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Factors Associated With Posttraumatic Stress Disorder and Mild Traumatic Brain Injury in Veterans of Operations Iraqi Freedom and Enduring Freedom: The Role of Neuropsychological Assessment

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FACTORS ASSOCIATED WITH POSTTRAUMATIC STRESS DISORDER AND MILD TRAUMATIC BRAIN INJURY IN VETERANS OF OPERATIONS IRAQI FREEDOM AND ENDURING FREEDOM: THE ROLE OF NEUROPSYCHOLOGICAL ASSESSMENT

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ABSTRACT

Traumatic Brain Injury (TBI) and Posttraumatic Stress Disorder (PTSD) have been referred to as "signature injuries" among veterans of Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF). The aims of the current study were to identify demographic and injury related variables associated with the co-occurrence of mild Traumatic Brain Injury (mTBI) and PTSD and to identify neuropsychological assessment measures that differentiate individuals with mTBI from those with co-occurring mTBI and PTSD.

A total of 81 OIF/OEF veterans participated in this study comprising the mTBI (n=21) and combined (n=60) groups. The results of logistic regression analyses indicated that Caucasians were 21% more likely to have a PTSD diagnosis (Wald χ^2 (1) = 4.576, p=.032, O.R. = .210). Individuals who reported loss of consciousness were over 3 times more likely to have a PTSD diagnosis (Wald χ^2 (1) = 4.421, p=.035, O.R. = 3.287). In terms of classification of individual participants into outcome groups, this model correctly classified 72.4% of participants (91.1% combined group, 20.0% mTBI).

With regard to cognitive variables, a significant discriminant function was found in which each of three predictor variables was significantly correlated with the discriminant function with loadings of .877 (CVLT-II recognition hits), .775 (CVLT-II

short delay free recall), and .728 (CVLT-II short delay cued recall). 74% of cases were correctly classified based on this model (98% combined group, 10% mTBI group). A second, significant discriminant function analysis was conducted using a theoretical model in which each of four predictor variables were significantly correlated with the discriminant function with loadings of .814 (CVLT-II recognition hits), .685 (CVLT-II short delay free recall), .590 (Trail Making Test Part B), and .565 (CVLT-II long delay free recall). 74% of cases were correctly classified (94% combined group and 20% accuracy for the mTBI group.

Overall, the current results indicate reported loss of conscious to be predictive of developing PTSD in the context of mTBI. While some aspects of verbal memory and executive functioning differed between groups, their predictive utility in differentiating individuals with mTBI versus those with combined mTBI and PTSD was limited.

Keywords: traumatic brain injury, posttraumatic stress disorder, neuropsychology, assessment

DEDICATION

This dissertation is dedicated to my family. To my mother, your love, your spirit, and all of the lessons you taught me lead to this point and made me who I am. I think of you every day. To my sisters, I am so grateful for all that you have done for me and am so happy that you are a huge part of my life. To my wife, I can't thank you enough for your love and support through all of this. You have somehow figured out how to calm me down when I'm getting ahead of myself while giving me a push so I don't fall behind. I love you and couldn't have done it without you. To my sons, Benjamin and Nicholas, the love and joy you've brought to my life goes beyond words.

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Introduction

Background:

Traumatic Brain Injury (TBI) and Posttraumatic Stress Disorder (PTSD) have been referred to as "signature injuries" among veterans of Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF; Department of Defense Task Force on Mental Health, 2007). This is due to both the prevalence of this type of injury as well as the impact it has on returning veterans and their families. The conflicts in Iraq and Afghanistan have presented new challenges to soldiers based on intense combat situations and the pervasive use of explosive weaponry by enemy combatants. Specifically, exposure to blasts from improvised explosive devices (IEDs) such as roadside bombs as well as rocket propelled grenades and land mines have been common among U.S. military personnel. Due to improved body armor and medical treatment in combat areas, survival rates of injured soldiers have increased compared to previous conflicts (Okie, 2005). However, the nature of injuries sustained as a result of blast injuries presents significant challenges to the survivors of these types of injuries as well as medical professionals.

Blast injuries, in the context of the physical and psychological trauma of combat, often result in multi-faceted injuries and impairments. The term "polytrauma" has been defined in the context of the Veterans Affairs (VA) health system as two or more injuries to physical regions or organ systems, one of which may be life threatening, resulting in

physical, cognitive, psychological, or psychosocial impairments and functional disability. This may include TBI, physical/orthopedic injuries, spinal cord injuries, and posttraumatic stress disorder. As will be discussed further, prevalence of TBI and PTSD in isolation and together has been particularly high in the wars in Iraq and Afghanistan (Tanielian & Jaycox, 2008; Hoge, 2008; Terrio, 2009). In addition to combat exposure, the prevalence of co-occurring conditions may be related to differences in the underlying processes associated with blast injuries versus other causes of TBI.

The following will seek to examine the convergence of TBI and PTSD in the context of combat veterans from OIF/OEF. Specifically, the similarities in how these conditions manifest in veterans following combat and the cognitive and psychological impact of blast injuries will be discussed. The hope for this study is that better understanding of assessment factors involving co-occurring PTSD and mTBI will lead to an improved ability to modify and target treatments to reduce the long term effects of these conditions.

Traumatic Brain Injury

TBI results from trauma to the brain which may arise from a blow to the head, rapid acceleration/deceleration, and/or rotation of the head. The mechanisms of damage to neural tissue are referred to as primary and secondary injuries. Primary injuries (pTBI) may include focal injuries such as cerebral contusions and/or intracerebral hemorrhages or hematomas as well as diffuse axonal injury in which neurons are damaged due to shear-strain forces (Zink, 1996). These occur immediately after and are a direct result of the initial trauma. The degree to which these occur and the resulting physiological and

cognitive effects depends on several factors, including the severity and etiology of injury. In a typical acceleration-deceleration injury (commonly seen in motor vehicle collisions) the brain encounters multiple forces including impact with the inside of the skull as well as severe torsion and tensile forces. As described by Bigler (2001), neurons have a finite tolerance for such forces which may cause damage to neurons throughout the brain. This diffuse axonal injury (DAI) in moderate to severe TBI is likely to result in widespread cell death.

While this can occur in more severe forms of TBI, mild TBI (mTBI) often results in cells that are temporarily dysfunctional due to the tensile stretching, twisting, and compression of axons, but survive and return to previous functioning. Bigler (2001) suggested "an injury can occur when the tensile effects on axons or parenchymal deformations do not surpass the level where structural damage occurs, but biochemical perturbations are induced. These can be transient … Therefore, at the mildest end of the spectrum, as would be predicted by a linear model, there may indeed be no lasting effect. However, once crossed, the linear model also predicts increasing grades of neuropathological and neurobehavioral sequela." Iverson et al. (2006) similarly suggested that this pattern of injury and recovery in which neurons are temporarily dysfunctional only to return to activity later, may, in part, explain the transient nature of observed symptoms post-mTBI. Overall, the extent of cell death related to pTBI increases with severity. How this manifests in mTBI is less clear, but likely involves primarily dysfunction of neurons with subsequent recovery and/or to a lesser extent direct damage to brain tissue.

Secondary injuries (sTBI) are those that result from physiological response to trauma and may include edema, hypoxemia, and hypotension. Secondary injuries also include neurological changes based on events at the cellular level. As described by Giza and Hovda (2001) there is a "metabolic cascade of events" that takes place in the immediate aftermath of brain trauma. Moments after injury, neurons experience an increase in cell permeability resulting in calcium influx. This increased calcium leads to degradation of the cellular cytoskeleton, particularly the microtubules and neurofilaments involved in anterograde transport. Disrupted transport of material down the axon causes organelle and vesicle accumulation which leads to swelling of the axon and disruption of synaptic connectivity. Also during this time there is an increase of excitatory neurotransmitters, predominantly glutamate, causing excessive excitation of NMDA receptors. The term excitotoxicity is used to describe this process which leads to further influx of calcium into the cell with increased flow of potassium out of neurons. Membrane pumps that work to maintain the balance between inter and intracellular ions become stressed and require additional energy via glucose and oxygen. However, cerebral blood flow can decrease to as little as half of normal immediately following injury. Calcium influx damages mitochondria, resulting in further reduction in energy available to neurons. Membrane pumps fail and neurons continue to swell, in more severe cases leading to cell death via lysis of the cell membrane. In addition, mitochondrial damage may result in the release of "pro-apoptotic" substances that trigger programmed cell death or apoptosis. This process causes cell bodies to shrink and nuclear DNA strands to become fragmented, ultimately leading to disassembly of the cell (Giza & Hovda, 2001; McCrea 2008).

These factors, particularly calcium influx and hypermetabolism of glucose, can last from several hours to several days following injury and leave the brain in a particular vulnerable state for further damage (Giza and Hovda, 2001). This may be of critical importance to soldiers as they may encounter multiple blasts in a close period of time and may have to continue engaging in a combat zone, without rest or assessment of injuries.

Blast Injury

With regard to blast injuries, the degree to which primary and secondary damage to brain tissue occurs remains unclear. In addition, other factors unique to this type of injury may occur. Different from the previously mentioned primary and secondary injuries associated with TBI, blast injuries involve multiple mechanisms termed primary, secondary, tertiary, and quaternary blast injuries. The primary blast injury resulting from blast exposure involves barotrauma, or rapidly changing atmospheric pressure. As described by Taber et al. (2006), explosions result in the rapid transition of solids and liquids to highly pressurized gasses. Due to this tremendous pressure, the gas expands rapidly which causes compression of surrounding air to form a blast wave. The authors refer to this as the "positive phase" of the blast wave. In a matter of milliseconds, this is followed by immediate underpressure of the atmosphere (negative phase) in which a reverse force is exerted. When this wave reaches an individual, different organs and structures in the body react at different rates of acceleration-deceleration based on factors such as mass and fluid volume, ultimately resulting in shearing and stretching forces similar to primary injuries (pTBI) from conventional TBI (Taber et al., 2006).

