodents (Petraglia et al., 2014). Further insults such as disordered sleep can further exacerbate inflammatory processes and psychiatric behaviors following TBI. This is an exciting area of research that is also involved in examining how inflammatory processes following TBI and stress experiences impact brain function with aging, and their connection with neurodegenerative disease (Witcher et al., 2015).

## Does PTSD/TBI Comorbidity Lead to Worse Outcomes Than Each Separately?

Archival reports suggest that for military personnel, having both mTBI and PTSD concurrently is associated with greater prevalence of postconcussion symptoms than either mTBI or PTSD alone (Brenner et al., 2010), supporting the notion that the combined impact of these two conditions is related to worse outcomes. One of the most alarming statistics is the increased rates of suicide attempts among Veterans suffering from TBI (Schneider et al., 2016). A recent prospective study examining TBI and PTSD concurrently showed that veterans with TBI had higher rates of attempted suicide, particularly when they had PTSD comorbidity (Fonda et al., 2017).

Conceptually, mTBI and PTSD are thought to be distinct disorders based on separable neuropathology, as discussed previously. However, there is growing recognition that shared neurobiological features such as neuroinflammation and glutamatergic toxicity—which occur in each diagnosis—may be further exacerbated in the context of mTBI and PTSD comorbidity (Kaplan et al., 2018). Neuroimaging work has demonstrated greater brain abnormalities among individuals with mTBI/PTSD comorbidity vs. PTSD alone. Lindemer and colleagues (2013) showed that comorbidity was associated with greater reduction in cortical thickness in the prefrontal cortex than those with PTSD only. In another study, the combination of traumatic re-experiencing symptoms and mTBI were related to greater weakened network coupling than re-experiencing alone without mTBI (Spielberg et al., 2015).

There is some evidence to suggest that comorbid mental health problems in college athletes are associated with slower recovery from concussion (Vargas et al., 2015). Much of the work conducted in elite and college athletes examined the link between depression and concussion (Rice et al., 2017). An important area of future research will need to examine TBI and PTSD comorbidity in athletes, as many athletes have significant histories of trauma and associated symptoms that may not be assessed or treated.

## Aging & Neurodegenerative Disease

An area of emerging research examines the notion that mTBI and PTSD accelerate cellular and brain aging. TBI is predictive of greater cortical atrophy than expected for one's chronological age (Cole et al. 2015), potentially reducing neural reserve to combat neurodegenerative processes. In the same vein, PTSD is associated with accelerated aging, as measured by deoxyribonucleic acid (DNA) methylation, which has been linked to increased odds of poor outcomes including lower cognitive performance (Wolf et al., 2016) and all-cause mortality (Marioni et al., 2015). Although studies are currently underway, the combined impact of TBI and PTSD comorbidity on aging trajectories is currently unknown.

Perhaps the most controversial topic in the concussion literature is that of the link between mTBI/concussion, chronic traumatic encephalopathy (CTE), and psychiatric disturbance. CTE is a neurodegenerative disease characterized by abnormal accumulation of hyperphosphorylated tau (p-tau) around small blood vessels in the depths of cortical sulci, and is thought to occur with repetitive head impacts. Although there is now greater consensus that CTE neuropathology is distinct from Alzheimer's disease and other dementias (McKee et al., 2015), the prevalence, course, and progression of CTE are still largely unknown. Over the last decade, an alarming trend was seemingly observed as several high profile NFL players who had committed suicide were diagnosed with CTE post-mortem. In 2017, Mez and colleagues reported that the majority of athletes they examined post-mortem showed CTE pathology, including 110 of 111 (99%) NFL players. Although this study was based on a convenience sample of individuals and thus could not directly speak to the epidemiology of CTE, several news outlets suggested that the prevalence of CTE was astoundingly high, called for the end to college football, and suggested that having CTE meant a "death sentence." A recent statement released by leading experts reproached the news media for inciting panic in the general public and promoting the perception that CTE is clinically well-defined and widespread following TBI (Stewart et al., 2019), particularly when there is evidence for CTE-like pathology in individuals who are asymptomatic for any type of behavioral disturbance (Ling et al., 2015) and lack of evidence for greater rates of suicide in NFL players. Further, there is ongoing debate among neuropathologists regarding what does and what does not constitute a CTE diagnosis, and the extent to which grave negative outcomes such as suicide and behavioral disturbances are attributable to CTE pathology (Iverson et al., 2016). To make sense of the varying symptoms attributed to CTE, subtypes have been proposed that feature either behavioral and mood symptoms, or feature cognitive or motor dysfunction. Taking together the literature at this time, one may conclude that CTE pathology is associated with repetitive traumatic brain injuries, even those of mild impact. CTE also appears to be associated with cognitive and mood dysfunction, although conclusions regarding the prevalence of CTE among individuals with head trauma, and whether CTE is associated with heightened risk for suicide and homicide cannot yet be determined. The work being conducted examining shared PTSD and TBI neurobiological alterations will likely also shed light on mechanisms of neuropsychiatric disturbance following CTE.

Although the relationship between TBI and CTE has been the primary focus in recent years, there is evidence that TBI is a risk factor for other neurodegenerative diseases including Alzheimer's disease and Parkinson's disease. In general, a dose-response

relationship is observed, with greater risk for neurodegenerative pathology with increasing levels of TBI severity. PTSD has also been linked to dementia in a retrospective cohort study, almost doubling the risk of any type of dementia (Yaffe et al., 2010). A shortcoming of many studies is that they are retrospective and cross-sectional, and cannot determine the course of disease. Longitudinal studies that deeply characterize each phenotype and biomarkers of neurodegeneration are necessary. Currently, intermediate endpoints such as MRI and PET are used to examine potential risk for dementia prior to the onset of clinical symptoms. Large consortia and publicly available databases such as the Department of Defense-sponsored Vietnam Veterans Alzheimer's Disease Neuroimaging Initiative Project (DoD-ADNI; Weiner et al., 2013) may be key in parsing out the course and long-term trajectory of TBI and PTSD. Further, the ENIGMA consortium has assembled teams of TBI and PTSD experts to consolidate datasets from around the globe that may be able to determine risk factors such as genetics and epigenetics that would otherwise be difficult to study without large sample sizes.

## Lessons for Treatment

A remaining question is whether individuals with comorbid PTSD and TBI benefit from evidence-based treatments developed to treat PTSD. It is plausible that chronic neurobiological disruptions following TBI would reduce the effectiveness of PTSD therapies. Some initial results suggest that individuals with comorbid mTBI and PTSD engaging in cognitive processing therapy (CPT) have similar adherence rates to those with PTSD alone (Davis et al., 2013). Further evidence suggests that prolonged exposure is equally efficacious in individuals with a history of mTBI as those without (Sripada et al., 2013). Most recently, a randomized clinical trial (RCT) reported benefits in combining CPT with a cognitive training routine (CogSMART) in individuals with comorbid PTSD and mild/moderate TBI. When compared to CPT alone, those in the CogSMART+CPT intervention group had the added benefit of improving cognitive functions including working memory, verbal memory, and problem solving (Jak et al., 2019). These results suggest that while individuals with comorbid mTBI and PTSD improve from evidence-based PTSD treatments alone, a modified therapy incorporating a cognitive rehabilitation component may be particularly beneficial for these patients. Few studies have systematically examined pharmacological treatments in comorbid PTSD and TBI. However, an accepted first-line treatment approach for PTSD is to prescribe Selective Serotonin Reuptake Inhibitors (SSRIs) such as sertraline (Capehart & Bass, 2012). The use of stimulants in this population is gaining greater attention. A small RCT of methylphenidate demonstrated reduced PTSD symptoms and improved cognition in individuals with either diagnosis or both (McAllister et al., 2015).

## Conclusions

One hundred years after the syndrome of shell shock was described, we now have a better framework to understand chronic changes associated with combined head injury and psychological trauma. What has not changed is the observation that behavioral symptoms greatly overlap in TBI and PTSD; however, we now know more about the neuropathology of each disorder than ever before. One important take-away from the literature is that there is evidence that mTBI and PTSD make independent contributions to chronic postconcussive syndrome, although the degree to which one diagnosis contributes more than the other continues to be debated. With the advent of sensitive neuropathology and neuroimaging techniques, researchers have found that TBI has a neural signature that can be dissociated from that of PTSD. For instance, spatially diffuse white matter abnormalities are more characteristic of mTBI than PTSD. Smaller hippocampal volume is more consistently found in PTSD, along with functional alterations in a discrete set of neural pathways that include midline structures such as the medial prefrontal cortex and amygdala. That said, there is a growing understanding that mTBI disrupts some of the same neurobiological pathways as PTSD, including inflammatory and oxidative stress processes that cannot be measured at the level of large-scale neural networks through currently available neuroimaging methods. Neuroendocrine and immune disturbances potentially account for post-TBI neuropsychiatric symptoms and shared behavioral manifestations with PTSD. Much of the work has been conducted in animal models and a challenge for future research will be to translate mechanistic findings to human studies. In addition, a natural next step will be to examine individual differences that may make one individual more susceptible to developing comorbidity than another, including genetic and epigenetic factors. Other preinjury and injury factors may elucidate vulnerability to psychiatric symptoms. For instance, axonal injury in mTBI tends to be spatially heterogeneous and thus it is possible that individuals who sustained injuries disrupting stress pathways are more susceptible to developing PTSD. The high rates of mTBI and PTSD comorbidity and the poorer outcomes associated with comorbidity and negative consequences such as social/occupational disturbances and in some cases, suicide, make a strong case for continued work in this area.

Encouraging RCT work has demonstrated that PTSD treatments are beneficial even among those with mTBI comorbidity, although treatment may be enhanced when it contains an additive cognitive rehabilitation element. With the current state of the art in treatment, some have argued that knowing whether symptoms are attributable to mTBI vs. PTSD is not extremely useful from a clinical standpoint. Fast forwarding to the future, the possibility that treatments can be developed to repair white matter disruptions following mTBI may make the dissociation of mTBI and PTSD a more clinically useful endeavor.

Some of the most active research is examining long-term outcomes following mTBI and PTSD diagnoses, including the possibility that these disorders induce brain vulnerabilities that may not be noticeable acutely, but emerge with aging. For instance, there is initial evidence that these disorders accelerate brain and cellular aging. Also, accumulating evidence exists for the association with neurodegenerative disease, as both mTBI and PTSD have been linked with increased risk for Alzheimer's disease. Repetitive mTBI has been linked with CTE, although studies are underway to examine how CTE-related neuropathology is associated with mood and cognitive disturbances. With the increased attention and resources applied to understanding each diagnosis as well as their comorbidity, it is plausible that the next decade will bring a stronger understanding of the treatment of neurobiological alterations to prevent long-term negative outcomes.

## FEATURED ARTICLES

Alway, Y., McKay, A., Gould, K. R., Johnston, L., & Ponsford, J. (2016). **Factors associated with posttraumatic stress disorder following moderate to severe traumatic brain injury: A prospective study.** *Depression and Anxiety, 33*, 19-26. doi:10.1002/da.22396

*Background:* This study prospectively examined the relationship between preinjury, injury-related, and postinjury factors and posttraumatic stress disorder (PTSD) following moderate to severe traumatic brain injury (TBI). *Method:* Two hundred and three participants were recruited during inpatient admission following moderate to severe TBI. Participants completed an initial assessment soon after injury and were reassessed at 3, 6, and 12 months, 2, 3, 4, and 5 years postinjury. The Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders–fourth edition was used to diagnose pre- and postinjury PTSD and other psychiatric disorders. The Glasgow Outcome Scale-Extended (GOSE) and the Quality of Life Inventory (QOLI) were used to evaluate functional and psychosocial outcome from 6 months postinjury. *Results:* The frequency of PTSD ranged between 0.5 and 9.4% during the 5-year period, increasing throughout the first 12 months and declining thereafter. After controlling for other predictors, shorter posttraumatic amnesia duration (odds ratio = 0.96, 95% *CI* = 0.92–1.00), other concurrent psychiatric disorder (odds ratio = 14.22, 95% *CI* = 2.68–75.38), and lower GOSE (odds ratio = 0.38, 95% *CI* = 0.20–0.72) and QOLI scores (odds ratio = 0.97, 95% *CI* = 0.95–0.97) were associated with greater odds of having injury-related PTSD. *Discussion:* The results of this study indicate that while shorter posttraumatic amnesia duration is associated with PTSD, greater TBI severity does not prevent PTSD from evolving. Patients with PTSD experienced high rates of psychiatric comorbidity and poorer functional and quality of life outcomes after TBI. *Conclusion:* There is a need to direct clinical attention to early identification and treatment of PTSD following TBI to improve outcomes.

Blumbergs, P. C., Scott, G., Vis, J. M., Wainwright, H., Simpson, D. A., & Mclean, A. J. (1995). **Topography of axonal injury as defined by amyloid precursor protein and the sector scoring method in mild and severe closed head injury.** *Journal of Neurotrauma, 12*, 565-572. doi:10.1089/neu.1995.12.565 Axonal injury (AI), as defined by amyloid precursor protein (APP) positive axonal swellings, was recorded on a series of line diagrams of standard brain sections divided into 116 sectors to provide an Axonal Injury Sector Score (AISS) ranging from 0 to 116. This sector scoring method of recording axonal damage and providing a topographic overview of AI was applied to a series of 6 mild head injury cases [Glasgow Coma Scale (GCS) 13–15] and six severe head injury cases (GCS 3–8). The AISS ranged from 4 to 107 overall and varied from 4 to 88 in the mildly injured group and 76 to 107 in the severe head injury group, supporting the concept that there is a spectrum of AI in traumatic head injury and that the AISS is a measure of the extent of AI. APP immunostaining demonstrated positive axonal swellings 1.75 h after head injury and analysis of the pattern of AI in the mild and severe head injury groups showed that axons were more vulnerable than blood vessels and that the axons in the corpus callosum and fornices were the most vulnerable of all.

Bremner, J. D., Randall, P., Scott, T. M., Bronen, R. A., Seibyl, J. P., Southwick, S. M., … & Innis, R. B. (1995). **MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder.** *American Journal of Psychiatry, 152*, 973-981. doi:10.1176/ajp.152.7.973 *Objective:* Studies in nonhuman primates suggest that high levels of cortisol associated with stress have neurotoxic effects on the hippocampus, a brain structure involved in memory. The authors previously showed that patients with combat-related posttraumatic stress disorder (PTSD) had deficits in short-term memory. The purpose of this study was to compare the hippocampal volume of patients with PTSD to that of subjects without psychiatric disorder. *Method:* Magnetic resonance imaging was used to measure the volume of the hippocampus in 26 Vietnam combat veterans with PTSD and 22 comparison subjects selected to be similar to the patients in age, sex, race, years of education, socioeconomic status, body size, and years of alcohol abuse. *Results:* The PTSD patients had a statistically significant 8% smaller right hippocampal volume relative to that of the comparison subjects, but there was no difference in the volume of other brain regions (caudate and temporal lobe). Deficits in short-term verbal memory as measured with the Wechsler Memory Scale were associated with smaller right hippocampal volume in the PTSD patients only. *Conclusions:* These findings are consistent with a smaller right hippocampal volume in PTSD that is associated with functional deficits in verbal memory.

Brenner, L. A., Ivins, B. J., Schwab, K., Warden, D., Nelson, L. A., Jaffee, M., & Terrio, H. (2010). **Traumatic brain injury, posttraumatic stress disorder, and postconcussive symptom reporting among troops returning from Iraq.** *Journal of Head Trauma Rehabilitation, 25*, 307-312. doi:10.1097/HTR.0b013e3181cada03 *Objectives:* Analyze the contribution of mild traumatic brain injury (mTBI) and/or posttraumatic stress disorder (PTSD) to the endorsement of postconcussive (PC) symptoms during Post Deployment Health Assessment. Determine whether a combination of mTBI and PTSD was more strongly associated with symptoms than either condition alone. *Methods:* Cross-sectional study design where both the exposure, mTBI and/or PTSD, and the outcomes of interest, PC symptoms, were ascertained after return from deployment. Subjects were injured soldiers ($n$ = 1247) from one Fort Carson Brigade Combat Team ($n$ = 3973). Main Outcome Measures: Positive history of PC symptoms. *Results:* PTSD and mTBI together were more strongly associated with having PC symptoms (adjusted prevalence ratio 6.27; 95% CI: 4.13-9.43) than either mTBI alone (adjusted prevalence ratio = 4.03; 95% CI: 2.67-6.07) or PTSD alone (adjusted prevalence ratio = 2.74; 95% CI: 1.58-4.74) after adjusting for age, gender, education, rank, and Military Occupational Specialty. *Conclusions:* In soldiers with histories of physical injury, mTBI and PTSD were independently associated with PC symptom reporting. Those with both conditions were at greater risk for PC symptoms than those with either PTSD, mTBI, or neither. Findings support the importance of continued screening for both conditions with the aim of early identification and intervention.

Bryant, R. (2011). **Post-traumatic stress disorder vs traumatic brain injury.** *Dialogues in Clinical Neuroscience, 13*, 251-262. Post-traumatic stress disorder (PTSD) and traumatic brain injury (TBI) often coexist because brain injuries are often sustained in traumatic experiences. This review outlines the significant overlap between PTSD and TBI by commencing with a critical outline of the overlapping symptoms and problems of differential diagnosis. The impact of TBI on PTSD is then described, with increasing evidence suggesting that mild TBI can increase risk for PTSD. Several explanations are offered for this enhanced risk. Recent evidence suggests that impairment secondary to mild TBI is largely attributable to stress reactions after TBI, which challenges the

long-held belief that postconcussive symptoms are a function of neurological insult This recent evidence is pointing to new directions for treatment of postconcussive symptoms that acknowledge that treating stress factors following TBI may be the optimal means to manage the effects of many TBIs.

Bryant, R. A., O'Donnell, M. L., Creamer, M., McFarlane, A. C., Clark, C. R., & Silove, D. (2010). **The psychiatric sequelae of traumatic injury.** *American Journal of Psychiatry, 167*, 312-320. doi:10.1176/appi.ajp.2009.09050617 *Objective:* Traumatic injury affects millions of people each year. There is little understanding of the extent of psychiatric illness that develops after traumatic injury or of the impact of mild traumatic brain injury (TBI) on psychiatric illness. The authors sought to determine the range of new psychiatric disorders occurring after traumatic injury and the influence of mild TBI on psychiatric status. *Method:* In this prospective cohort study, patients were drawn from recent admissions to four major trauma hospitals across Australia. A total of 1,084 traumatically injured patients were initially assessed during hospital admission and followed up 3 months (*N*=932, 86%) and 12 months (*N*=817, 75%) after injury. Lifetime psychiatric diagnoses were assessed in hospital. The prevalence of psychiatric disorders, levels of quality of life, and mental health service use were assessed at the follow-ups. The main outcome measures were 3- and 12-month prevalence of axis I psychiatric disorders, levels of quality of life, and mental health service use and lifetime axis I psychiatric disorders. *Results:* Twelve months after injury, 31% of patients reported a psychiatric disorder, and 22% developed a psychiatric disorder that they had never experienced before. The most common new psychiatric disorders were depression (9%), generalized anxiety disorder (9%), posttraumatic stress disorder (6%), and agoraphobia (6%). Patients were more likely to develop posttraumatic stress disorder (odds ratio=1.92, 95% *CI*=1.08–3.40), panic disorder (odds ratio=2.01, 95% *CI*=1.03–4.14), social phobia (odds ratio=2.07, 95% *CI*=1.03–4.16), and agoraphobia (odds ratio=1.94, 95% *CI*=1.11–3.39) if they had sustained a mild TBI. Functional impairment, rather than mild TBI, was associated with psychiatric illness. *Conclusions:* A significant range of psychiatric disorders occur after traumatic injury. The identification and treatment of a range of psychiatric disorders are important for optimal adaptation after traumatic injury.

Capehart, B., & Bass, D. (2012). **Managing posttraumatic stress disorder in combat veterans with comorbid traumatic brain injury.** *Journal of Rehabilitation Research and Development, 49*, 789-812. doi:10.1682/JRRD.2011.10.0185 Military deployments to Afghanistan and Iraq have been associated with elevated prevalence of both posttraumatic stress disorder (PTSD) and traumatic brain injury (TBI) among combat veterans. The diagnosis and management of PTSD when a comorbid TBI may also exist presents a challenge to interdisciplinary care teams at Department of Veterans Affairs (VA) and civilian medical facilities, particularly when the patient reports a history of blast exposure. Treatment recommendations from VA and Department of Defense's (DOD) recently updated VA/DOD Clinical Practice Guideline for Management of Post-Traumatic Stress are considered from the perspective of simultaneously managing comorbid TBI.

Cole, J. H., Leech, R., Sharp, D. J., & the Alzheimer's Disease Neuroimaging Initiative. (2015). **Prediction of brain age suggests accelerated atrophy after traumatic brain injury.** *Annals of Neurology, 77*, 571-581. doi:10.1002/ana.24367 *Objective:* The long-term effects of traumatic brain injury (TBI) can resemble observed in normal ageing, suggesting that TBI may accelerate the ageing process. We investigate this using a neuroimaging model that predicts brain age in healthy individuals and then apply it to TBI patients. We define individuals' differences in chronological and predicted structural "brain age," and test whether TBI produces progressive atrophy and how this relates to cognitive function. *Methods:* A predictive model of normal ageing was defined using machine learning in 1,537 healthy individuals, based on magnetic resonance imaging–derived estimates of gray matter (GM) and white matter (WM). This ageing model was then applied to test 99 TBI patients and 113 healthy controls to estimate brain age. *Results:* The initial model accurately predicted age in healthy individuals ($r=0.92$). TBI brains were estimated to be "older," with a mean predicted age difference (PAD) between chronological and estimated brain age of 4.66 years (±10.8) for GM and 5.97 years (±11.22) for WM. This PAD predicted cognitive impairment and correlated strongly with the time since TBI, indicating that brain tissue loss increases throughout the chronic postinjury phase. *Interpretation:* TBI patients' brains were estimated to be older than their chronological age. This discrepancy increases with time since injury, suggesting that TBI accelerates the rate of brain atrophy. This may be an important factor in the increased susceptibility in TBI patients for dementia and other age-associated conditions, motivating further research into the age-like effects of brain injury and other neurological diseases.

Corne, R., Leconte, C., Ouradou, M., Fassina, V., Zhu, Y., Déou, E., … & Mongeau, R. (2019) **Spontaneous resurgence of conditioned fear weeks after successful extinction in brain injured mice.** *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 88*, 276-286. doi:10.1016/j.pnpbp.2018.07.023 Mild traumatic brain injury (TBI) is a major risk factor for post-traumatic stress disorder (PTSD), and both disorders share common symptoms and neurobiological defects. Relapse after successful treatment, known as long-term fear resurgence, is common in PTSD patients and a major therapeutic hurdle. We induced a mild focal TBI by controlled cortical impact (CCI) in male C57BL/6 J mice and used fear conditioning to assess PTSD-like behaviors and concomitant alterations in the fear circuitry. We found for the first time that mild TBI, and to a lesser extent sham (craniotomy), mice displayed a spontaneous resurgence of conditioned fear when tested for fear extinction memory recall, despite having effectively acquired and extinguished conditioned fear 6 weeks earlier in the same context. Other characteristic symptoms of PTSD are risk-taking behaviors and cognitive deficits. CCI mice displayed risk-taking behaviors, behavioral inflexibility and reductions in processing speed compared to naïve mice. In conjunction with these changes there were alterations in amygdala morphology 3 months post-trauma, and decreased myelin basic protein density at the primary lesion site and in distant secondary sites such as the hippocampus, thalamus, and amygdala, compared to sham mice. Furthermore, activity-dependent brain-derived neurotrophic factor (BDNF) transcripts were decreased in the prefrontal cortex, a key region for fear extinction consolidation, following fear extinction training in both TBI and, to a lesser extent, sham mice. This study shows for the first time that a mild brain injury can generate a spontaneous resurgence of conditioned fear associated with defective BDNF signalling in the prefrontal cortex, PTSD-like behaviors, and have enduring effects on the brain.