Specifically, air filled organs such as lungs, bowel, and inner ear are most vulnerable to the effects of blast waves.

Secondary blast injuries may result when projectiles are propelled by the blast wave into an individual. Shrapnel or other debris may strike individuals in close proximity to a blast resulting in bodily injury and possible head injury in addition to the effects of the blast wave. Tertiary blast injuries may be sustained if the blast wave propels an individual into an object and/or to the ground (Taber, 2006, Kocsis, 2009). Finally, quaternary blast injuries may result from burns and/or toxic fume inhalation (Ling et al., 2009). Thus blast injuries can cause injuries similar to traditional mTBI due to falls, objects striking the head, and/or acceleration-deceleration in which the head strikes an object. In addition, blast injury can confer additional damage related to the primary overpressure and underpressure effects of the primary blast injury as well as burns and exposure to toxic fumes. The exact nature of damage caused by primary blast injury is not fully understood, as there are few human studies currently available. It is proposed that DAI may be common in these injuries and that shock waves cause elevations in pressure in the cerebrospinal fluid and blood vessels which may lead to diffuse microhemorrhages (Kocsis, 2009). However, human research regarding blast injury is extremely limited at present.

Animal studies have found changes in neuronal activity, ultrastructural changes in the brain, and impaired cognitive performance following blast exposure. In a study by Cernak et al. (2001), Wistar rats were exposed to either whole body blast injury (WBBI) or local blast injury (LBI, chest only). Small structural changes, predominantly in the hippocampus, were noted in both groups, though to a greater extent in the WBBI group.

In addition, performance on a previously learned avoidance task was impaired in both groups 3 hours following injury. However, only the WBBI group continued to exhibit these cognitive deficits at 1 and 5 days post-injury. The authors concluded that blast injuries may lead to neurological changes even when not involving direct head injury and that specific hippocampal damage may be related to memory impairment following this type of injury. Blood vessels outside the brain acting as a conduit of blast damage was proposed as one mechanism of cerebral structural changes noted in the LBI group (Cernak et al., 2001).

Long et al. (2009) assessed neurological and neurocognitive effects of blast injury in rats. The authors used high intensity air blast to simulate the explosive blast experienced by military personnel in OIF/OEF. Individual animals were exposed to blasts of two different intensities. One group of animals at each intensity level was covered in a small Kevlar wrap around the thorax and abdomen while leaving the head exposed to mimic protective vests worn by soldiers. All rats wearing the protective vests survived blast exposure while only 4 of 11 at higher intensity and 5 of 8 at lower intensity survived 24 hours post blast. In addition, the vest attenuated neuropathological effects in the lower intensity group and not in the group exposed to the higher intensity blast.

Significant neurological damage was noted in the highest intensity group to include prominent areas of cell loss as well as hemorrhage and necrosis regardless of Kevlar protection. In the lower intensity group, widespread damage to commissures and other white matter tracts were noted in the no-Kevlar group with animals in the Kevlar protected group showing virtually no notable damage. In addition, animals exposed to the lower intensity blast demonstrated deficits in a previously learned water maze task

post injury, though performance returned to baseline at three days. These results suggest that blast injuries are capable of causing widespread cellular loss in severe cases and diffuse white matter disruption in milder cases (Long et al., 2009). The greater extent of damage noted in the non-Kevlar protected group is consistent with the previously mentioned study by Cernak et al. (2001).

Again, this is suggestive that blast exposure to the chest and abdomen can lead to cerebral damage. This was discussed in a review article by Hicks et al. (2010) in which the authors proposed three mechanisms for transduction of a blast wave to the brain. These were direct propogation through the skull, through the vascular system, and/or through the cerebrospinal fluid in the spinal column. Overall, it appears that blast injuries may produce additional cerebral damage through non-head injury mechanisms in a manner different from other forms of TBI.

Given the difference in mechanism of injury resulting from blast as compared to non-blast TBI as well as the combined effects of primary, secondary, tertiary, and quaternary components of blast injuries, it is reasonable to conclude that blast injuries confer more complex if not greater cell loss and subsequent increased long-term effects. This has become particularly relevant in recent years due to the high prevalence of blast related mTBI among soldiers in Iraq and Afghanistan. In a study conducted at an echelon II military facility in Iraq, 78% of all injuries were caused by blast explosions (Murray et al., 2005). As mentioned previously, blast exposure has the potential to result in polytrauma involving multiple injuries with the potential for long-term physical, cognitive, and psychological impairment.

Prevalence of TBI in OIF/OEF

Figures regarding rates of mTBI following military deployment have varied across studies based on multiple factors including the definition of mTBI used, screening or assessment methods, population studied, and time since injury. In a study by the RAND Corporation (Tanielian & Jaycox, 2008), 1965 OIF/OEF veterans across military branches were surveyed regarding combat experience, injuries sustained, and psychosocial outcomes. The report indicated that 19.5% of respondents screened positive for a probable TBI. Extrapolating this data to the 1.64 million service members who had deployed to Iraq and Afghanistan at the time of the study, the authors suggested an estimated prevalence of 320,000 soldiers who may have experienced a TBI during OIF/OEF. Hoge et al. (2008) surveyed 2525 soldiers from 2 U.S. Army brigades within 3-4 months after returning from serving in Iraq. The authors found 15.2% of the sample reported injuries involving loss of consciousness or altered mental status consistent with mild traumatic brain injury.

In a study by Terrio et al. (2009), the authors administered questionnaires to 3973 soldiers from a U.S. Army Brigade Combat Team. This was followed by clinical interviews by Master's and Doctoral level clinicians to confirm diagnoses. A total of 1292 reported sustaining some injury during combat. Of these, 907 reported injuries that met criteria for an mTBI as confirmed during the clinical interview which accounts for 22.8% of the entire brigade. Perhaps more significant is that these results indicate that 70.2% of all injuries reported involved mTBI. These estimated rates of head injury are significantly elevated in comparison to previous wars, such as during the Vietnam War in which 12-14% of injuries were head injuries (Okie, 2005). As mentioned previously, this

is likely due to the fact that more soldiers are surviving what would have been life threatening injuries in previous wars due to improved medical services in the field, advanced body armor, and increased use of explosive devices in the combat zone.

Some variability across studies is evident in the manner in which mTBI is assessed and defined. The majority of studies have involved questionnaires administered at different time points (months to years following deployment) and locations (predominantly military bases, hospitals, and VA Medical Centers). With regard to defining mTBI, studies have typically used the core criteria previously outlined by the American Congress of Rehabilitation Medicine (1993; see Table 1) and have included loss of consciousness or alteration of consciousness secondary to a potential injury process such as blast exposure, motor vehicle crash, fall, or having been struck by an object. More recent studies investigating mTBI due to combat related events such as explosive blast injuries typically rely on the definition of mTBI generated by the Defense and Veterans Brain Injury Center (DVBIC) Working Group on Acute Management of Mild Traumatic Brain Injury in Military Operational Settings (2006). This definition states:

> "Mild Traumatic Brain Injury in military operational settings will be defined as an injury to the brain resulting from an external force and/or acceleration/deceleration mechanism from an event such as a blast, fall, direct impact, or motor vehicle accident which causes an alteration in mental status typically resulting in the temporally related onset of symptoms such as: headache, nausea, vomiting, dizziness/balance problems, fatigue, trouble sleeping/sleep disturbances, drowsiness, sensitivity to light/noise, blurred vision, difficulty remembering, and/or difficulty concentrating" (DVBIC, 2006).

Table 1:
American Congress of Rehabilitation Diagnostic Criteria for Mild Traumatic Brain Injury

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The individual experiences a traumatically induced physiological disruption of brain function as manifested by at least one of the following:

- Any loss of consciousness
- Any loss of memory for events immediately before or after the traumatic event
- Any alteration in mental state at the time of the event (i.e. feeling dazed, disoriented, or confused)
- Focal neurological deficit(s) that may or may not be transient.

However, the severity of the injury falls within the following parameters:

- Loss of consciousness of 30 minutes or less
- An initial Glasgow Coma Scale of 13-15 after 30 minutes
- Posttraumatic Amnesia not to exceed 24 hours

Mild Traumatic Brain Injury Committee, American Congress of Rehabilitation Medicine, Head Injury Interdisciplinary Special interest Group. (1993).

While there is no conflict in these definitions, that is to say that meeting criteria for the military criteria is likely to result in meeting criteria from the ACRM, there still remains less than perfect agreement across studies. In addition, several factors may affect accurate diagnosis of mTBI and proper inclusion of participants into studies. The first of these is the attempt to capture a set of potentially transient conditions in battle conditions or other military operations. As discussed by Vasterling et al. (2009), injuries that may include brief loss of consciousness or altered mental status often go untreated and undocumented. For many soldiers who sustain these types of injuries, particularly in combat, the option to stop what they are doing and evaluate their injury may be life threatening to themselves and others. The second factor impacting accurate diagnosis involves the use of primarily self report to diagnose a condition that, by definition, involves alteration or loss of consciousness.

Finally, the nature of symptoms and how they overlap with multiple conditions makes diagnosis difficult for health care providers both on and off the field. As described by Hoge et al. (2009) an alteration of consciousness or awareness may result from other etiologies during combat such as sleep deprivation, acute stress, response to physical injury, dissociation, syncope, or "the confusion of war". The authors point out that most participants are included in studies based solely on an affirmative response to a single screening question regarding exposure to a blast or other potentially traumatic event followed by alteration of consciousness.

Issues regarding mTBI diagnosis are described further in the National Academy of Neuropsychology education paper on recommendations for diagnosing mTBI (Ruff et al., 2009). The authors suggest that misdiagnosis of mTBI may result when relying solely on self-report. With regard to loss of consciousness, the authors suggest that individuals who become disoriented or dazed following an mTBI may assume loss of consciousness due to an inability to remember the events immediately following the traumatic event, resulting in over-reporting of TBI-like events. On the other hand, some individuals may underreport loss of consciousness for similar reasons in that they do not recall regaining consciousness and instead recall what they were doing seconds to minutes after the event. The authors also point out that an individual reporting feeling confused or disoriented may have experienced this due to feeling overwhelmed by the event. Differentiating alteration in mental status due to psychological factors related to stress and anxiety from those generated by biomechanical force can be exceedingly difficult and according to Ruff et al. (2009), is best accomplished through a thorough interview.

Postconcussive Symptoms

This problem of overlapping psychological and physiological symptoms in the acute phase is equally, if not more problematic in survivors of mTBI months or years post-injury. This is particularly evident in studies where participants were injured several months to years prior, as is the case for this and most studies conducted in the Veterans Affairs (VA) hospitals and clinics. For most individuals, symptoms related to mTBI resolve after several weeks to months following injury. However, for a subset of those injured (10-20%), symptoms persist beyond 3 months and are collectively referred to as postconcussive syndrome (PCS; Alexander, 1995; Bernstein, 1999). This has been defined by the World Health Organization and by the American Psychiatric Association (see table 2) to include cognitive (attention, concentration, memory), somatic (headache, fatigue, insomnia, tinnitus, dizziness, sensitivity to noise/light), and mood related (anxiety, depression, irritability) symptoms (McCallister & Aciniegas, 2002).

Table 2: Research diagnostic criteria for Postconcussive Disorder from the DSM-IV.

A. A history of head trauma that has caused a significant cerebral concussion. Note. The manifestations of concussion include loss of consciousness, post-traumatic amnesia, and less commonly, post-traumatic onset of seizures. Specific approaches for defining this criterion need to be refined by further research.
B. Evidence from neuropsychological testing or quantified cognitive assessment of difficulty in attention (concentrating, shifting focus of attention, performing simultaneous cognitive tasks) or memory.
C. Three (or more) of the following occur shortly after the trauma and last at least 3 months.
    1. becoming fatigued easily
    2. disordered sleep
    3. headache
    4. vertigo or dizziness
    5. irritability or aggression on little or no provocation

6. anxiety, depression, or affective liability
7. changes in personality (e.g., social or sexual inappropriateness)
8. apathy or lack of spontaneity.

D. The symptoms in criteria B or C have their onset following head trauma or else represent a substantial worsening of preexisting symptoms.
E. The disturbance causes significant impairment in social or occupational functioning and represents a significant decline from a previous level of functioning. In school age children, the impairment may be manifested by a significant worsening in school or academic performance dating from the trauma.
F. The symptoms do not meet criteria for Dementia due to Head Trauma and are not better accounted for by another mental disorder (e.g., Amnestic Disorder due to Head Trauma, Personality Change Due to Head Trauma.

Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition, Text Revision (DSM-IV-TR, 2000)

As with acute symptoms, there is significant overlap of postconcussive symptoms (PCSx) and those reported by individuals with other PTSD, Depression, and even by otherwise healthy adults. Iverson and Lange (2004) administered a questionnaire to assess PCSx frequency and severity to 104 healthy adults who had never experienced a brain injury. The questionnaire used was based on PCSx outlined by the World Health Organization ICD-10 which include headache, dizziness, nausea, fatigue, sensitivity to noise, irritability, sadness, nervousness, problems with temper, memory problems, concentration problems, difficulty reading, and poor sleep. Participants endorsed these symptoms as occurring at least 1-2 times during the past two weeks at a rate ranging from 35.9% (difficulty reading) to 75.7% (fatigue). In addition, between 2.9% (headaches) and 19.4% (fatigue) of participants reported these symptoms as occurring "often" during the same time frame. Respondents also indicated that these symptoms were at least moderately problematic at a rate of 5.8% (sensitivity to noise) to 19.4% (sadness). Of the total sample, 87.3% reported 3 or more PCSx of mild intensity and 16.5% endorsed 3+ symptoms of moderate to severe intensity consistent with WHO and APA diagnostic

criteria. These results suggest that a large proportion of healthy individuals report frequent, problematic PCSx.

Depression has also been identified as a contributing factor with regard to self-report of PCSx in the absence of head injury. In the previous study (Iverson & Lange, 2004), participants with higher scores on the Beck Depression Inventory (BDI) reported PCSx as more frequent and of greater intensity than those with low BDI scores. Similar results were evident in a study by Suhr and Gunstad (2002), in which self-report of PCSx was evaluated among 138 young adults with a history of mTBI (n=31), mTBI with depression (n=32), depression without head injury (n=25), or healthy controls (n=50) using the 97-item PCS checklist (Gunstad & Suhr, 2001). The authors found that significantly more PCS items were endorsed by depressed individuals regardless of head injury status. In addition, across head injury groups, those with co-occurring depression reported a greater number of symptoms. The head injury without depression group did not differ from healthy controls. It should be noted that the head injury only group primarily included individuals with a history of mTBI, all of whom sustained their injury at least 6 months prior to the study. Because of this, one would expect the symptoms for most participants to have resolved at the time of the study. Nevertheless, this has implications in the context of the current study and for assessment of mTBI and PCSx within the VA healthcare system. Individuals treated in this setting are often seen months or even years post-injury and present with substantial co-occurring diagnoses. As such, particular attention should be devoted to the role that co-occurring conditions may play in self reported PCSx.

Posttraumatic Stress Disorder and its relationship with mild TBI and Postconcussive Symptoms

PTSD as defined in the Diagnostic and Statistical Manual for Mental Disorders – Fourth Edition (DSM-IV-TR, American Psychiatric Association, 2000) requires exposure to a potentially life-threatening traumatic event followed by symptoms related to re-experiencing of the event, avoidance of stimuli associated with the event or numbing, and symptoms of increased arousal (see table 3). The course of these symptoms is often chronic and may worsen over time. In addition, PTSD resulting from combat may be more severe and chronic than PTSD from other etiologies (Kennedy et al., 2007).

Table 3: Diagnostic criteria for Posttraumatic Stress Disorder from the DSM-IV

A. The person has been exposed to a traumatic event in which both of the following have been present:
    1. The person experienced, witnessed, or was confronted with an event(s) that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others.
    2. The person's response involved intense fear, helplessness, or horror.
B. The traumatic event is persistently reexperienced in one (or more) of the following ways:
    1. recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions.
    2. recurrent distressing dreams of the event.
    3. acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur upon awakening or when intoxicated).
    4. intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.
    5. physiological reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.
C. Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by three (or more) of the following:
    1. efforts to avoid thoughts, feelings, or conversations associated with the trauma

2. efforts to avoid activities, places, or people that arouse recollections of trauma
3. inability to recall an important aspect of the trauma
4. markedly diminished interest or participation in significant activities
5. feeling of detachment or estrangement from others
6. restricted range of affect (e.g., unable to have loving feelings)
7. sense of a foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal life span)

D. Persistent symptoms of increased arousal (not present before the trauma), as indicated by two (or more) of the following:
   1. difficulty falling or staying asleep
   2. irritability or outbursts of anger
   3. difficulty concentrating
   4. hypervigilance
   5. exaggerated startle response

E. Duration of the disturbance (symptoms in Criteria B, C, and D) is more than one month.

F. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition, Text Revision (DSM-IV-TR, 2000)

The potential for developing PTSD following TBI has been controversial, particularly when there is considerable loss of consciousness and/or posttraumatic amnesia. This is due to the fact that criterion B from the DSM-IV requires that the individual is subject to some form of re-experiencing of the traumatic event which would seem to be prohibited by posttraumatic amnesia. Bryant (2001) outlines several potential mechanisms to explain why research has found a relationship between mTBI and PTSD regardless of memory for the event. The first of these notes that trauma related to TBI may not be limited to the event itself, but may also involve distress and anxiety associated with events leading to the injury or in the immediate aftermath, at which point posttraumatic amnesia may be less of a factor. Second, traumatic stimuli may be encoded in implicit memory outside of consciousness. In a previous study by Bryant (2000), participants who sustained an mTBI and had no recall of the event nevertheless

demonstrated psychological distress and physiological reactivity to cues and reminders of the traumatic experience which satisfies diagnostic criterion B from the DSM-IV. This may be due to memory that is not consciously accessible or reconstruction of memory based on partial recall.

One theory involving memory of traumatic events outside of conscious awareness was proposed by Brewin et al. (1996). The authors described a dual representation theory of memory comprised of two independent forms of memory that play different roles in the development of PTSD. The first, referred to as verbally accessible memory (VAM), refers to memory of trauma related information that can be intentionally recalled by the individual at a later date. These autobiographical memories arise as the individual attends to events during trauma in a manner sufficient for conscious processing of information and subsequent encoding into long-term memory with resulting availability for explicit recall (Brewin & Holmes, 2003).

The second form of memory, proposed by Brewin et al. (1996), is referred to as situationally accessible memory (SAM). These are non-autobiographical memories that are associated with sensory information processed during the traumatic event that received extremely brief or minimal conscious attention. These memories are not encoded through verbal processes and therefore are not available for intentional retrieval. Instead, the authors propose that these memories are triggered by situational cues outside of the individual's control and are thus associated with the sudden and uncontrollable emergence of flashbacks for individuals diagnosed with PTSD.

The third justification of PTSD following TBI (Bryant, 2001) states that posttraumatic amnesia may be only partial in mTBI (Vasterling et al., 2008) such that

cues, images, and reminders of the traumatic event may allow for some level of "reconstruction" of memories, particularly when others present at the time of injury provide information or details the survivor does not independently recall. Finally, neurobiological changes secondary to mTBI may alter brain functioning in such a way as to promote the development of PTSD. This will be discussed in greater detail later. Overall, these results offer plausible explanations for studies that find co-occurrence and even a relationship in which mTBI increases the likelihood of developing PTSD. Specific to military combat veterans who sustain an mTBI, posttraumatic amnesia and exposure to multiple traumatic events may result in an atypical presentation of PTSD. Severe reactions to and avoidance of stimuli reminiscent of combat (e.g. movies, loud noises, etc.) may constitute distress related to re-experiencing more commonly than nightmares or flashbacks.