Davis, J. J., Walter, K. H., Chard, K. M., Parkinson, R. B., & Houston, W. S. (2013). **Treatment adherence in cognitive processing therapy for combat-related PTSD with history of mild TBI.** *Rehabilitation Psychology, 58*, 36-42. doi:10.1037/a0031525 *Objective:* This retrospective study examined treatment adherence in Cognitive Processing Therapy (CPT) for combat-related posttraumatic stress disorder (PTSD) in Veterans of Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) with and without history of mild traumatic brain injury (mTBI). *Method:* Medical record review of consecutive referrals to an outpatient PTSD clinic identified veterans diagnosed with combat-related PTSD who began treatment with CPT. The sample (*N* = 136) was grouped according to positive (*n* = 44) and negative *(n* = 92) mTBI history. Groups were compared in terms of presenting symptoms and treatment adherence. *Results:* The groups were not different on a pretreatment measure of depression, but self-reported and clinician-rated PTSD symptoms were higher in veterans with history of mTBI. The treatment completion rate was greater than 61% in both groups. The number of sessions attended averaged 9.6 for the PTSD group and 7.9 for the mTBI/PTSD group (*p* = .05). Implications: Given the lack of marked group differences in treatment adherence, these initial findings suggest that standard CPT for PTSD may be a tolerable treatment for OEF/OIF veterans with a history of PTSD and mTBI as well as veterans with PTSD alone.

Elder, G. A., Dorr, N. P., De Gasperi, R., Gama Sosa, M. A., Shaughness, M. C., Maudlin-Jeronimo, E., … & Ahlers, S. T. (2012). **Blast exposure induces post-traumatic stress disorder-related traits in a rat model of mild traumatic brain injury.** *Journal of Neurotrauma, 29*, 2564-2575. doi:10.1089/neu.2012.2510 Blast related traumatic brain injury (TBI) has been a major cause of injury in the wars in Iraq and Afghanistan. A striking feature of the mild TBI (mTBI) cases has been the prominent association with post-traumatic stress disorder (PTSD). However, because of the overlapping symptoms, distinction between the two disorders has been difficult. We studied a rat model of mTBI in which adult male rats were exposed to repetitive blast injury while under anesthesia. Blast exposure induced a variety of PTSD-related behavioral traits that were present many months after the blast exposure, including increased anxiety, enhanced contextual fear conditioning, and an altered response in a predator scent assay. We also found elevation in the amygdala of the protein stathmin 1, which is known to influence the generation of fear responses. Because the blast overpressure injuries occurred while animals were under general anesthesia, our results suggest that a blast-related mTBI exposure can, in the absence of any psychological stressor, induce PTSD-related traits that are chronic and persistent. These studies have implications for understanding the relationship of PTSD to mTBI in the population of veterans returning from the wars in Iraq and Afghanistan.

Fonda, J. R., Fredman, L., Brogly, S. B., McGlinchey, R. E., Milberg, W. P., & Gradus, J. L. (2017). **Traumatic brain injury and attempted suicide among veterans of the wars in Iraq and Afghanistan.** *American Journal of Epidemiology, 186*, 220-226. doi:10.1093/aje/kwx044 Studies of the association between traumatic brain injury (TBI) and suicide attempt have yielded conflicting results. Furthermore, no studies have examined the possible mediating role of common comorbid psychiatric conditions in this association. This study used Veterans Affairs registry data to evaluate the associations between deployment-related TBI, psychiatric diagnoses, and attempted suicide among 273,591 veterans deployed in support of Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn, and who received care from the Department of Veterans Affairs during 2007–2012. We performed Cox proportional hazards regression analyses, adjusting for demographic characteristics. Mediation analyses were conducted to quantify the impact of psychiatric conditions (posttraumatic stress disorder, depression, anxiety, and substance abuse) on this association. The sample was predominantly male (84%); mean age = 28.7 years. Veterans with TBI (16%) were more likely to attempt suicide than those without (0.54% vs. 0.14%): adjusted hazards ratio = 3.76, 95% confidence interval: 3.15, 4.49. This association was attenuated in mediation analyses (adjusted hazards ratio = 1.25, 95% confidence interval: 1.07, 1.46), with 83% of the association of TBI with attempted suicide mediated by co-occurring psychiatric conditions and with posttraumatic stress disorder having the largest impact. These results suggest that veterans with these conditions should be closely monitored for suicidal behavior.

Glenn, D. E., Acheson, D. T., Geyer, M. A., Nievergelt, C. M., Baker, D. G., Risbrough, V. B., & MRS-II Team. (2017). **Fear learning alterations after traumatic brain injury and their role in development of posttraumatic stress symptoms.** *Depression and Anxiety, 34*, 723-733. doi:10.1002/da.22642 *Background:* It is unknown how traumatic brain injury (TBI) increases risk for posttraumatic stress disorder (PTSD). One potential mechanism is via alteration of fear-learning processes that could affect responses to trauma memories and cues. We utilized a prospective, longitudinal design to determine if TBI is associated with altered fear learning and extinction, and if fear processing mediates effects of TBI on PTSD symptom change. *Methods:* Eight hundred fifty two active-duty Marines and Navy Corpsmen were assessed before and after deployment. Assessments included TBI history, PTSD symptoms, combat trauma and deployment stress, and a fear-potentiated startle task of fear acquisition and extinction. Startle response and self-reported expectancy and anxiety served as measures of fear conditioning, and PTSD symptoms were measured with the Clinician-Administered PTSD Scale. *Results:* Individuals endorsing "multiple hit" exposure (both deployment TBI and a prior TBI) showed the strongest fear acquisition and highest fear expression compared to groups without multiple hits. Extinction did not differ across groups. Endorsing a deployment TBI was associated with higher anxiety to the fear cue compared to those without deployment TBI. The association of deployment TBI with increased postdeployment PTSD symptoms was mediated by postdeployment fear expression when recent prior-TBI exposure was included as a moderator. TBI associations with increased response to threat cues and PTSD symptoms remained when controlling for deployment trauma and postdeployment PTSD diagnosis. *Conclusions:* Deployment TBI, and multiple-hit TBI in particular, are associated with increases in conditioned fear learning and expression that may contribute to risk for developing PTSD symptoms.

Harvey, A. G., Brewin, C. R., Jones, C., & Kopelman, M. D. (2003). **Coexistence of posttraumatic stress disorder and traumatic brain injury: Towards a resolution of the paradox.** *Journal of the International Neuropsychological Society, 9*, 663-676. doi:10.1017/S1355617703940069 The coexistence of posttraumatic stress

disorder (PTSD) and traumatic head or brain injury (TBI) in the same individual has been proposed to be paradoxical. It has been argued that individuals who sustain a TBI and have no conscious memory of their trauma will not experience fear, helplessness and horror during the trauma, nor will they develop reexperiencing symptoms or establish the negative associations that underlie avoidance symptoms. However, single case reports and incidence studies suggest that PTSD can be diagnosed following TBI. We highlight critical issues in assessment, definitions, and research methods, and propose two possible resolutions of the paradox. One resolution focuses on ambiguity in the criteria for diagnosing PTSD. The other involves accepting that TBI patients do experience similar symptoms to other PTSD patients, but that there are crucial differences in symptom content.

Hoge, C. W., McGurk, D., Thomas, J. L., Cox, A. L., Engel, C. C., & Castro, C. A. (2008). **Mild traumatic brain injury in US soldiers returning from Iraq.** *New England Journal of Medicine, 358*, 453-463. doi:10.1056/NEJMoa072972 *Background:* An important medical concern of the Iraq war is the potential long-term effect of mild traumatic brain injury, or concussion, particularly from blast explosions. However, the epidemiology of combat-related mild traumatic brain injury is poorly understood. *Methods:* We surveyed 2525 U.S. Army infantry soldiers 3 to 4 months after their return from a year-long deployment to Iraq. Validated clinical instruments were used to compare soldiers reporting mild traumatic brain injury, defined as an injury with loss of consciousness or altered mental status (e.g., dazed or confused), with soldiers who reported other injuries. *Results:* Of 2525 soldiers, 124 (4.9%) reported injuries with loss of consciousness, 260 (10.3%) reported injuries with altered mental status, and 435 (17.2%) reported other injuries during deployment. Of those reporting loss of consciousness, 43.9% met criteria for post-traumatic stress disorder (PTSD), as compared with 27.3% of those reporting altered mental status, 16.2% with other injuries, and 9.1% with no injury. Soldiers with mild traumatic brain injury, primarily those who had loss of consciousness, were significantly more likely to report poor general health, missed workdays, medical visits, and a high number of somatic and postconcussive symptoms than were soldiers with other injuries. However, after adjustment for PTSD and depression, mild traumatic brain injury was no longer significantly associated with these physical health outcomes or symptoms, except for headache. *Conclusions:* Mild traumatic brain injury (i.e., concussion) occurring among soldiers deployed in Iraq is strongly associated with PTSD and physical health problems 3 to 4 months after the soldiers return home. PTSD and depression are important mediators of the relationship between mild traumatic brain injury and physical health problems.

Iverson, G. L. (2016). **Suicide and chronic traumatic encephalopathy.** *Journal of Neuropsychiatry and Clinical Neurosciences, 28*, 9-16. doi.org/10.1176/appi.neuropsych.15070172 For nearly 80 years, suicidality was not considered to be a core clinical feature of chronic traumatic encephalopathy (CTE). In recent years, suicide has been widely cited as being associated with CTE, and now depression has been proposed to be one of three core diagnostic features alongside cognitive impairment and anger control problems. This evolution of the clinical features has been reinforced by thousands of media stories reporting a connection between mental health problems in former athletes and military veterans, repetitive neurotrauma, and CTE. At present, the science underlying the causal assumption between repetitive neurotrauma, depression, suicide, and the neuropathology believed to be unique to CTE is inconclusive. Epidemiological evidence indicates that former National Football League players, for example, are at lower, not greater, risk for suicide than men in the general population. This article aims to discuss the critical issues and literature relating to these possible relationships.

Jak, A. J., Jurick, S., Crocker, L. D., Sanderson-Cimino, M., Aupperle, R., Rodgers, C. S., … & Twamley, E. W. (2019). **SMART-CPT for veterans with comorbid post-traumatic stress disorder and history of traumatic brain injury: A randomised controlled trial.** *Journal of Neurology, Neurosurgery, & Psychiatry, 90*, 333-341. doi:10.1136/jnnp-2018-319315 *Objective:* To better concurrently address emotional and neuropsychological symptoms common in veterans with comorbid post-traumatic stress disorder (PTSD) and history of traumatic brain injury (TBI), we integrated components of compensatory cognitive training from the Cognitive Symptom Management and Rehabilitation Therapy (CogSMART) programme into cognitive processing therapy (CPT) for PTSD to create a hybrid treatment, SMART-CPT (CogSMART+CPT). This study compared the efficacy of standard CPT with SMART-CPT for treatment of veterans with comorbid PTSD and history of TBI reporting cognitive symptoms. *Methods:* One hundred veterans with PTSD, a history of mild to moderate TBI and current cognitive complaints were randomised and received individually delivered CPT or SMART-CPT for 12 weeks. Participants underwent psychological, neurobehavioural and neuropsychological assessments at baseline, on completion of treatment and 3 months after treatment. *Results:* Both CPT and SMART-CPT resulted in clinically significant reductions in PTSD and postconcussive symptomatology and improvements in quality of life. SMART-CPT resulted in additional improvements in the neuropsychological domains of attention/working memory, verbal learning/memory and novel problem solving. *Conclusion:* SMART-CPT, a mental health intervention for PTSD, combined with compensatory cognitive training strategies, reduces PTSD and neurobehavioural symptoms and also provides added value by improving cognitive functioning.