A study by Creamer et al. (2005) provides evidence that PTSD and TBI may co-occur despite interference with memory for the traumatic event. The authors assessed PTSD among 307 individuals who were admitted to a level 1 trauma center after sustaining a mTBI. In this study, rates of PTSD 12 months following injury did not differ depending upon recall of the traumatic event. Results revealed 9% of participants with full recall, 14% of those with partial recall, and 7% with no recall developed PTSD one year after injury. However, Glaesser et al. (2004) found the rate of PTSD differed based on injury severity in terms of loss of consciousness. The authors found 26.7% of a group of TBI survivors with loss of consciousness less than 1 hour developed PTSD within 5 years of injury. This was significantly greater than the 3.2% of individuals who developed PTSD following injuries involving 12 hours or more of loss of consciousness.

Taken together with the Creamer (2005) study, these results suggest that while lack of memory for a traumatic event may not be associated with subsequent PTSD, more severe injuries with extended loss of consciousness may limit PTSD development. This is likely to be less of a factor when discussing mTBI since, by definition, loss of consciousness is not to exceed 30 minutes. In relation to combat veterans, there may also be the potential for PTSD to develop as a result of the context of war regardless of memory for a specific trauma related to or producing TBI (Vasterling et al., 2009).

Prevalence of PTSD and co-occurrence with mTBI in OIF/OEF veterans

The previously cited RAND study (2008) reported that 14.5% of OIF/OEF veterans report symptoms consistent with PTSD. In addition to observed rates of PTSD in isolation, high rates of co-occurring PTSD and mTBI have been reported. Among the 2525 veterans in the previously cited Hoge et al. (2008) study, 4.9% reported loss of conscious associated with head injury and 10.3% indicated altered mental status subsequent to head injury for a total of 15.2% of study participants screening positive for mTBI. Rates of PTSD were highest among participants with reported loss of consciousness (43.9%) followed by those with altered mental status (27.3%), participants who sustained other (non-head) injuries (16.2%), and those who were uninjured (9.1%). These results were consistent with the previously mentioned Creamer (2005) study suggesting co-occurring head injury and PTSD may be common despite loss of consciousness.

Schneiderman et al. (2008) used questionnaires sent to 7259 veterans who had returned from deployment in Iraq and/or Afghanistan to assess mTBI occurrence, post

concussive symptoms, and symptoms of PTSD. Included were the Brief Traumatic Brain Injury Screen, the PCL-17 PTSD checklist, and additional descriptive questions regarding PCSx. Of the 2235 respondents, 11% reported symptoms consistent with PTSD and 12% met criteria for a previous mTBI. A total of 35% of those who screened positive for mTBI also met criteria for postconcussive syndrome with 3 or more PCSx. Consistent with other studies, mild TBI was a significant predictor of PTSD. Taken together, these results again suggest that mTBI and PTSD frequently co-occur among OIF/OEF veterans and may result in long-term, problematic symptoms.

Unlike the Hoge et al. (2008) and Schneiderman et al. (2008) studies which investigated mTBI and PTSD among veterans recently returning from combat, Lew et al. (2009) assessed prevalence for PTSD, chronic pain, and persistent PCSx at a Veterans Health Administration Polytrauma Network Site (PNS). Time since injury was not documented, but was likely greater than 3-4 months given the typical time between return from deployment to transferring to the PNS. Participants in this study included 340 veterans enrolled for care at the PNS within a 22-month time frame. The authors found that 81.5% of participants reported chronic pain, 68.2% were diagnosed with PTSD, and 66.8% reported persistent PCSx. Persistent PCSx were defined by a history of mTBI with 3 or more PCSx reported. In addition, 48.9% were diagnosed with co-occurring PTSD and persistent PCS while 42.1% were diagnosed with all 3 conditions (chronic pain, PTSD, and PCSx). As these results are based on veterans who are currently receiving inpatient medical/rehabilitative treatment, they cannot be generalized to all military personnel serving in OIF/OEF. However, they do shed light on the significant

prevalence of co-occurring mTBI and PTSD observed in the VA health system, particularly at polytrauma sites.

Several explanations have been proposed for high rates of co-occurring mTBI and PTSD. As reported by Hoge et al. (2008), soldiers with PTSD were more likely to have experienced more intense combat situations and to have been exposed to blast mechanisms of injury. Similarly, Vasterling et al. (2009) proposed that soldiers often encounter multiple traumatic events while deployed, beyond a single episode which may lead to TBI. Therefore, repeated, intense combat experiences in addition to TBI may be sufficient to promote PTSD in the future regardless of memory for any one event. This is consistent with other literature that reported a higher rate of PTSD following mTBI in military populations compared to civilians (Hesdorffer et al., 2009).

Differentiating mTBI from PTSD: Commonalities in cognitive symptoms and neural substrates

The co-occurrence of PTSD and PCSx following mTBI is of particular importance due to the potential challenges this presents to health care professionals attempting to diagnose and treat these conditions. With regard to assessment, commonalities in cognitive deficits and affected brain regions exacerbate this challenge. Cognitive deficits in moderate to severe head injury can include multiple domains such as attention/concentration, memory, language, visuospatial processing, mental processing speed, and executive functioning. However the type and degree of cognitive impairment following mTBI is less clear.

Dikmen et al. (2009) reviewed literature pertaining to cognitive impairment secondary to TBI across severity classifications. The authors found what has been previously described as a dose-response pattern of neurocognitive effects based on injury severity (McCrea, 2008). Strong evidence for neurocognitive decline was found among survivors of severe TBI. Evidence for such a relationship among those who sustained a moderate TBI was considered limited but suggestive of a possible relationship. Finally, with regard to mTBI, the authors found inadequate/insufficient evidence to determine if neurocognitive deficits persist (Dikmen et al., 2009).

Frencham et al. (2005) conducted a meta-analysis of effect size across studies of neurocognitve performance with mTBI participants. The results revealed significant, positive effect sizes related to processing speed, working memory/attention, memory, and executive functioning based on impaired performance in comparison to controls. However, when differentiating studies that evaluated cognitive abilities at the acute versus post-acute stages, the effects trended toward zero with greater time since injury. The effect size, though small, failed to remain significant when looking at the post-acute group only. This is consistent with theories of temporary impairment following mTBI.

By contrast several studies reviewed by Bernstein (1999) suggest small, but significant effect sizes related to divided and sustained attention as well as processing speed in the post-acute (> 3 months) stage of recovery from mTBI. The author, noting the difference in strength of evidence between acute and post-acute studies, proposed that mTBI may produce infrequent and subtle cognitive deficits in the long term. In addition, while cognitive symptoms clearly improve and in most cases resolve, other symptoms of

PCS may continue. As mentioned previously, self-reported PCSx commonly follow mTBI suggesting ongoing impairment.

However, PCSx do not adequately differentiate mTBI from other injuries, psychological disorders, or even from healthy adults. As described by Alexander (1995), PCSx are neither sufficient nor necessary for a diagnosis of mTBI. Also evident is that PTSD plays a significant role in reported PCSx among OIF/OEF veterans. Hoge et al. (2008) found participants with a history of mTBI with loss of consciousness report significantly more physical symptoms 3-4 months post deployment compared to soldiers with other (non TBI) injuries. However, after accounting for PTSD and depression, physical symptoms no longer differed between groups (with the exception of headache), suggesting that psychological factors primarily accounted for physical complaints.

As mentioned previously, individuals with PTSD may present with similar postcocncussive symptoms as those who suffered an mTBI. In addition to these similarities, individuals diagnosed with PTSD have also been found to exhibit overlapping symptoms of cognitive impairment with those who have suffered an mTBI. In a review by Horner & Hamner (2002), the most consistent findings of cognitive deficits among military veterans involved attention as well as immediate and delayed recall. These results were similar to those reported by Golier & Yehuda (2002) who described consistent findings of attention and memory deficits across veteran and civilian populations. Both reviews noted few studies in the area of PTSD and neurocognitive deficits, and those available for review were often marred by small sample size and methodological flaws. However, more recent studies have continued to demonstrate deficits related to attention (Veltmeyer et al., 2005) and memory (Brewin et al., 2007),

and have also indicated executive deficits related to PTSD, particularly in the areas of working memory (Brandes et al. 2002) and response inhibition (Leskin et al., 2007).

The neural substrates of PTSD are consistent with previously mentioned cognitive deficits. Rauch et al. (2006) describe a neural circuit of PTSD involving the amygdala, hippocampus, and prefrontal cortex (PFC). Structurally, decreased volume has been reported in the hippocampus (Rauch et al., 2006; Vasterling et al., 2008; Horner & Hamner, 2002) and frontal cortex (Vasterling et al., 2008). Functional neuroimaging has found an exaggerated amygdala response with concurrent decrease response from areas such as the ventromedial PFC (vmPFC), orbital PFC (oPFC), and hippocampus (Rauch et al., 2006). The authors propose that hyperactivity of the amygdala combined with decreased activity of the vmPFC (particularly the rostral anterior cingulated cortex) leads to hyperarousal and fear conditioning. In addition, a lack of regulation of the amygdala due to decreased hippocampus and PFC activity is thought to result in an inability to moderate hyperarousal and to identify safe contexts and may be related to a lack of extinction of trauma memories.

Unlike PTSD, TBI can involve both diffuse and focal neurological changes that may be unique to the individual based on multiple injury factors. However, as reviewed by Bigler (2002) hippocampus and other medial temporal regions are particularly vulnerable to even mild TBI. Part of the reason for this may be the impact of DAI on deep white matter projections from subcortical and medial temporal regions (Povlishock, 1993). In addition, Wood (2002) described functional imaging studies in which hypometabolism in frontal and temporal regions of the brain was evident in individuals who sustained mTBI with no noted abnormalities on structural imaging. Again, as with

PCSx, there is some evidence of overlap between mTBI and PTSD in cognitive impairments, particularly related to attention, memory, and executive functioning as well as neural substrates, particularly in the medial temporal regions and prefrontal cortex.

Study rationale, aims, and hypotheses:

Despite the high rates of co-occurring mTBI and PTSD, few studies have examined cognitive performance when both conditions are present. Nelson et al. (2009) conducted such a study with 53 OIF/OEF veterans previously diagnosed with mTBI. A subset of 19 participants was also diagnosed with PTSD prior to the study. Results revealed poorer performance related to processing speed and response inhibition among veterans with co-occurring PTSD and mTBI when compared to the mTBI only group. It should be noted that significant impairment was not evident on neuropsychological measures in either group, only mild impairment on the Stroop Color and Stroop Word tests in the co-occurring group.

Brenner et al. (2010) assessed neurocognitive abilities among 45 OIF veterans with a history of mTBI secondary to blast injury. A subset of 17 participants also met criteria for PTSD. Results indicated no significant differences in neuropsychological measures of attention, processing speed, memory, and executive functions between OIF veterans with mTBI only and mTBI+PTSD groups. However, the authors point out that moderate effect sizes were noted across multiple executive tests which may have failed to reach statistical significance due to the small sample assessed and resulting limited power.

Gordon et al., (2010) assessed differences on neuropsychological test performance among 82 veterans diagnosed with mTBI, mTBI and PTSD, or mTBI and another psychiatric condition. These veterans varied in cause of injury and conflict in which they served ranging from Vietnam to OIF/OEF. The authors found no differences with regard to performance on measures of verbal and visual memory, attention, executive functioning, or processing speed across groups.

Vasterling et al. (2006) assessed neurocognitive performance change based on deployment to Iraq. In this study, 654 soldiers were assessed just prior to deployment and again upon return. A group of 307 soldiers who did not deploy were also assessed, though time between assessments differed (means: 16.9 months deployed, 8.3 months non-deployed). The groups did not differ with regard to age, race, marital status, years of education, and years of military service. Results indicated that those who deployed to Iraq demonstrated a significant decline in performance on measures of sustained attention and memory with improved performance on simple reaction time. Non-deployed participants showed no declines. Adjustment for mTBI and PTSD related to deployment did not affect the significance of differences in test results. The authors conclude that deployment in and of itself may be related to neuropsychological decline. This may add yet another component to the puzzle when using neuropsychological measures as a diagnostic tool following deployment. However, the authors point out that these effects were relatively subtle and may be transient as testing occurred 73 days following return from deployment on average.

As a whole, there exists a body of literature on the neuropsychological performance of individuals with mTBI or PTSD, but little is known with regard to

neurocognitive impairment related to a combination of these conditions. However, this area of research is of great importance due to the previously mentioned high rates of these conditions, in isolation and co-occurring among returning OIF/OEF veterans. Specifically, as discussed by Vasterling et al. (2008), there is potential for cognitive deficits associated with mTBI to exert adverse effects on PTSD treatments such as Prolonged Exposure and Cognitive Behavioral Therapy (CBT). The authors propose that executive deficits may limit one's ability to inhibit and reappraise negative thoughts. The authors also note that among non-injured participants, previous studies have demonstrated poor treatment response in relation to poor verbal memory/encoding (Wild & Gur, 2008), decreased volume in the rostral anterior cingulate cortex (Bryant et al, 2008) and increased activation of the amygdala and ventral anterior cingulate (Bryant et al., 2008; Vasterling et al., 2008, p. 681). As mentioned previously, these areas of medial temporal and frontal brain regions are susceptible to mTBI and implicated with PTSD.

Conversely, as described by Hoge et al. (2008), while limited research exists on treatment of mTBI, some is available to suggest that patient education involving normalization of symptoms and expectations of normal recovery is beneficial. As such, the authors advocate the use of the term "concussion" rather than brain injury as it may imply transient impairment with expectations of full recovery. When examining this in light of co-occurring PTSD, it is plausible to think that negative affect and cognitions associated with PTSD may have an adverse effect on these important, positive expectations of recovery from mTBI.

Overall, research has indicated a high rate of co-occurring mTBI and PTSD, particularly among OIF/OEF veterans. There are significant amounts of shared features

between these conditions in terms of symptom reporting, neurological substrates, and neuropsychological test performance. Because of this, questions have been raised as to the accuracy of assessment of these conditions, particularly the role and effectiveness of neuropsychological measures. As suggested by Brenner et al. (2010), it is unclear if neuropsychological testing is an effective approach in understanding impairments related to mTBI and/or PTSD. In addition, the use of postconcussive symptoms as a measure of past mTBI has been shown to be unreliable. The current study was intended to address these issues.

Aim 1: The first aim was to assess factors predictive of a diagnosis of PTSD among veterans with a history of mTBI. These included demographic (age at time of injury, race, years of education), injury (injury mechanism, number of injuries, loss of consciousness, posttraumatic amnesia), and psychological (co-occurring disorders and treatment at the time of testing) factors.

Hypothesis 1.1: Individuals diagnosed with co-occurring PTSD will be older and have fewer years of education.

Hypothesis 1.2: PTSD is more likely to develop as a result of blast injury, multiple injuries, and following injuries involving loss of consciousness.

Hypothesis 1.3: Individuals diagnosed with PTSD are more likely to be involved in psychotherapy and prescribed a greater number of psychoactive medications at the time of testing.

Aim 2: A second aim was to determine how individuals with mTBI differ from those with mTBI and co-occurring PTSD in terms of performance on neuropsychological tests and to what degree these tests differentiate these groups.

Hypothesis 2.1: Veterans in the co-occurring group (mTBI + PTSD) will perform worse than veterans from the mTBI group on measures of attention, verbal memory, visual memory, and executive functioning.

Hypothesis 2.2: Performance on a subset of neuropsychological tests will differentiate veterans with mTBI from those with mTBI and co-occurring PTSD.

Research Design and Methods

Subjects

Veterans who screened positive for a TBI and were seen in the TBI Clinic of the Birmingham VAMC were eligible for study inclusion based on the criteria listed below (see table 4). The VA TBI screening process for possible TBI as of April 2007 consists of four questions that assess: 1. Exposure to an event (blast, fall, motor vehicle crash, gunshot wound above neck) that could potentially cause a TBI; 2. Altered mental status, loss of consciousness, head injury, or posttraumatic amnesia immediately following the event; 3. Postconcussive symptoms that began and/or worsened after the event including memory problems, balance problems, sensitivity to light, irritability, headaches, and sleep disturbance; and 4. Persistence of symptoms from question 3.

An affirmative response on all of the TBI questions results in a positive screen which leads to follow up evaluation with a VA physician in the TBI Clinic. Based on the presence of cognitive, emotional or behavioral difficulties experienced by the veteran, a

referral for appropriate services including neuropsychological assessment may follow. Two groups were established from this pool. The first of these was a group of participants who have screened positive for an mTBI at the Birmingham VAMC. The mTBI group was comprised of veterans who screened positive and were referred for neuropsychological evaluation through the TBI clinic at the Birmingham VAMC (TBI Group). The second group was comprised of individuals who also screened positive for TBI, were referred for a neuropsychological assessment, and carry a diagnosis of PTSD prior to participation in the study (Combined Group). Diagnosis of PTSD was made prior to neuropsychological testing by a mental health provider or at the time of assessment by a neuropsychologist.

General Experimental Procedures

The neuropsychological assessment data of all veterans who underwent neuropsychological assessment in the TBI clinic at the Birmingham VAMC from April 2007 through April 2011 were reviewed to determine eligibility for inclusion in this study (see Table 4 for inclusion criteria). Veterans were excluded from this study based on a history of TBI prior to or since military service or a previous diagnosis of ADHD or ADD based on self report and/or evidence in the medical record. In addition, diagnoses of a psychotic disorder (schizophrenia, schizoaffective disorder, psychotic disorder, psychosis, NOS) or current substance abuse resulted in exclusion. Substance abuse was based on self report during interview or documentation in the medical record.

Veterans were also excluded based on insufficient effort during the neuropsychological assessment as evidenced by a score of 45 or less on trials 2 or 3 from

the Test of Memory Malingering (TOMM) and/or a raw score below 15 out of 16 on the California Verbal Learning Test – Second Edition (CVLT-II) forced choice recognition (FCR) subtest. This cutoff to detect inadequate effort is consistent with previous research. In a study by Root et al. (2006), among individuals referred for clinical assessment who scored greater than 1.5 standard deviations below the mean on the long delay free recall subtest of the CVLT-II, none scored below 15/16 on the FCR. This suggests that poor performance on the FCR is not related to clinically significant memory impairment. The authors also point out that the FCR was most sensitive to detecting inadequate effort at a cutoff of 15 correct responses. Specific to TBI, Moore and Donders (2004) found that financial compensation seeking resulted in an almost four fold increase in the likelihood of performing below criteria for inadequate effort (<45/50 on trial 2 of the TOMM and/or <15/16 on the CVLT-II FCR).

Table 4: Inclusion/Exclusion Criteria

Inclusion Criteria:

- Combat veterans requiring a minimum of one tour of duty involving combat in OIF/OEF.
- Participants were between the ages of 19-65.
- All participants had undergone neuropsychological evaluation in the TBI Clinic of the Birmingham VAMC.
- Participants screened positive for TBI with affirmative responses to questions 1-4 on the level 1 screening and subsequent physician diagnosis of mTBI and referral for testing following level 2 screening.

Exclusion Criteria:

- Veterans with active psychosis .
- Participants exhibiting suboptimal effort as evidenced by a score below 15 on the FCR of the CVLT-II and/or a score below 45/50 on trial 2 of the TOMM .
- Individuals diagnosed with a neurological disorder (other than TBI) to include dementias or other neurodegenerative disorders .
- Individuals who have been diagnosed, self-report, or are currently in active treatment for substance abuse.