Jorge, R. E., Acion, L., Starkstein, S. E., & Magnotta, V. (2007). **Hippocampal volume and mood disorders after traumatic brain injury.** *Biological Psychiatry, 62*, 332-338. doi:10.1016/j.biopsych.2006.07.024 *Background:* Recent evidence from clinical studies and animal models of traumatic brain injury (TBI) suggest that neuronal and glial loss might progress after the initial insult in selectively vulnerable regions of the brain such as the hippocampus. There is also evidence that hippocampal dysfunction plays a role in the pathogenesis of mood disorders. We examined the relationship between hippocampal damage and mood disorders after TBI and the effect of hippocampal atrophy on the outcome of TBI patients. *Methods:* The study group consisted of 37 patients with closed head injury who were evaluated at baseline and at 3, 6, and 12 months after trauma. Psychiatric diagnosis was made with a structured clinical interview and DSM-IV criteria. Quantitative magnetic resonance imaging scans were obtained at 3-months follow-up. *Results:* Patients with moderate to severe head injury had significantly lower hippocampal volumes than patients with mild TBI. Patients who developed mood disorders had significantly lower hippocampal volumes than patients without mood disturbance.

Furthermore, there was a significant interaction between mood disorders diagnosis and severity of TBI, by which patients with moderate to severe TBI who developed mood disorders had significantly smaller hippocampal volumes than patients with equivalent severe TBI who did not develop mood disturbance. Finally, reduced hippocampal volumes were associated with poor vocational outcome at 1-year follow-up. *Conclusions:* Our findings are consistent with a "double-hit" mechanism by which neural and glial elements already affected by trauma are further compromised by the functional changes associated with mood disorders (e.g., the neurotoxic effects of increased levels of cortisol or excitotoxic damage resulting from overactivation of glutaminergic pathways). Finally, patients with greater hippocampal damage were less likely to return to a productive life 1 year after trauma.

Kinnunen, K. M., Greenwood, R., Powell, J. H., Leech, R., Hawkins, P. C., Bonnelle, V., … & Sharp, D. J. (2011). **White matter damage and cognitive impairment after traumatic brain injury**. *Brain, 134*, 449-463. doi:10.1093/brain/awq347 White matter disruption is an important determinant of cognitive impairment after brain injury, but conventional neuroimaging underestimates its extent. In contrast, diffusion tensor imaging provides a validated and sensitive way of identifying the impact of axonal injury. The relationship between cognitive impairment after traumatic brain injury and white matter damage is likely to be complex. We applied a flexible technique—tract-based spatial statistics—to explore whether damage to specific white matter tracts is associated with particular patterns of cognitive impairment. The commonly affected domains of memory, executive function and information processing speed were investigated in 28 patients in the post-acute/chronic phase following traumatic brain injury and in 26 age-matched controls. Analysis of fractional anisotropy and diffusivity maps revealed widespread differences in white matter integrity between the groups. Patients showed large areas of reduced fractional anisotropy, as well as increased mean and axial diffusivities, compared with controls, despite the small amounts of cortical and white matter damage visible on standard imaging. A stratified analysis based on the presence or absence of microbleeds (a marker of diffuse axonal injury) revealed diffusion tensor imaging to be more sensitive than gradient-echo imaging to white matter damage. The location of white matter abnormality predicted cognitive function to some extent. The structure of the fornices was correlated with associative learning and memory across both patient and control groups, whilst the structure of frontal lobe connections showed relationships with executive function that differed in the two groups. These results highlight the complexity of the relationships between white matter structure and cognition. Although widespread and, sometimes, chronic abnormalities of white matter are identifiable following traumatic brain injury, the impact of these changes on cognitive function is likely to depend on damage to key pathways that link nodes in the distributed brain networks supporting high-level cognitive functions.

Klimova, A., Korgaonkar, M. S., Whitford, T., & Bryant, R. A. (2019). **Diffusion tensor imaging analysis of mild traumatic brain injury and posttraumatic stress disorder.** *Biological Psychiatry 4*, 81-90. doi:10.1016/j.bpsc.2018.10.004 *Background:* Debate exists over the extent to which dysfunctions arising from mild traumatic brain injury (mTBI) are distinct from posttraumatic stress disorder (PTSD). *Methods:* This study investigated 1) the white matter integrity of participants with either mTBI or PTSD, and 2) the relationship between white matter integrity andpostconcussive syndrome. The sample comprised 110 civilians (mTBI group = 40; PTSD group = 32; age- and sex-matched trauma-exposed control subjects = 38) recruited from community advertising. Indicators of white matter abnormalities were fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity. PTSD symptoms were indexed by the Clinician-Administered PTSD Scale, and postconcussive symptoms were assessed using the Somaticand Psychological Health Report measure. *Results:* Fractional anisotropy was reduced in mTBI participants in the corpus callosum, tracts of the brainstem, projection fibers,association fibers, and limbic fibers compared with both PTSD and trauma-exposed control subjects. This decrease in fractional anisotropy was observed in the context of concurrent changes in radial diffusivity, axial diffusivity, and mean diffusivity. Postconcussive symptoms were largely explained by PTSD severity rather than by changes in brain white matter. mTBI appears to be characterized by distinct reductions in white matter integrity, and this cannot be attributed to PTSD. *Conclusions:* PTSD symptoms appear to be more strongly associated with postconcussive syndrome than with white matter compromise. These findings extend epidemiological evidence of the relative associations of PTSD and mTBI with postconcussive syndrome.

Lindemer, E. R., Salat, D. H., Leritz, E. C., McGlinchey, R. E., & Milberg, W. P. (2013). **Reduced cortical thickness with increased lifetime burden of PTSD in OEF/OIF Veterans and the impact of comorbid TBI.** *Neuroimage: Clinical, 2*, 601-611. doi:10.1016/j.nicl.2013.04.009 Posttraumatic stress disorder (PTSD) and mild traumatic brain injury (mTBI) in military personnel is increasing dramatically following the OEF/OIF conflicts and is associated with alterations to brain structure. The present study examined the relationship between PTSD and cortical thickness, and its possible modification by mTBI, in a 104-subject OEF/OIF veteran cohort ranging in age from 20 to 62 years. For each participant, two T1-weighted scans were averaged to create high-resolution images for calculation of regional cortical thickness. PTSD symptoms were assessed using the Clinician Administered PTSD Scale (CAPS) and scores were derived based on the previous month's symptoms ("current") and a Cumulative Lifetime Burden of PTSD (CLB-P) reflecting the integral of CAPS scores across the lifetime. Mild TBI was diagnosed using the Boston Assessment of TBI-Lifetime (BAT-L). Results demonstrated a clear negative relationship between current PTSD severity and thickness in both postcentral gyri and middle temporal gyri. This relationship was stronger and more extensive when considering lifetime burden (CLB-P), demonstrating the importance of looking at trauma in the context of an individual's lifetime, rather than only at their current symptoms. Finally, interactions with current PTSD only and comorbid current PTSD and mTBI were found in several regions, implying an additive effect of lifetime PTSD and mTBI on cortical thickness.

Ling, H., Holton, J. L., Shaw, K., Davey, K., Lashley, T., & Revesz, T. (2015). **Histological evidence of chronic traumatic encephalopathy in a large series of neurodegenerative diseases.** *Acta Neuropathologica, 13*0, 891-893. doi:10.1007/s00401-015-1496-y Chronic traumatic encephalopathy (CTE) is a long-term neurodegenerative consequence of repetitive traumatic brain injury (rTBI). The histological features of CTE are characterised by

neurofibrillary tangles (NFTs) composed of both 3-repeat and 4-repeat tau isoforms and astrocytic tau pathology (ATs) commonly in the frontal and temporal cortices and are distinct from other tauopathies. The recent classification delineates 4 pathological stages with progression of tau pathology from multifocal (I and II) to widespread disease (III and IV). Of 68 CTE cases in the McKee series with history of rTBIs, only 43 had pure CTE pathology, the other 25 cases (37 %) had co-morbid neurodegenerative disorders (NDDs) including Lewy body disease, motor neuron disease, Alzheimer's disease (AD), frontotemporal lobar degeneration (FTLD), Pick's disease and progressive supranuclear palsy (PSP). TDP-43 pathology was found in 85 % of CTE cases across all disease stages. Our group reported an ex-professional boxer with dual pathologies of CTE and PSP. It is possible that rTBIs or the existence of chronic CTE-tau pathology play a role in triggering the deposition of other abnormal proteins in the brain. The existing literature mainly focused on high-risk individuals especially contact sport athletes. This study aimed to investigate the prevalence of histological evidence of CTE in the general population with or without NDDs which is currently not known.

Logue, M. W., van Rooij, S. J. H., Dennis, E. L., Davis, S. L., Hayes, J. P., Stevens, J. S., … & Morey, R. A. (2018). **Smaller hippocampal volume in posttraumatic stress disorder: A multisite ENIGMA-PGC study: Subcortical volumetry results from posttraumatic stress disorder consortia.** *Biological Psychiatry, 83*, 244-253. doi:10.1016/j.biopsych.2017.09.006 *Background:* Many studies report smaller hippocampal and amygdala volumes in posttraumatic stress disorder (PTSD), but findings have not always been consistent. Here, we present the results of a large-scale neuroimaging consortium study on PTSD conducted by the Psychiatric Genomics Consortium (PGC)–Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) PTSD Working Group. *Methods:* We analyzed neuroimaging and clinical data from 1868 subjects (794 PTSD patients) contributed by 16 cohorts, representing the largest neuroimaging study of PTSD to date. We assessed the volumes of eight subcortical structures (nucleus accumbens, amygdala, caudate, hippocampus, pallidum, putamen, thalamus, and lateral ventricle). We used a standardized image-analysis and quality-control pipeline established by the ENIGMA consortium. *Results:* In a meta-analysis of all samples, we found significantly smaller hippocampi in subjects with current PTSD compared with trauma-exposed control subjects (Cohen's $d = -0.17$, $p = .00054$), and smaller amygdalae ($d = -0.11$, $p = .025$), although the amygdala finding did not survive a significance level that was Bonferroni corrected for multiple subcortical region comparisons ($p < .0063$). *Conclusions:* Our study is not subject to the biases of meta-analyses of published data, and it represents an important milestone in an ongoing collaborative effort to examine the neurobiological underpinnings of PTSD and the brain's response to trauma.

Marioni, R. E., Shah, S., McRae, A. F., Chen, B. H., Colicino, E., Harris, S. E., … & Deary, I. J. (2015). **DNA methylation age of blood predicts all-cause mortality in later life.** *Genome Biology, 16*, 25. doi:10.1186/s13059-015-0584-6 *Background:* DNA methylation levels change with age. Recent studies have identified biomarkers of chronological age based on DNA methylation levels. It is not yet known whether DNA methylation age captures aspects of biological age. *Results:* Here we test whether differences between people's chronological ages and estimated ages, DNA methylation age, predict all-cause mortality in later life. The difference between DNA methylation age and chronological age (Δage) was calculated in four longitudinal cohorts of older people. Meta-analysis of proportional hazards models from the four cohorts was used to determine the association between Δage and mortality. A 5-year higher Δage is associated with a 21% higher mortality risk, adjusting for age and sex. After further adjustments for childhood IQ, education, social class, hypertension, diabetes, cardiovascular disease, and *APOE* e4 status, there is a 16% increased mortality risk for those with a 5-year higher Δage. A pedigree-based heritability analysis of Δage was conducted in a separate cohort. The heritability of Δage was 0.43. *Conclusions:* DNA methylation-derived measures of accelerated aging are heritable traits that predict mortality independently of health status, lifestyle factors, and known genetic factors.