- Individuals who had experienced a TBI prior to or since military service.
- Individuals previously diagnosed with Attention Deficit/Hyperactivity Disorder or Attention Deficit Disorder.

A total of approximately 350 records were reviewed. From these, 81 met inclusion criteria with the majority excluded as a result of a lack of evidence of an mTBI and/or injuries that occurred in other conflicts outside of OIF/OEF. Among the remaining participants, demographic, injury-related, treatment, and neuropsychological testing variables (described below) were entered into a data base for analysis. Demographic variables included age at the time of testing, age at the time of injury (estimated based on self report), race, and years of education. Injury related variables included the number of potential brain injuries, cause of injury/injuries (blast exposures, falls, motor vehicle crashes, and/or gunshot wounds above the neck), time in months from most recent injury to testing, reported loss of consciousness associated with any injury, and reported posttraumatic amnesia. Variables were obtained through clinical interview as well as through a review of the CPRS medical record. Specific attention was paid to the second level TBI screening which is available in the medical record and includes structured interview questions assessing multiple injury variables including those previously mentioned.

Subjects assessed in the TBI clinic underwent neuropsychological assessment using a flexible battery of tests based on clinical judgment to meet the specific needs of the veteran. As such, not all participants were administered an identical battery of tests. Specific tests that are typically administered include the following:

- Grooved Pegboard Test
- Wechsler Abbreviated Scale of Intelligence (WASI)

- Selected subtests comprising the Processing Speed and Working Memory Indexes of the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III)
- Trail Making Test – Parts A and B
- Controlled Oral Word Association Test (COWAT) – Phonemic and Semantic Fluency
- California Verbal Learning Test – Second Edition (CVLT-II)
- Wisconsin Card Sorting Test (WCST)
- Rey Complex Figure Test
- Test of Memory Malingering (TOMM)

Results from these measures were entered into the previously mentioned database for analysis. For information regarding the reliability and validity of these measures as well as use with individuals with TBI and/or PTSD please see the following references: *A compendium of Neuropsychological Tests,* Spreen and Strauss, 1998; *Neuropsychological Assessment* – Fourth Edition, Lezak et al., 2004).

Data Analysis

With regard to demographic and injury related variables that may pose a relative risk for developing PTSD following mTBI, a series of binary logistic regressions were performed with group membership (TBI versus combined) as the outcome variable. Due to sample size, a limited number of predictor variables could be entered into a logistic regression model. To eliminate variables that were likely to add little to the analysis, nonparametric Mann-Whitney U tests were performed to identify differences in means of continuous predictor variables based on group membership. Similarly, Chi-Square tests were performed to assess differences in categorical variables between individuals in the mTBI versus combined groups (see table 5). Variables in which significant group differences were found as well as those in which the difference approached significance were included in subsequent analyses.

To further identify variables that may differentiate groups, two preliminary logistic regression analyses were conducted. The first of these analyses examined demographic predictor variables to include age at the time of most recent injury, race, years of education, and IQ from the WASI. A second logistic regression was conducted examining injury factors including number of potential brain injuries (1 versus multiple), cause of injury/injuries (blast versus other), reported loss of consciousness, and reported posttraumatic amnesia to predict group membership. Overall model fit and individual beta values were analyzed for each variable. Odds ratios for significant variables were used to determine the degree to which they predict a diagnosis of PTSD post-mTBI. Significant or near significant variables from these preliminary logistic regression models were combined to form the final model.

With regard to neuropsychological test results, two discriminant analyses were performed. To limit the number of potential predictor variables, only tests that were completed by greater than 90% of participants were considered for inclusion in the analysis. These tests were the Vocabulary and Matrix Reasoning subtests of the WASI, the Digit Span subtest of the WAIS-III, the TMT Parts A and B, the COWAT phonemic and semantic fluency tests, and the CVLT-II. Again group differences were first assessed using nonparametric Mann-Whitney U tests with variables at or approaching significance included in subsequent analyses.

The first discriminant function analysis assessed the degree to which groups could be differentiated based on cognitive tests in which the two groups' performances were significantly different. These included selected subtests from the CVLT-II. The second discriminant function analysis involved expanded predictor variables to include other

aspects of memory as well as executive functioning based on previously mentioned research. The influence of specific neuropsychological tests was analyzed within this procedure using a structure matrix of correlations between individual predictors (neuropsychological tests) and the discriminant functions. Finally, classification functions were analyzed to assess how well neuropsychological test performance can be used to predict group membership. A priori adjustments to the classification function were made based on differing sample size across groups.

This process of developing a logistic regression model was repeated on a subset of participants whose cause of injury was blast exposure. In addition, nonparametric tests were used in an exploratory analysis to assess differences in cognitive performance between individuals whose injuries were the result of blast exposure versus those with injuries from other causes (regardless of PTSD diagnosis). It is anticipated that some participants may have incurred multiple brain injuries. If an individual suffered a blast injury, even if among several injuries of other etiologies, they were assessed as a blast injury. This is due to the fact that most blast injuries involve secondary, tertiary, and quaternary injuries previously mentioned that may be similar to TBI's of other etiologies. The rationale for this is to determine possible effects of blast injuries above and beyond those seen as a result of other etiologies.

Results

Documentation of neuropsychological assessment (e.g. test materials, interview forms) for all veterans assessed in the TBI clinic from April 2007 to April 2011 was reviewed to identify individuals meeting study inclusion criteria. This was followed by further review of the CPRS medical record. A total of 81 participants were included in

this study comprising the mTBI (n=21) and combined (n=60) groups. The groups did not significantly differ with regard to age, race, years of education, or Full Scale IQ. In addition, injury related factors such as cause of injury (blast versus other), reported posttraumatic amnesia, number of potential injuries (one versus multiple), were not significantly different across groups. However, loss of consciousness was reported at a much higher rate among individuals from the combined group (71.7%) than those in the mTBI group (38.1%), χ^2 (1) = 7.52, p=.006; Fisher's Exact Test p=.009.

Table 5: Demographic and injury related variables

Total Sample (mTBI vs. combined)			
Variable	**mTBI (n=21)**	**Combined (n=60)**	**Total (n=81)**
Age at injury	30.2 (8.8)	31.3 (10.3)	30.9 (9.9)
Race (% Caucasian)	66.7%	83.3%	79.0%
Years of education	13.7 (1.9)	13.3 (2.3)	13.4 (2.2)
Full Scale IQ	104.4 (14.0)	100.6 (12.4)	101.6 (12.9)
# of mTBI's (% 1 injury)	71.4%	51.7%	56.8%
Loss of Consciousness	***38.1%***	***71.7%****	***63.0%***
Mechanism of Injury (% Blast)	71.4%	73.3%	72.8%
Total Sample (blast vs. other mechanism of injury)			
	Blast Inj. (n=59)	**Other (n=22)**	**Total (n=81)**
Age at injury	29.5 (9.5)	35.1 (10.0)	30.9 (9.9)
Race (% Caucasian)	81.4%	72.7%	79.0%
Years of education	13.4 (2.2)	13.6 (2.3)	13.4 (2.2)
Full Scale IQ	102.4 (13.6)	99.7 (10.9)	101.6 (12.9)
# of mTBI's (% 1 injury)	52.5%	68.2%	56.8%
Loss of Consciousness	***55.9%***	***81.8% ****	***63.0%***
PTSD	73.3%	71.4%	72.8%
Blast Injury Sample (mTBI vs. combined)			
	mTBI (n=15)	**Combined (n=44)**	**Total (n=59)**
Age at injury	29.7 (8.6)	29.4 (9.9)	29.5 (9.5)
Race (% Caucasian)	73.3%	84.1%	81.4%
Years of education	13.7 (2.0)	13.2 (2.3)	13.4 (2.2)
Full Scale IQ	104.3 (15.7)	101.7 (13.0)	102.4 (13.6)
# of mTBI's (% 1 injury))	***73.3%***	***45.5% ****	***52.5%***
Loss of Consciousness	***33.3%***	***63.6%****	***55.9%***

*** Significant difference between groups (p<.05) based on χ^2**

Aim 1: The first aim is to assess factors predictive of a diagnosis of PTSD among veterans with a history of mTBI to include demographic, injury, and psychological factors. .

A binary logistic regression was conducted to predict group membership based on demographic variables to include age at time of injury, race, and IQ as mentioned above. Overall model fit was not statistically significant with an omnibus χ^2 (3) = 7.384, p=.061.

Within this model, race (Wald χ^2 (1) = 5.940, p=.035) and IQ (Wald χ^2 (1) = 3.694, p=.055) represented significant and near significant predictors respectively. Because the model fit did not reach statistical significance, the degree to which these individual predictors differentiated groups may not be reliable. As such, the above statistics are not interpreted in that context, but rather are used as indicators that these variables may discriminate these groups and should be included in the final analysis.

A second logistic regression was conducted examining injury related factors as predictors of group membership. Predictor variables were number of mTBIs, loss of consciousness, posttraumatic amnesia, and mechanism of injury (blast versus other). The overall model fit was good with an omnibus χ^2 (4) = 10.743, p=.030 suggesting that the model as a whole reliably differentiates the outcome groups. Hosmer and Lemeshow test was non-significant further indicating good model fit. However, the Nagelkerke R^2 of 0.182 indicates that the model as a whole accounts for a modest 18.2% of the variance between outcome groups. In terms of individual predictors, only loss of consciousness was statistically significant (Wald χ^2 (1) = 7.508, p=.006). The odds ratio attained was 4.995 suggesting that individuals who report a loss of consciousness are nearly 5 times as likely to be in the combined (mTBI + PTSD) group in the context of this model of injury related factors. In terms of classification of participants into group outcomes, the model correctly classified 77.8% of the overall sample. However, the model was predominantly successful in classifying individuals from the combined group at a rate of 96.7% correct; but considerably less successful in identifying individuals with mTBI alone at a rate of 23.8%. The model tended to over-classify individuals as having mTBI and PTSD.