McAllister, T. W., Zafonte, R., Jain, S., Flashman, L. A., George, M. S., Grant, G. A., … & Stein, M. B. (2016). **Randomized placebo-controlled trial of methylphenidate or galantamine for persistent emotional and cognitive symptoms associated with PTSD and/or traumatic brain injury.** *Neuropsychopharmacology, 41*, 1191-1198. doi:10.1038/npp.2015.282 We report findings from a 12-week randomized double-blinded placebo-controlled trial of methylphenidate or galantamine to treat emotional and cognitive complaints in individuals ($n$=32) with a history of PTSD, TBI, or both conditions. In this small pilot study, methylphenidate treatment was associated with clinically meaningful and statistically significant improvement compared with placebo on the primary outcome, a measure of cognitive complaints (Ruff Neurobehavioral Inventory—Postmorbid Cognitive Scale), as well as on the secondary outcomes reflecting post-concussive (Rivermead Post Concussive Symptom Questionnaire) and post-traumatic stress symptoms (Posttraumatic Stress Disorder Checklist). Treatment was well tolerated. These results suggest the need for a larger RCT to replicate and confirm these findings. Design considerations for such a trial should include the need for multiple sites to facilitate adequate recruitment and extension of the treatment and follow-up periods.

McKee, A. C., Cairns, N. J., Dickson, D. W., Folkerth, R. D., Keene, C. D., Litvan, I., … & the TBI/CTE group. (2016). **The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy.** *Acta Neuropathologica, 131*, 75-86. doi:10.1007/s00401-015-1515-z Chronic traumatic encephalopathy (CTE) is a neurodegeneration characterized by the abnormal accumulation of hyperphosphorylated tau protein within the brain. Like many other neurodegenerative conditions, at present, CTE can only be definitively diagnosed by post-mortem examination of brain tissue. As the first part of a series of consensus panels funded by the NINDS/NIBIB to define the neuropathological criteria for CTE, preliminary neuropathological criteria were used by 7 neuropathologists to blindly evaluate 25 cases of various tauopathies, including CTE, Alzheimer's disease, progressive supranuclear palsy, argyrophilic grain disease, corticobasal degeneration, primary age-related tauopathy, and parkinsonism dementia complex of Guam. The results demonstrated that there was good agreement among the neuropathologists who reviewed

the cases (Cohen's kappa, 0.67) and even better agreement between reviewers and the diagnosis of CTE (Cohen's kappa, 0.78). Based on these results, the panel defined the pathognomonic lesion of CTE as an accumulation of abnormal hyperphosphorylated tau (p-tau) in neurons and astroglia distributed around small blood vessels at the depths of cortical sulci and in an irregular pattern. The group also defined supportive but non-specific p-tau-immunoreactive features of CTE as: pretangles and NFTs affecting superficial layers (layers II–III) of cerebral cortex; pretangles, NFTs or extracellular tangles in CA2 and pretangles and proximal dendritic swellings in CA4 of the hippocampus; neuronal and astrocytic aggregates in subcortical nuclei; thorn-shaped astrocytes at the glial limitans of the subpial and periventricular regions; and large grain-like and dot-like structures. Supportive non-p-tau pathologies include TDP-43 immunoreactive neuronal cytoplasmic inclusions and dot-like structures in the hippocampus, anteromedial temporal cortex and amygdala. The panel also recommended a minimum blocking and staining scheme for pathological evaluation and made recommendations for future study. This study provides the first step towards the development of validated neuropathological criteria for CTE and will pave the way towards future clinical and mechanistic studies.

Mez, J., Daneshvar, D. H., Kiernan, P. T., Abdolmohammadi, B., Alvarez, V. E., Huber, B. R., … & McKee, A., C. (2017). **Clinicopathological evaluation of chronic traumatic encephalopathy in players of American football.** *JAMA, 318*, 360-370. doi:10.1001/jama.2017.8334 Importance: Players of American football may be at increased risk of long-term neurological conditions, particularly chronic traumatic encephalopathy (CTE). *Objective:* To determine the neuropathological and clinical features of deceased football players with CTE. Design, Setting, And Participants: Case series of 202 football players whose brains were donated for research. Neuropathological evaluations and retrospective telephone clinical assessments (including head trauma history) with informants were performed blinded. Online questionnaires ascertained athletic and military history. Exposures: Participation in American football at any level of play. Main Outcomes And Measures: Neuropathological diagnoses of neurodegenerative diseases, including CTE, based on defined diagnostic criteria; CTE neuropathological severity (stages I to IV or dichotomized into mild [stages I and II] and severe [stages III and IV]); informant-reported athletic history and, for players who died in 2014 or later, clinical presentation, including behavior, mood, and cognitive symptoms and dementia. *Results:* Among 202 deceased former football players (median age at death, 66 years [interquartile range, 47-76 years]), CTE was neuropathologically diagnosed in 177 players (87%; median age at death, 67 years [interquartile range, 52-77 years]; mean years of football participation, 15.1 [SD, 5.2]), including 0 of 2 pre-high school, 3 of 14 high school (21%), 48 of 53 college (91%), 9 of 14 semiprofessional (64%), 7 of 8 Canadian Football League (88%), and 110 of 111 National Football League (99%) players. Neuropathological severity of CTE was distributed across the highest level of play, with all 3 former high school players having mild pathology and the majority of former college (27 [56%]), semiprofessional (5 [56%]), and professional (101 [86%]) players having severe pathology. Among 27 participants with mild CTE pathology, 26 (96%) had behavioral or mood symptoms or both, 23 (85%) had cognitive symptoms, and 9 (33%) had signs of dementia. Among 84 participants with severe CTE pathology, 75 (89%) had behavioral or mood symptoms or both, 80 (95%) had cognitive symptoms, and 71 (85%) had signs of dementia. Conclusions And Relevance: In a convenience sample of deceased football players who donated their brains for research, a high proportion had neuropathological evidence of CTE, suggesting that CTE may be related to prior participation in football.

Miller, D. R., Hayes, S. M., Hayes, J. P., Spielberg, J. M., Lafleche, G., & Verfaellie, M. (2017). **Default mode network subsystems are differentially disrupted in posttraumatic stress disorder.** *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 2*, 363-371. doi:10.1016/j.bpsc.2016.12.006 *Background:* Posttraumatic stress disorder (PTSD) is a psychiatric disorder characterized by debilitating re-experiencing, avoidance, and hyperarousal symptoms following trauma exposure. Recent evidence suggests that individuals with PTSD show disrupted functional connectivity in the default mode network, an intrinsic network that consists of a midline core, a medial temporal lobe (MTL) subsystem, and a dorsomedial prefrontal cortex (PFC) subsystem. The present study examined whether functional connectivity in these subsystems is differentially disrupted in PTSD. *Methods:* Sixty-nine returning war veterans with PTSD and 44 trauma-exposed veterans without PTSD underwent resting-state functional magnetic resonance imaging. To examine functional connectivity, seeds were placed in the core hubs of the default mode network, namely the posterior cingulate cortex (PCC) and anterior medial PFC, and in each subsystem. *Results:* Compared to control subjects, individuals with PTSD had reduced functional connectivity between the PCC and the hippocampus, a region of the MTL subsystem. Groups did not differ in connectivity between the PCC and dorsomedial PFC subsystem or between the anterior medial PFC and any region within either subsystem. In the PTSD group, connectivity between the PCC and hippocampus was negatively associated with avoidance/numbing symptoms. Examination of the MTL and dorsomedial PFC subsystems revealed reduced anticorrelation between the ventromedial PFC seed of the MTL subsystem and the dorsal anterior cingulate cortex in the PTSD group. *Conclusions:* Our results suggest that selective alterations in functional connectivity in the MTL subsystem of the default mode network in PTSD may be an important factor in PTSD pathology and symptomatology.

Miller, D. R., Hayes, J. P., Lafleche, G., Salat, D. H., & Verfaellie, M. (2016). **White matter abnormalities are associated with chronic postconcussion symptoms in blast-related mild traumatic brain injury.** *Human Brain Mapping, 37*, 220-229. doi:10.1002/hbm.23022 Blast-related mild traumatic brain injury (mTBI) is a common injury among Iraq and Afghanistan military veterans due to the frequent use of improvised explosive devices. A significant minority of individuals with mTBI report chronic postconcussion symptoms (PCS), which include physical, emotional, and cognitive complaints. However, chronic PCS are nonspecific and are also associated with mental health disorders such as posttraumatic stress disorder (PTSD). Identifying the mechanisms that contribute to chronic PCS is particularly challenging in blast-related mTBI, where the incidence of comorbid PTSD is high. In this study, we examined whether blast-related mTBI is associated with diffuse white matter changes, and whether these neural changes are associated with chronic PCS.

Ninety Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) veterans were assigned to one of three groups including a blast-exposed no – TBI group, a blast-related mTBI without loss of consciousness (LOC) group (mTBI – LOC), and a blast-related mTBI with LOC group (mTBI + LOC). PCS were measured with the Rivermead Postconcussion Questionnaire. Results showed that participants in the mTBI + LOC group had more spatially heterogeneous white matter abnormalities than those in the no – TBI group. These white matter abnormalities were significantly associated with physical PCS severity even after accounting for PTSD symptoms, but not with cognitive or emotional PCS severity. A mediation analysis revealed that mTBI + LOC significantly influenced physical PCS severity through its effect on white matter integrity. These results suggest that white matter abnormalities are associated with chronic PCS independent of PTSD symptom severity and that these abnormalities are an important mechanism explaining the relationship between mTBI and chronic physical PCS.

Petraglia, A. L., Plog, B. A., Dayawansa, S., Chen, M., Dashnaw, M. L., Czerniecka, K., … & Huang, J. H. (2014). **The spectrum of neurobehavioral sequelae after repetitive mild traumatic brain injury: A novel mouse model of chronic traumatic encephalopathy.** *Journal of Neurotrauma, 31*, 1211-1224. doi:10.1089/neu.2013.3255 There has been an increased focus on the neurological sequelae of repetitive mild traumatic brain injury (TBI), particularly neurodegenerative syndromes, such as chronic traumatic encephalopathy (CTE); however, no animal model exists that captures the behavioral spectrum of this phenomenon. We sought to develop an animal model of CTE. Our novel model is a modification and fusion of two of the most popular models of TBI and allows for controlled closed-head impacts to unanesthetized mice. Two-hundred and eighty 12-week-old mice were divided into control, single mild TBI (mTBI), and repetitive mTBI groups. Repetitive mTBI mice received six concussive impacts daily for 7 days. Behavior was assessed at various time points. Neurological Severity Score (NSS) was computed and vestibulomotor function tested with the wire grip test (WGT). Cognitive function was assessed with the Morris water maze (MWM), anxiety/risk-taking behavior with the elevated plus maze, and depression-like behavior with the forced swim/tail suspension tests. Sleep electroencephalogram/electromyography studies were performed at 1 month. NSS was elevated, compared to controls, in both TBI groups and improved over time. Repetitive mTBI mice demonstrated transient vestibulomotor deficits on WGT. Repetitive mTBI mice also demonstrated deficits in MWM testing. Both mTBI groups demonstrated increased anxiety at 2 weeks, but repetitive mTBI mice developed increased risk-taking behaviors at 1 month that persist at 6 months. Repetitive mTBI mice exhibit depression-like behavior at 1 month. Both groups demonstrate sleep disturbances. We describe the neurological sequelae of repetitive mTBI in a novel mouse model, which resemble several of the neuropsychiatric behaviors observed clinically in patients sustaining repetitive mild head injury.

Rice, S. M., Parker, A. G., Rosenbaum, S., Bailey, A., Mawren, D., & Purcell, R. (2018). **Sport-related concussion and mental health outcomes in elite athletes: A systematic review.** *Sports Medicine, 48*, 447-465. doi:10.1007/s40279-017-0810-3 *Background:* Elite athletes can experience a diverse range of symptoms following post-concussive injury. The impact of sport-related concussion on specific mental health outcomes is unclear in this population. *Objective:* The aim was to appraise the evidence base regarding the association between sport-related concussion and mental health outcomes in athletes competing at elite and professional levels. *Methods:* A systematic search of PubMed, EMBASE, SPORTDiscus, PsycINFO, Cochrane, and Cinahl databases was conducted. *Results:* A total of 27 studies met inclusion criteria for review. Most of the included studies (67%,*n* = 18) were published in 2014 or later. Study methodology and reporting varied markedly. The extant research has been conducted predominantly in North America (USA, *n* = 23 studies; Canada, *n* = 3), often in male only (44.4%, *n* = 12) and college (70.4%, *n* = 19) samples. Depression is the most commonly studied mental health outcome (70.4%, *n* = 19 studies). Cross-sectional retrospective studies and studies including a control comparison tend to support an association between concussion exposure and depression symptoms, although several studies report that these symptoms resolved in the medium term (i.e. 1 month) post-concussion. Evidence for anxiety is mixed. There are insufficient studies to draw conclusions for other mental health domains. *Conclusion:* Consistent with current recommendations to assess mood disturbance in post-concussive examinations, current evidence suggests a link between sports-related concussion and depression symptoms in elite athletes. Causation cannot be determined at this stage of enquiry because of the lack of well-designed, prospective studies. More research is required that considers a range of mental health outcomes in diverse samples of elite athletes/sports.

Russell, A. L., Richardson, M. R., Bauman, B. M., Hernandez, I. M., Saperstein, S., Handa, R. J., & Wu, T. J. (2018). **Differential responses of the HPA axis to mild blast traumatic brain injury in male and female mice.** *Endocrinology, 159*, 2363-2375. doi:10.1210/en.2018-00203 Traumatic brain injury (TBI) affects 10 million people worldwide, annually. TBI is linked to increased risk of psychiatric disorders. TBI, induced by explosive devices, has a unique phenotype. Over one-third of people exposed to blast-induced TBI (bTBI) have prolonged neuroendocrine deficits, shown by anterior pituitary dysfunction. Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis is linked to increased risk for psychiatric disorders. Not only is there limited information on how the HPA axis responds to mild bTBI (mbTBI), sex differences are understudied. We examined central and peripheral HPA axis reactivity, 7 to 10 days after mbTBI in male and female mice. Males exposed to mbTBI had increased restraint-induced serum corticosterone (CORT), but attenuated restraint-induced corticotropin-releasing factor (CRF)/c-Fos-immunoreactivity (ir) in the paraventricular nucleus of the hypothalamus (PVN). Females displayed an opposite response, with attenuated restraint-induced CORT and enhanced restraint-induced PVN CRF/c-Fos-ir. We examined potential mechanisms underlying this dysregulation and found that mbTBI did not affect pituitary (pro-opiomelanocortin and CRF receptor subtype 1) or adrenal (11β-hydroxylase, 11β-dehydrogenase 1, and melanocortin 2 receptor) gene expression. mbTBI did not alter mineralocorticoid or glucocorticoid gene expression in the PVN or relevant limbic structures. In females, but not males, mbTBI decreased c-Fos-ir in non-neuroendocrine (presumably preautonomic) CRF neurons in the PVN. Whereas we demonstrated a sex-dependent link to stress dysregulation of preautonomic neurons in females, we hypothesize

that mbTBI may disrupt limbic pathways involved in HPA axis coordination in males. Overall, mbTBI altered the HPA axis in a sex-dependent manner, highlighting the importance of developing therapies to target individual strategies that males and females use to cope with mbTBI.

Schneider, A. L., Hostetter, T. A., Homaifar, B. Y., Forster, J. E., Olson-Madden, J. H., Matarazzo, B. B., … & Brenner, L. A. (2016). **Responses to traumatic brain injury screening questions and suicide attempts among those seeking Veterans Health Administration mental health services.** *Frontiers in Psychiatry, 7*, 59. doi:10.3389/fpsyt.2016.00059 *Background:* Psychometrically sound screening tools available to aid in the identification of lifetime history of traumatic brain injury (TBI) are limited. As such, the Traumatic Brain Injury-4 (TBI-4) was developed and implemented in a Veterans Health Administration (VHA) mental health clinic. To provide information regarding both the predictive validity and clinical utility of the TBI-4, the relationship between screening results and future suicide attempts was evaluated. *Objective:* The aim of this study was to determine whether a positive screen on the TBI-4 was associated with increased risk for suicide attempt within 1-year post screening. *Methods:* The TBI-4 was administered to 1,097 Veterans at the time of mental health intake. Follow-up data regarding suicide attempts for the year post-mental health intake were obtained from suicide behavior reports (SBRs) in Veteran electronic medical records (EMRs). Fisher's exact tests were used to determine the proportion of suicide attempts by TBI-4 status. *Results:* In the year post TBI-4 screening, significantly more Veterans who screened positive had a documented suicide attempt as compared to those who screened negative ($p = 0.003$). *Conclusion:* Those with a positive TBI screen at mental health intake had a higher proportion of SBRs than those who screened negative for TBI. Findings provided further psychometric support for the TBI-4. Moreover, results suggest the inclusion of this screen could prove to be helpful in identifying those who may be at risk for future suicide attempt within 1-year post screening.

Schneiderman, A. I., Braver, E. R., & Kang, H. K. (2008). **Understanding sequelae of injury mechanisms and mild traumatic brain injury incurred during the conflicts in Iraq and Afghanistan: Persistent postconcussive symptoms and posttraumatic stress disorder.** *American Journal of Epidemiology, 167*, 1446-1452. doi:10.1093/aje/kwn068 A cross-sectional study of military personnel following deployment to conflicts in Iraq or Afghanistan ascertained histories of combat theater injury mechanisms and mild traumatic brain injury (TBI) and current prevalence of posttraumatic stress disorder (PTSD) and postconcussive symptoms. Associations among injuries, PTSD, and postconcussive symptoms were explored. In February 2005, a postal survey was sent to Iraq/Afghanistan veterans who had left combat theaters by September 2004 and lived in Maryland; Washington, DC; northern Virginia; and eastern West Virginia. Immediate neurologic symptoms postinjury were used to identify mild TBI. Adjusted prevalence ratios and 95% confidence intervals were computed by using Poisson regression. About 12% of 2,235 respondents reported a history consistent with mild TBI, and 11% screened positive for PTSD. Mild TBI history was common among veterans injured by bullets/shrapnel, blasts, motor vehicle crashes, air/water transport, and falls. Factors associated with PTSD included reporting multiple injury mechanisms (prevalence ratio = 3.71 for three or more mechanisms, 95% confidence interval: 2.23, 6.19) and combat mild TBI (prevalence ratio = 2.37, 95% confidence interval: 1.72, 3.28). The strongest factor associated with postconcussive symptoms was PTSD, even after overlapping symptoms were removed from the PTSD score (prevalence ratio = 3.79, 95% confidence interval: 2.57, 5.59).

Schuff, N., Zhang, Y., Zhan, W., Lenoci, M., Ching, C., Boreta, L., … & Neylan, T. C. (2011). **Patterns of altered cortical perfusion and diminished subcortical integrity in posttraumatic stress disorder: An MRI study.** *Neuroimage, 54*, S62-S68. doi:10.1016/j.neuroimage.2010.05.024 Posttraumatic stress disorder (PTSD) accounts for a substantial proportion of casualties among surviving soldiers of the Iraq and Afghanistan wars. Currently, the assessment of PTSD is based exclusively on symptoms, making it difficult to obtain an accurate diagnosis. This study aimed to find potential imaging markers for PTSD using structural, perfusion, and diffusion magnetic resonance imaging (MRI) together. Seventeen male veterans with PTSD (45 ± 14 years old) and 15 age-matched male veterans without PTSD had measurements of regional cerebral blood flow (rCBF) using arterial spin labeling (ASL) perfusion MRI. A slightly larger group had also measurements of white matter integrity using diffusion tensor imaging (DTI) with computations of regional fractional anisotropy (FA). The same subjects also had structural MRI of the hippocampal subfields as reported recently (W. Zhen et al. Arch Gen Psych 2010;67(3):296–303). On ASL-MRI, subjects with PTSD had increased rCBF in primarily right parietal and superior temporal cortices. On DTI, subjects with PTSD had FA reduction in white matter regions of the prefrontal lobe, including areas near the anterior cingulate cortex and prefrontal cortex as well as in the posterior angular gyrus. In conclusion, PTSD is associated with a systematic pattern of physiological and structural abnormalities in predominantly frontal lobe and limbic brain regions. Structural, perfusion, and diffusion MRI together may provide a signature for a PTSD marker.

Shin, L. M., Orr, S. P., Carson, M. A., Rauch, S. L., Macklin, M. L., Lasko, N. B., . . . & Pitman, R. K. (2004). **Regional cerebral blood flow in the amygdala and medial prefrontal cortex during traumatic imagery in male and female Vietnam veterans with PTSD.** *Archives of General Psychiatry, 61*, 168-176. doi:10.1001/archpsyc.61.2.168 *Context:* Theoretical neuroanatomic models of posttraumatic stress disorder (PTSD) and the results of previous neuroimaging studies of PTSD highlight the potential importance of the amygdala and medial prefrontal regions in this disorder. However, the functional relationship between these brain regions in PTSD has not been directly examined. *Objective:* To examine the relationship between the amygdala and medial prefrontal regions during symptom provocation in male combat veterans (MCVs) and female nurse veterans (FNVs) with PTSD. *Design:* Case-control study. *Setting:* Academic medical center. Participants: Volunteer sample of 17 (7 men and 10 women) Vietnam veterans with PTSD (PTSD group) and 19 (9 men and 10 women) Vietnam veterans without PTSD (control group). Main Outcome Measures: We used positron emission tomography and the script-driven imagery paradigm to study regional cerebral blood flow (rCBF) during the recollection of personal traumatic and neutral events. Psychophysiologic and emotional self-report data also were

obtained to confirm the intended effects of script-driven imagery. *Results:* The PTSD group exhibited rCBF decreases in medial frontal gyrus in the traumatic vs neutral comparison. When this comparison was conducted separately by subgroup, MCVs and FNVs with PTSD exhibited these medial frontal gyrus decreases. Only MCVs exhibited rCBF increases in the left amygdala. However, for both subgroups with PTSD, rCBF changes in medial frontal gyrus were inversely correlated with rCBF changes in the left amygdala and the right amygdala/periamygdaloid cortex. Furthermore, in the traumatic condition, for both subgroups with PTSD, symptom severity was positively related to rCBF in the right amygdala and negatively related to rCBF in medial frontal gyrus. *Conclusions:* These results suggest a reciprocal relationship between medial prefrontal cortex and amygdala function in PTSD and opposing associations between activity in these regions and symptom severity consistent with current functional neuroanatomic models of this disorder.

Shively, S. B., Horkayne-Szakaly, I., Jones, R. V., Kelly, J. P., Armstrong, R. C., & Perl, D. P. (2016). **Characterisation of interface astroglial scarring in the human brain after blast exposure: A post-mortem case series.** *Lancet Neurology, 15*, 944-953. doi:10.1016/S1474-4422(16)30057-6 *Background:* No evidence-based guidelines are available for the definitive diagnosis or directed treatment of most blast-associated traumatic brain injuries, partly because the underlying pathology is unknown. Moreover, few neuropathological studies have addressed whether blast exposure produces unique lesions in the human brain, and if those lesions are comparable with impact-induced traumatic brain injury. We aimed to test the hypothesis that blast exposure produces unique patterns of damage, differing from that associated with impact-induced, non-blast traumatic brain injuries. *Methods:* In this post-mortem case series, we investigated several features of traumatic brain injuries, using clinical histopathology techniques and markers, in brain specimens from male military service members with chronic blast exposures and from those who had died shortly after severe blast exposures. We then compared these results with those from brain specimens from male civilian (ie, non-military) cases with no history of blast exposure, including cases with and without chronic impact traumatic brain injuries and cases with chronic exposure to opiates, and analysed the limited associated clinical histories of all cases. Brain specimens had been archived in tissue banks in the USA. Findings: We analysed brain specimens from five cases with chronic blast exposure, three cases with acute blast exposure, five cases with chronic impact traumatic brain injury, five cases with exposure to opiates, and three control cases with no known neurological disorders. All five cases with chronic blast exposure showed prominent astroglial scarring that involved the subpial glial plate, penetrating cortical blood vessels, grey–white matter junctions, and structures lining the ventricles; all cases of acute blast exposure showed early astroglial scarring in the same brain regions. All cases of chronic blast exposure had an antemortem diagnosis of post traumatic stress disorder. The civilian cases, with or without history of impact traumatic brain injury or a history of opiate use, did not have any astroglial scarring in the brain regions analysed. *Interpretation:* The blast exposure cases showed a distinct and previously undescribed pattern of interface astroglial scarring at boundaries between brain parenchyma and fluids, and at junctions between grey and white matter. This distinctive pattern of scarring may indicate specific areas of damage from blast exposure consistent with the general principles of blast biophysics, and further, could account for aspects of the neuropsychiatric clinical sequelae reported. The generalisability of these findings needs to be explored in future studies, as the number of cases, clinical data, and tissue availability were limited.