A final binary logistic regression for the total sample examined a model using the strongest predictors from the prior two analyses to differentiate groups. Predictor variables were reported loss of consciousness as well as race and IQ. Loss of consciousness and race were both significant predictors in previous models and IQ approached significance (p=.055). Overall fit of the current model was good as evidenced by an omnibus χ^2 (3) = 11.03, p=.012 and a non-significant Hosmer and Lemeshow test. The model accounted for 19.7% of the variance, Nagelkerke R^2 = .197. The results indicated that race (Wald χ^2 (1) = 4.576, p=.032) and reported loss of consciousness (Wald χ^2 (1) = 4.421, p=.035) were significant predictors of group membership. Specifically, Caucasians were 21% more likely to have a PTSD diagnosis (O.R. = .210). Most notably, individuals who reported loss of consciousness were over 3 times more likely to have a PTSD diagnosis (O.R. = 3.287). In terms of classification of individual participants into outcome groups, this model correctly classified 72.4% of participants. Similar to previous results, the model was much better at classifying individuals in the combined group (91.1%) than those in the mTBI group (20.0%).

Non-parametric tests and chi-square analyses were used to assess the degree to which the mTBI and combined groups differed with regard to co-occurring conditions and treatment at the time of assessment. As expected, individuals with PTSD were significantly more likely to be involved in psychotherapy (χ^2 (1) = 11.260, p=.001; Fisher's Exact Test p=.001). In addition, participants from the combined group were more likely to have a co-occurring diagnosis of depression which occurred for 50% of participants in the combined group versus 14% from the mTBI group (χ^2 (1) = 8.218, p=.004; Fisher's Exact Test p=.003). Individuals from the combined group were also

prescribed a greater number of psychoactive medications (Mann Whitney U, p=.001) averaging 2.2 medications compared to 0.95 in the mTBI group. The groups differed with regard to the specific classes of medications prescribed. The combined group was more likely to be prescribed antidepressants (χ^2 (1) = 15.543, p<.001; Fisher's Exact Test p<.001). Antipsychotic medication and narcotic pain medications approached significance at p=.057 and p=.051 respectively.

Table 6: Binary Logistic Regression - Results of Individual Predictors of Group Membership (mTBI vs Combined)

Logistic Regression: Demographic Predictors				
Variable	**β**	**Wald χ^2**	**Sig.**	**Odds Ratio**
Age	-0.301	1.080	.299	0.969
Race	-1.867	5.940	.015	0.155
IQ	0.048	3.694	.055	1.049
Logistic Regression: Injury Related Predictors				
Variable	**β**	**Wald χ^2**	**Sig.**	**Odds Ratio**
Loss of consciousness	1.609	7.508	.006	4.995
Posttraumatic amnesia	0.158	0.073	.787	1.171
# mTBIs	0.895	2.355	.125	2.447
Injury Mechanism (Blast vs other)	-0.456	0.498	.480	0.634
Logistic Regression: Final				
Variable	**β**	**Wald χ^2**	**Sig.**	**Odds Ratio**
Loss of consciousness	1.190	4.431	.035	3.287
Race	-1.560	4.576	.032	0.210
IQ	0.044	3.179	.075	1.045

Aim 2: A second aim is to determine how individuals with mTBI differ from those with mTBI and co-occurring PTSD in terms of performance on neuropsychological tests and to what degree these tests differentiate these groups.

The results of Mann Whitney U tests indicated no significant differences between groups on the WASI subtests, WAIS subtests, or COWAT. Significant differences between groups were found on the short delay free recall (Mann Whitney U, p=.040), short delay cued recall (Mann Whitney U, p=.048), and recognition hits (Mann Whitney U, p=.017) subtests of the CVLT-II. The long delay free recall and long delay cued recall subtests approached statistical significance at p=.066 and p=.062 respectively. Though there was no statistical difference between groups on Trail Making Tests Part A or B, these tests were notable in that mean performance on both was roughly one standard deviation below the mean in the combined group with mean standard scores of 85.0 for TMTA and 87.7 for TMTB. This represented the most deficient performance on any test administered (see table 7).

Two direct discriminant analyses were conducted using performance on cognitive testing to predict group membership (mTBI versus combined). The first was based solely on cognitive variables that were significantly different across groups, namely the short delay free recall, short delay cued recall, and recognition hits subtests of the CVLT-II. The data was assessed to ensure that the assumptions of discriminant function analysis were met, specifically with regard to multivariate normality, outliers, homogeneity of variance-covariance matrices, and absence of multicollinearity and singularity. No univariate outliers were observed and a Mahalanobis test among variables did not indicate multivariate outliers. Box's M test was not significant suggesting homogeneity of the variance-covariance matrices. There were high correlations between measures used in the discriminant function, particularly between those from the CVLT-II.

Pearson's r statistic ranged from 0.432 to 0.844 between CVLT-II subtests, though not to the degree to violate the multicollinearity assumption.

A significant discriminant function was found (Wilk's Lambda = .893, χ^2 (4) = 7.874, p=.049). However, a modest 10.7% of the variance is explained by the discriminant function (canonical correlation=0.327). In looking at the individual role of the predictor variables, the structure matrix indicated that each of the three variables was significantly correlated with the discriminant function with loadings of .877 (CVLT-II recognition hits), .775 (CVLT-II short delay free recall), and .728 (CVLT-II short delay free recall). In general, a loading (correlation) greater than .3 is considered significant (Tabachnick and Fidell, 2007). In terms of classification of participants into groups based on the discriminant function, a cross validated procedure was used in which each case is classified based on the discriminant function derived when that case is excluded. Probabilities for classification were adjusted based on group size. This resulted in 74% of cases correctly classified with 98% accuracy for the combined group and 10% accuracy for the mTBI group.

A second discriminant function analysis was conducted using a theoretical model based on previous research in which predictor variables included differing aspects of memory (short delay recall, long delay recall, and recognition) as well as executive functioning (TMTB). Again assumptions were explored and were found to be acceptable for analysis. Box's M test was significant at .015 suggesting some heterogeneity in the variance-covariance matrix. However, this test is generally considered to be overly sensitive and more concerning at $p \leq .001$ (Tabachnick and Fidell, 2007). Correlations remained high between CVLT-II subtests as mentioned previously and to a lesser degree

between CVLT-II subtests and the TMT Part B (pearson's r statistic ranged from 0.252 to 0.344).

A significant discriminant function was found (Wilk's Lambda = .871, χ^2 (4) = 9.509, p=.050). However, this model again explained only a limited amount of variance in outcome at 12.9% (canonical correlation=0.359). In looking at the individual role of the predictor variables, the structure matrix indicated that each of the four variables was significantly correlated with the discriminant function with loadings of .814 (CVLT-II recognition hits), .685 (CVLT-II short delay free recall), .590 (Trail Making Test Part B), and .565 (CVLT-II long delay free recall). In terms of classification of participants into groups based on the discriminant function, a cross validated procedure was used in which each case is classified based on the discriminant function derived when that case is excluded. Probabilities for classification were adjusted based on group size. This resulted in 74% of cases correctly classified with 94% accuracy for the combined group and 20% accuracy for the mTBI group.

Exploratory Analyses of Factors Associated with Blast Injury and the relationship of Blast Injury to mTBI and PTSD:

Additional exploratory analyses were conducted to assess factors related to mTBI resulting from an explosive blast versus those caused by other mechanisms. These analyses examined group differences in previously mentioned demographic, injury related, and cognitive variables. Only loss of consciousness and age were statistically different across groups. Specifically, individuals who experienced a blast injury were less likely to have reported a loss of consciousness and were younger at the time of

injury. A logistic regression analysis was conducted to predict cause of injury (blast versus other) based on these variables, age and loss of consciousness.

The overall model fit was good with an omnibus χ^2 (3) = 11.96 p=.003 and a non-significant Hosmer and Lemeshow test. The model accounted for 20.7% of the variance between groups (Nagelkerke R^2=.207) and correctly classified 76.9% of participants. Specifically, the model was better at classifying individuals into the blast injury group than the other cause of injury group at rates of 93.0% and 33.0% respectively. In terms of specific predictor variables, age at the time of injury (Wald χ^2 (1) = 4.608, p=.032) and loss of consciousness (Wald χ^2 (1) = 5.720, p=.017) were significant predictors of group membership. In the context of this model, individuals who reported a loss of consciousness were 81% more likely to have been injured by a cause other than an explosive blast. In addition, each additional year of age resulted in a 6% increase in the likelihood of experiencing an injury from a non-blast mechanism.

Finally, differences on variables of interest between mTBI versus combined groups were assessed in a subset of participants who experienced a blast injury. This resulted in a constricted sample size with 15 participants in the mTBI group and 44 participants in the combined group for a total of 59 participants. Due to the small sample of mTBI participants, logistic regression and/or discriminant function analyses could not be performed. Group differences were assessed based on the results of Mann-Whitney U and Chi-Square tests (see table 7). There were no differences found between the mTBI and combined groups on any demographic factors. Individuals in the combined group were more likely to have experienced multiple injuries and to have reported loss of consciousness associated with injury (see table 5).

In terms of cognitive variables in this subsample, individuals in the combined group performed significantly worse on several CVLT-II measures including the short delay free and cued recall, long delay free and cued recall, recognition hits, and recognition discriminability. This pattern was similar to that seen in the entire sample, though more significant differences were observed in this subset in terms of the degree of difference and the number of subtests achieving statistical significance. Finally, similar to the total sample, among individuals who experienced a blast injury, participants in the combined group were more likely to have a co-occurring diagnosis of depression (χ^2 (1) = 5.563, p=.018; Fisher's Exact Test p=.017) and to be prescribed antidepressant medications (χ^2 (1) = 8.251, p=.004; Fisher's Exact Test p=.008). Individuals in the combined group were also prescribed more psychoactive medications on average (Mann Whitney U, p=-016). However, the combined group was not more likely to be engaged in psychotherapy in this sample.