Spielberg, J. M., McGlinchey, R. E., Milberg, W. P., & Salat, D. H. (2015). **Brain network disturbance related to posttraumatic stress and traumatic brain injury in veterans.** *Biological Psychiatry, 78*, 210-216. doi:10.1016/j.biopsych.2015.02.013 *Background:* Understanding the neural causes and consequences of posttraumatic stress disorder (PTSD) and mild traumatic brain injury (mTBI) is a high research priority, given the high rates of associated disability and suicide. Despite remarkable progress in elucidating the brain mechanisms of PTSD and mTBI, a comprehensive understanding of these conditions at the level of brain networks has yet to be achieved. The present study sought to identify functional brain networks and topological properties (measures of network organization and function) related to current PTSD severity and mTBI. *Methods:* Graph theoretic tools were used to analyze resting-state functional magnetic resonance imaging data from 208 veterans of Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn, all of whom had experienced a traumatic event qualifying for PTSD criterion A. Analyses identified brain networks and topological network properties linked to current PTSD symptom severity, mTBI, and the interaction between PTSD and mTBI. *Results:* Two brain networks were identified in which weaker connectivity was linked to higher PTSD re-experiencing symptoms, one of which was present only in veterans with comorbid mTBI. Re-experiencing was also linked to worse functional segregation (necessary for specialized processing) and diminished influence of key regions on the network, including the hippocampus. *Conclusions:* Findings of this study demonstrate that PTSD re-experiencing symptoms are linked to weakened connectivity in a network involved in providing contextual information. A similar relationship was found in a separate network typically engaged in the gating of working memory, but only in veterans with mTBI.

Sripada, R. K., Rauch, S. A. M., Tuerk, P. W., Smith, E., Defever, A. M., Mayer, R. A., … & Venners, M. (2013). **Mild traumatic brain injury and treatment response in prolonged exposure for PTSD.** *Journal of Traumatic Stress, 26*, 369-375. doi:10.1002/jts.21813 A proportion of U.S. veterans returning from Iraq and Afghanistan have experienced mild traumatic brain injury (mTBI), which is associated with increased risk for developing posttraumatic stress disorder (PTSD). Prolonged Exposure (PE) has proven effectiveness in the treatment of PTSD; however, some clinicians have reservations about using PE with individuals with a history of mTBI. We examined the impact of PE for veterans with PTSD and with or without a history of mTBI in a naturalistic sample of 51 veterans who received PE at a Veterans Health Administration PTSD clinic. We also analyzed previously collected data from a controlled trial of 22 veterans randomly assigned to PE or present centered therapy. For both sets of data, we found that PE reduced symptom levels and we also did not detect an effect for mTBI, suggesting that PE may be helpful for individuals with PTSD and a history of mTBI.

Stein, M. B., & McAllister, T. W. (2009). **Exploring the convergence of posttraumatic stress disorder and mild traumatic brain injury.** *American Journal of Psychiatry, 166*, 768-776. doi:10.1176/appi.ajp.2009.08101604 The authors examine the relationship of the two signature injuries experienced by military personnel serving in Afghanistan and Iraq: posttraumatic stress disorder (PTSD) and mild traumatic brain injury (mild TBI). Studies show that a substantial minority of those serving develop persistent emotional sequelae (such as PTSD and other psychological health problems) and/or somatic or cognitive sequelae (postconcussive symptoms) of traumatic exposure. Remarkably, the mechanism (emotional versus biomechanical) and locus (head versus other regions) of injury are weak determinants of whether an individual develops PTSD, persistent postconcussive symptoms, or both. Preexisting or traumatically acquired cognitive dysfunction can increase the risk for these syndromes, probably by reducing cognitive reserve. Structural and functional neuroimaging studies can be interpreted to explain part of the shared symptomatic and functional variance in these syndromes, but this literature is far from consistent and serves mainly to raise new, challenging questions about mutual pathophysiology. The frequent confluence of PTSD and persistent postconcussive symptoms in military personnel strains the bounds of these constructs. New studies are needed to improve our understanding of how emotional and biomechanical stressors can yield these adverse outcomes and how such outcomes can be prevented and treated.

Vargas, G., Rabinowitz, A., Meyer, J., & Arnett, P. A. (2015). **Predictors and prevalence of postconcussion depression symptoms in collegiate athletes.** *Journal of Athletic Training, 50*, 250-255. doi:10.4085/1062-6050-50.3.02 *Context:* Depression is common after concussion and is associated with functional outcome and quality of life after injury. However, few baseline predictors of postconcussion depressive symptoms (PCDS) have been found. *Objective:* To describe the prevalence of depressive symptoms in a collegiate athlete sample at baseline and postconcussion, compare these levels of symptoms and change in symptoms with those of a control group with no reported concussions in the past year, and examine the baseline predictors for PCDS. *Design:* Case-control study. *Setting:* Undergraduate institution. *Patients or Other Participants:* Participants were 84 collegiate athletes (65 men, 19 women) with concussion and 42 individuals (23 men, 21 women) with no history of recent concussion who served as controls. *Main Outcome Measure(s):* The Beck Depression Inventory–Fast Screen was administered to the concussion group at baseline and postconcussion and to the control group at 2 time points. *Results:* Seventeen athletes (20%) showed a reliable increase in depression, and more athletes reported clinically important depression postconcussion than at baseline. Only 2 participants (5%) in the control group showed a reliable increase in depression. Concussed athletes were more likely to show a reliable increase in depression symptoms than control participants ($\chi 21 = 5.2$, $P = .02$). We also found several predictors of PCDS in the athletes, including baseline depression symptoms ($r = 0.37$, $P < .001$), baseline postconcussion symptoms ($r = 0.25$, $P = .03$), estimated premorbid intelligence (full-scale IQ; $r = –0.29$, $P = .009$), and age of first participation in organized sport ($r = 0.34$, $P = .002$). For the control group, predictors of depression symptoms at time 2 were number of previous head injuries ($r = 0.31$, $P = .05$) and baseline depression symptoms ($r = 0.80$, $P < .001$). *Conclusions:* A large proportion of athletes showed a reliable increase in depression after concussion, and we identified several baseline predictors. Given that depression affects quality of life and recovery from concussion, more research is necessary to better understand why certain athletes show an increase in PCDS and how these can be better predicted and prevented.

Vasterling, J. J., Aslan, M., Lee, L. O., Proctor, S. P., Ko, J., Jacob, S., & Concato, J. (2018). **Longitudinal associations among posttraumatic stress disorder symptoms, traumatic brain injury, and neurocognitive functioning in Army soldiers deployed to the Iraq war.** *Journal of the International Neuropsychological Society, 24*, 311-323. doi:10.1017/S1355617717001059 *Objectives:* Military deployment is associated with increased risk of adverse emotional and cognitive outcomes. Longitudinal associations involving posttraumatic stress disorder (PTSD), relatively mild traumatic brain injury (TBI), and neurocognitive compromise are poorly understood, especially with regard to long-term outcomes, and rigorous research is necessary to better understand the corresponding relationships. The objective of this study was to examine short-term and long-term (>5 years) longitudinal associations among PTSD, neurocognitive performance, and TBI following military deployment. *Methods:* In this prospective study, *N*=315 U.S. Army soldiers were assessed at military installations before (2003–2005) and after (2004–2006) an index deployment to the Iraq War, and again an average of 7.6 years later (2010–2014) as a nationally dispersed cohort of active duty soldiers, reservists, and veterans. Thus, the study design allowed for two measurement intervals over which to examine changes. All assessments included the PTSD Checklist, civilian version, and individually-administered performance-based neurocognitive tests. TBI history was derived from clinical interview. *Results:* Autoregressive analyses indicated that visual reproduction scores were inversely related to subsequent PTSD symptom severity at subsequent assessments. Conversely, increases in PTSD symptom severity over each measurement interval were associated with poorer verbal and/or visual recall at the end of each interval, and less efficient reaction time at post-deployment. TBI, primarily mild in this sample, was associated with adverse PTSD symptom outcomes at both post-deployment and long-term follow-up. *Conclusions:* These results suggest longitudinal relationships among PTSD symptoms, TBI, and neurocognitive decrements may contribute to sustained emotional and neurocognitive symptoms over time.

Witcher, K. G., Eiferman, D. S., & Godbout, J. P. (2015). **Priming the inflammatory pump of the CNS after traumatic brain injury.** *Trends in Neurosciences, 38*, 609-620. doi:10.1016/j.tins.2015.08.002 Microglia are rapidly activated following TBI and produce cytokines and chemokines in addition to exhibiting morphological alterations such as hypertrophy and de-ramification of processes. Experimental and clinical evidence indicates that microglia do not return to homeostasis after injury but instead develop a primed and potentially hyper-reactive phenotype. Primed microglia are characterized by exaggerated responses to secondary insults such as repeated TBI, immune challenge, or stress. This results in amplified and prolonged neuroinflammation that negatively influences cognitive and behavioral processes. TBI patients are at increased risk for the development of depression or neuropathologies (tau, Aβ) after injury. Microglia-mediated inflammatory processes may represent a useful clinical target in the treatment of neurological and psychiatric complications associated with TBI.

Wolf, E. J., Logue, M. W., Hayes, J. P., Sadeh, N., Schichman, S. A., Stone, A., ... & Miller, M. W. (2016). **Accelerated DNA methylation age: Associations with PTSD and neural integrity.** *Psychoneuroendocrinology, 63*, 155-162. doi:10.1016/j.psyneuen.2015.09.020 *Background:* Accumulating evidence suggests that posttraumatic stress disorder (PTSD) may accelerate cellular aging and lead to premature morbidity and neurocognitive decline. *Methods:* This study evaluated associations between PTSD and DNA methylation (DNAm) age using recently developed algorithms of cellular age by Horvath (2013) and Hannum et al. (2013). These estimates reflect accelerated aging when they exceed chronological age. We also examined if accelerated cellular age manifested in degraded neural integrity, indexed via diffusion tensor imaging. *Results:* Among 281 male and female veterans of the conflicts in Iraq and Afghanistan, DNAm age was strongly related to chronological age (rs ~.88). Lifetime PTSD severity was associated with Hannum DNAm age estimates residualized for chronological age ($\beta$ = .13, $p$ = .032). Advanced DNAm age was associated with reduced integrity in the genu of the corpus callosum ($\beta$ = –.17, $p$ = .009) and indirectly linked to poorer working memory performance via this region (indirect $\beta$ = –.05, $p$ = .029). Horvath DNAm age estimates were not associated with PTSD or neural integrity. *Conclusions:* Results provide novel support for PTSD-related accelerated aging in DNAm and extend the evidence base of known DNAm age correlates to the domains of neural integrity and cognition.

Yaffe, K., Vittinghoff, E., Lindquist, K., Barnes, D., Covinsky, K. E., Neylan, T., ... & Marmar, C. (2010). **Posttraumatic stress disorder and risk of dementia among US veterans.** *Archives of General Psychiatry, 67*, 608-613. doi:10.1001/archgenpsychiatry.2010.61 *Context:* Posttraumatic stress disorder (PTSD) is highly prevalent among US veterans because of combat and may impair cognition. *Objective:* To determine whether PTSD is associated with the risk of developing dementia among older US veterans receiving treatment in the Department of Veterans Affairs medical centers. *Design:* A stratified, retrospective cohort study conducted using the Department of Veterans Affairs National Patient Care Database. *Setting:* Department of Veterans Affairs medical centers in the United States. Participants: A total of 181 093 veterans 55 years or older without dementia from fiscal years 1997 through 2000 (53 155 veterans with and 127 938 veterans without PTSD). Main Outcome Measures: During the follow-up period between October 1, 2000, and December 31, 2007, 31 107 (17.2%) veterans were ascertained to have newly diagnosed dementia according to International Classification of Diseases, Ninth Revision, Clinical Modification codes. *Results:* The mean baseline age of the veterans was 68.8 years, and 174 806 (96.5%) were men. Veterans with PTSD had a 7-year cumulative incident dementia rate of 10.6%, whereas those without had a rate of 6.6% (P < .001). With age as the time scale, Cox proportional hazards models indicated that patients with PTSD were more than twice as likely to develop incident dementia compared with those without PTSD (hazard ratio, 2.31; 95% confidence interval, 2.24-2.39). After multivariable adjustment, patients with PTSD were still more likely to develop dementia (hazard ratio, 1.77; 95% confidence interval, 1.70-1.85). Results were similar when we excluded those with a history of head injury, substance abuse, or clinical depression. *Conclusions:* In a predominantly male veteran cohort, those diagnosed as having PTSD were at a nearly 2-fold-higher risk of developing dementia compared with those without PTSD. Mechanisms linking these important disorders need to be identified with the hope of finding ways to reduce the increased risk of dementia associated with PTSD.

Yurgil, K. A., Barkauskas, D. A., Vasterling, J. J., Nievergelt, C. M., Larson, G. E., Schork, N. J., … & Baker, D. G. (2014). **Association between traumatic brain injury and risk of posttraumatic stress disorder in active-duty Marines.** *JAMA Psychiatry, 71*, 149-157. doi:10.1001/jamapsychiatry.2013.3080 Importance: Whether traumatic brain injury (TBI) is a risk factor for posttraumatic stress disorder (PTSD) has been difficult to determine because of the prevalence of comorbid conditions, overlapping symptoms, and cross-sectional samples. *Objective:* To examine the extent to which self-reported predeployment and deployment-related TBI confers increased risk of PTSD when accounting for combat intensity and predeployment mental health symptoms. Design, Setting, And Participants: As part of the prospective, longitudinal Marine Resiliency Study (June 2008 to May 2012), structured clinical interviews and self-report assessments were administered approximately 1 month before a 7-month deployment to Iraq or Afghanistan and again 3 to 6 months after deployment. The study was conducted at training areas on a Marine Corps base in southern California or at Veterans Affairs San Diego Medical Center. Participants for the final analytic sample were 1648 active-duty Marine and Navy servicemen who completed predeployment and postdeployment assessments. Reasons for exclusions were nondeployment ($n$ = 34), missing data ($n$ = 181), and rank of noncommissioned and commissioned officers ($n$ = 66). Main Outcomes And Measures: The primary outcome was the total score on the Clinician-Administered PTSD Scale (CAPS) 3 months after deployment. *Results:* At the predeployment assessment, 56.8% of the participants reported prior TBI; at postdeployment assessment, 19.8% reported sustaining TBI between predeployment and postdeployment assessments (ie, deployment-related TBI). Approximately 87.2% of deployment-related TBIs were mild; 250 of 287 participants (87.1%) who reported posttraumatic amnesia reported less than 24 hours of posttraumatic amnesia (37 reported ≥ 24 hours), and 111 of 117 of those who lost consciousness (94.9%) reported less than 30 minutes of unconsciousness. Predeployment CAPS score and combat intensity score raised predicted 3-month postdeployment CAPS scores by factors of 1.02 (P < .001; 95% CI, 1.02-1.02) and 1.02 (P < .001; 95% CI, 1.01-1.02) per unit increase, respectively. Deployment-related mild TBI raised predicted CAPS scores by a factor of 1.23 (P < .001; 95% CI, 1.11-1.36), and moderate/severe TBI raised predicted scores by a factor of 1.71 (P < .001; 95% CI, 1.37-2.12). Probability of PTSD was highest for participants with severe predeployment symptoms, high combat intensity, and deployment-related TBI. Traumatic brain injury doubled or nearly doubled the PTSD rates for participants with less severe predeployment PTSD symptoms. Conclusions And Relevance: Even when accounting for predeployment symptoms, prior TBI, and combat intensity, TBI during the most recent deployment is the strongest predictor of postdeployment PTSD symptoms.

Zhao, J., Huynh, J., Hylin, M. J., O'Malley, J. J., Perez, A., Moore, A. N., & Dash, P. K. (2018). **Mild traumatic brain injury reduces spine density of projection neurons in the medial prefrontal cortex and impairs extinction of contextual fear memory.** *Journal of Neurotrauma, 35*, 149-156. doi:10.1089/neu.2016.4898

## FEATURED ARTICLES *continued*

Epidemiology studies have found that a comorbidity exists between traumatic brain injury (TBI) and stress-related disorders. However, the anatomical and cellular bases for this association is poorly understood. An inability to extinguish the memory of a traumatic event lies at the core of many stress-related disorders. Experimental studies have shown that the medial pre-frontal cortex (mPFC), especially the infralimbic (IL) cortex, is required for extinction and for storing the memory of extinction. The output from the central nucleus of amygdala projects to the lateral hypothalamus, paraventricular nucleus, and central gray to regulate heart rate, stress hormone release, and freezing behavior, respectively. Projection neurons of the IL (layers II/III pyramidal neurons) are thought to stimulate GABAergic neurons in the amygdala, which, in turn, inhibit central amygdala output and reduce fear expression. Thus, loss and/or altered morphology of projection neurons of IL as a result of a mild TBI (mTBI) can compromise their ability to effectively inhibit the central amygdala, allowing the original fear memory to drive behavior. Using lateral mild fluid percussion injury (mFPI) in rats, we found that mFPI did not reduce neuronal numbers in the IL, but caused a significant reduction in overall dendritic spine density of both basal and apical dendrites on layer II/III pyramidal neurons. Spine numbers on layer V/VI pyramidal neurons were not significantly changed as a result of mFPI. The reduction in spine density on layer II/III pyramidal neurons we observed may diminish the efficacy of these neurons to inhibit the output of the central amygdala, thereby reducing the ability of the IL to suppress fear responses after extinction training. Consistent with this, mFPI rats display enhanced freezing behavior during and after extinction training as compared to sham-operated controls, although the ability to form contextual fear memories was not impaired. These results may have implications in stress-related disorders associated with mTBI.

## ADDITIONAL CITATIONS


Hayes, J. P., Miller, D. R., Lafleche, G., Salat, D. H., & Verfaellie, M. (2015). **The nature of white matter abnormalities in blast-related mild traumatic brain injury.** *Neuroimage: Clinical, 8*, 148-156. doi:10.1016/j.nicl.2015.04.001 This experimental paper studied 114 Iraq and Afghanistan war Veterans and determined that mTBI (with loss-of-consciousness) was associated with spatially distributed white matter abnormalities, whereas PTSD was not. mTBI influenced verbal memory performance through white matter integrity.

Kaplan, G. B., Leite-Morris, K. A., Wang, L., Rumbika, K. K., Heinrichs, S. C., Zeng, X., … & Teng, Y. D. (2018). **Pathophysiological bases of comorbidity: Traumatic brain injury and post-traumatic stress disorder.** *Journal of Neurotrauma, 35*, 210-225. doi:10.1089/neu.2016.4953 This paper reviews overlapping neurobiological alterations in TBI and PTSD. The authors suggest that because both diagnoses are associated with neuroinflammation, excitotoxicity, and oxidative stress, treatments that reverse these processes may provide a novel approach to treat TBI/PTSD comorbidity.

Lange, R. T., Brickell, T., French, L. M., Ivins, B., Bhagwat, A., Pancholi, S., & Iverson, G. L. (2013). **Risk factors for postconcussion symptom reporting after traumatic brain injury in US military service members.** *Journal of Neurotrauma, 30*, 237-246. doi:10.1089/neu.2012.2685 This experimental paper found that postconcussion symptom reporting was most associated with poor motivation/effort on neuropsychological tests, traumatic stress symptoms, and depression. The authors suggest that postconcussion syndrome should not be assumed to reflect brain injury.

Manley, G., Gardner, A. J., Schneider, K. J., Guskiewicz, K. M., Bailes, J., Cantu, R. C., … & Iverson, G. L. (2017). **A systematic review of potential long-term effects of sport-related concussion.** *British Journal of Sports Medicine, 51*, 969-977. doi:10.1136/bjsports-2017-097791 This systematic review paper examined the evidence for negative long-term neurobiological and behavioral outcomes following sports-related concussion. The authors suggest that there is evidence for increased risk for mild cognitive impairment and neuroimaging abnormalities in retired athletes, as well as neurodegenerative pathology at autopsy. The authors urge caution in these interpretations however, outlining gaps in the evidence, and ways to improve future research in this area.

Pitman, R. K., Rasmusson, A. M., Koenen, K. C., Shin, L. M., Orr, S. P., Gilbertson, M. W., … & Liberzon, I. (2012). **Biological studies of post-traumatic stress disorder.** *Nature Reviews: Neuroscience, 13*, 769-787. doi:10.1038/nrn3339 This paper comprehensively reviews the neurobiology of PTSD, including psychophysiological, neuroimaging, endocrine, genetic studies and animal models that have examined PTSD over the last few decades.

Simmons, A. N., & Matthews, S. C. (2012). **Neural circuitry of PTSD with or without mild traumatic brain injury: A meta-analysis.** *Neuropharmacology, 62*, 598-606. doi:10.1016/j.neuropharm.2011.03.016 This meta-analytic review of fMRI studies found limited overlap among regions functionally active in PTSD and those active in TBI.

Smith, G. E., & Pear, T. H. (1918). *Shell shock and its lessons, 2nd Ed.* Manchester, England: University Press. This book written in the midst of World War I provides a fascinating view of shell shock from the point of view of an anatomist and a psychologist. They argue that shell shock is equivalent to "a nervous breakdown" and those with previous traumatic experiences were at greater risk for developing shell shock.

Stewart, W., Allinson, K., Al-Sarraj, S., Bachmeier, C., Barlow, K., Belli, A., … & Smith, D. H. (2019). **Primum non nocere: A call for balance when reporting on CTE.** *The Lancet Neurology, 18*, 231-233. doi:10.1016/S1474-4422(19)30020-1 This correspondence statement from several well-established scientists suggests that current reporting of CTE can have harmful effects and calls upon the scientific field and the news media to better acknowledge the limitations of our current understanding of CTE.

Stewart, W., & Smith, D. H. (2016). **Time to be blunt about blast traumatic brain injury.** *The Lancet Neurology, 15*, 896-898. doi:10.1016/S1474-4422(16)30058-8 This comment paper is in response to a study by Shively & colleagues (2016) and urges caution in the interpretation is there is a specific neuropathology related to blast TBI without additional samples and controls.

Valera, E. M., Campbell, J., Gill, J., & Iverson, K. M. (2019). **Correlates of brain injuries in women subjected to intimate partner violence: Identifying the dangers and raising awareness.** *Journal of Aggression, Maltreatment & Trauma, 28,* 695-713.

## ADDITIONAL CITATIONS *continued*

doi:10.1080/10926771.2019.1581864 In this timely and informative paper, the authors review health outcomes following intimate-partner violence (IPV) related TBI. They suggest that IPV related head injury is associated with multiple negative outcomes, including mental health disturbance, cognitive difficulty, and brain abnormalities as assessed by neuroimaging methods. They provide both clinical practice and research recommendations on this topic.

Weiner, M. W., Friedl, K. E., Pacifico, A., Chapman, J. C., Jaffee, M. S., Little, D. M., … & Carrillo, M. C. (2013). **Military risk factors for Alzheimer's disease.** *Alzheimer's & Dementia, 9*, 445-451. doi:10.1016/j.jalz.2013.03.005 This paper outlines the rationale for the Vietnam Veterans Alzheimer's Disease Neuroimaging Initiative Project (DoD-ADNI), which aims to investigate the hypothesis that Veterans with TBI and/or PTSD have increased risk for Alzheimer's disease than Veteran controls.