Table 7 – Cognitive Performance by Group

	Total Sample (n=81)			Blast Injury Only (n=59)		
Variable	**mTBI (n=21)** ***mean (s.d.)***	**Combined (n=60)** ***mean (s.d.)***	**Sig (p)**	**mTBI (n=15)** ***mean (s.d.)***	**Combined (n=44)** ***mean (s.d.)***	**Sig (p)**
CVLT-II Trials 1-5*	50.70 (12.4)	46.49 (9.9)	.125	49.86 (11.8)	45.20 (9.4)	.116
CVLT-II Learning Slope	0.02 (1.2)	0.13 (0.9)	.990	0.21 (1.3)	-0.03 (0.9)	.333
CVLT-II Short Delay Free Recall	***-0.03 (1.2)***	***-0.59 (1.0)***	***.040***	***0.04 (1.2)***	***-0.71 (1.0)***	***.025***
CVLT-II Short Delay Cued Recall	***-0.03 (1.1)***	***-0.60 (1.1)***	***.048***	***0.07 (1.1)***	***-0.73 (1.1)***	***.021***
CVLT-II Long Delay Free Recall	-0.18 (1.2)	-0.71 (1.2)	.066	***-0.12 (1.3)***	***-0.89 (1.2)***	***.025***
CVLT-II Long Delay Cued Recall	-0.23 (1.2)	-0.75 (1.1)	.062	***-0.18 (1.2)***	***-0.93 (1.1)***	***.033***
CVLT-II Recognition Hits	***-0.33 (1.6)***	***-1.47 (1.7)***	***.017***	***-0.29 (1.9)***	***-1.48 (1.7)***	***.025***
CVLT-II Recog. Discriminability	-0.32 (1.3)	-0.67 (1.1)	.163	***-0.21 (1.4)***	***-0.80 (1.1)***	***.049***
Trail Making Test-Part A†	91.57 (18.8)	85.01 (15.1)	.158	93.53 (17.4)	86.49 (13.5)	.131
Trail Making Test-Part B†	94.00 (17.5)	87.72 (16.0)	.165	94.00 (17.4)	89.60 (15.0)	.488

* Scores reported in T Score units (mean=50, s.d.=10)

† Scores reported in Standard Score units (mean=100, s.d.=15)

All other scores reported in Z Score units (mean=0, s.d.=1)

Discussion

The aims of the current study were to examine factors predictive of a diagnosis of PTSD following mTBI and to assess the degree to which neuropsychological assessment can effectively differentiate individuals who experience PTSD following an mTBI from those who do not. In terms of identifying factors associated with PTSD following mTBI, specific hypotheses were (1) individuals diagnosed with co-occurring PTSD will be older and have fewer years of education; (2) PTSD is more likely to develop in individuals who experienced blast injuries, multiple injuries, and following injuries involving loss of consciousness; and (3) individuals diagnosed with PTSD are more likely to be involved in psychotherapy and prescribed a greater number of psychoactive medications at the time of testing.

With regard to the first hypothesis, there were no significant differences between groups with regard to age or years of education. Individuals from the combined group were more likely to have reported experiencing a loss of consciousness, though other injury-related factors mentioned were not related to group membership. The results of a binary logistic regression analysis indicated that among demographic factors only race was associated with group membership. IQ approached statistical significance. However, the model as a whole was not significant so the relationship between these variables and group membership is not reliable. A second binary logistic regression analysis predicting group membership from injury-related factors yielded a significant overall model. Among the injury-related factors in this model, only reported loss of consciousness was a significant predictor of group membership.

Based on these results, a third binary logistic regression model was completed using the significant and near significant factors derived from the separate demographic and injury-related models. This model consisting of race, IQ, and reported loss of consciousness demonstrated good overall fit and accounted for 19.7% of the variability in group membership. Results indicated that participants who reported loss of consciousness associated with injury were over three times as likely to be diagnosed with PTSD. In addition, Caucasians were 21% more likely to have a PTSD diagnosis. IQ approached statistical significance as a predictor of group membership; it is unclear if greater power from an increase in the sample size would have resulted in statistical significance.

Though this model accurately classified approximately 72% of participants, it was predominantly successful in classifying individuals in the combined group at 91% as opposed to the mTBI group at 20%. This was likely due to an uneven sample size. As mentioned previously, the logistic regression analyses were aimed at identifying pre-existing factors associated with co-occuring PTSD and mTBI. Classification of individuals based on these variables has less utility in the context of these specific variables and is instead reserved for subsequent analyses using discriminant function described below.

The third hypothesis that groups would differ based on psychological and treatment factors was supported. Specifically, individuals with mTBI and PTSD were more likely to have a co-occurring depression diagnosis, to be prescribed antidepressants, and to be involved in psychotherapy. Individuals in the combined group were also prescribed over twice the number of psychotropic medications compared to the mTBI

group. They were more likely to be prescribed antidepressants as well as antipsychotics and narcotic pain meds, the latter two approaching statistically significant difference.

Overall, with regard to factors that are associated with a diagnosis of PTSD following mTBI, the results of this study indicate that Caucasians were more likely to develop PTSD. This is contrary to previous research (Dohrenwend et al., 2008) that indicated that African American Vietnam veterans were more likely to develop PTSD. However, that study also pointed out that this difference in PTSD prevalence between Caucasians and African-Americans was accounted for by differences in combat exposure/severity. This variable was not accounted for in the current study. In addition, there were no direct group differences in PTSD rates between racial groups; the model was significant only in the context of predicting PTSD in the aforementioned logistic regression model.

Reported loss of consciousness may be the single, best predictor of PTSD following mTBI. The controversies over the possibility of developing PTSD following a loss of consciousness were previously discussed. In the current study, those who experienced a brief loss of consciousness were more likely to develop PTSD compared to those with no loss of consciousness. In a study by Glaesser et al. (2004), a large proportion (26.7%) of a group of TBI survivors with no or brief loss of consciousness lasting less than 1 hour developed PTSD within 5 years of injury, significantly more than 3.2% of individuals who experienced severe TBIs with more extensive loss of consciousness.

Taken together, these results suggest that individuals who suffer a TBI with brief loss of consciousness are more likely to develop PTSD than those whose injuries involve

either no loss of consciousness or lengthier durations of loss of consciousness. This may indicate that there is a threshold in which transient neurological disruption associated with a brief loss of consciousness increases the likelihood of PTSD. However, more severe head injuries involving extensive loss of consciousness may limit the likelihood of PTSD due to associated posttraumatic amnesia and the inability to consolidate memories for the traumatic event. As such, individuals who suffer mTBIs with brief loss of consciousness may be particularly vulnerable to developing PTSD.

One problem with this is the use of self reported loss of consciousness. As mentioned previously, Ruff et al. (2009) suggest that individuals who become disoriented or dazed following an mTBI may assume loss of consciousness due to an inability to remember the events immediately following the traumatic event, resulting in over-reporting of TBI-like events. On the other hand, some individuals may under-report loss of consciousness for similar reasons in that they do not recall regaining consciousness and instead recall what they were doing seconds to minutes after the event. In addition, reported loss of consciousness may or may not be related to the event(s) leading to PTSD. For these reason, the current results are not interpreted as a direct link between loss of consciousness and PTSD. Rather, they suggest that individuals who report loss of consciousness are at significantly greater risk of developing PTSD.

Also assessed were psychological and treatment factors associated with PTSD following mTBI. Results indicated that individuals diagnosed with PTSD were more likely to have a co-occurring diagnosis of depression and to be prescribed antidepressant medications. In addition, these participants were prescribed a greater number of medications on average and medications not directly related to PTSD (antipsychotics and

narcotic pain medications) were prescribed more often in the combined group at a rate that approached statistical significance. These results suggest that individuals diagnosed with PTSD in addition to mTBI are likely to experience additional burdens beyond the direct effects of PTSD.

A second set of hypotheses were put forth to examine the role of neuropsychological tests in differentiating individuals with mTBI from those with combined mTBI and PTSD. Group differences on cognitive measures were found only in three subtests of the CVLT-II, a measure of verbal learning/memory. There were no differences found on measures of attention, visual memory, or executive functioning. Both groups typically performed in the average range across most tasks, though the TMT Parts A and B approached 1.5 standard deviations below the mean and were the most impaired. Taken together, these results suggest that individuals with co-occurring PTSD and mTBI may be particularly prone to difficulties in verbal memory and executive functioning.

With regard to discriminant function analysis based on cognitive variables, two analyses were conducted. In both analyses, a single, significant discriminant function was found with all of the predictor variables significantly loaded on the discriminant function. However, both functions as a whole accounted for a relatively low proportion of the variance between groups at approximately 11-13%. One of the primary goals of these analyses was to derive a function that would provide accurate classification of individuals into an mTBI group or a combined mTBI plus PTSD group. Using a cross validated procedure described previously, 74% of cases were correctly classified in each analysis with 94%-98% accuracy for the combined group and 10-20% accuracy for the

mTBI group. Probabilities for classification were adjusted based on group size suggesting that the discrepancy in the classification across groups was a function of the model as opposed to differences in sample size. As a result, both models were poor at discriminating groups.

The other goal of this analysis was to identify a subset of tests that reliably differentiates the outcome groups. The Recognition Hits subtest was the most significant in terms of group differentiation in this model suggesting that initial encoding of verbal information may be worse in individuals in which mTBI is complicated by PTSD. These individuals in the combined group also performed worse on recall measures which were significantly associated with the empirical and theoretical models. This may be partially explained by poor encoding as mentioned; but may also be a function of difficulties related to retrieval of information. While encoding and retrieval are primarily aspects of memory, like the TMTB, they are also associated with attention and executive functioning.

It is important to note that significant impairment was not found for any of the cognitive variables assessed in either group. Significant impairment is defined for this study as performance greater than 1.5 standard deviations below the mean. Only the performance of the combined group on the Recognition Hits subtest (z=-1.47) and Trail Making Test Part B (standard score=87.72) approached this level. It should be noted that because the mean group performance across tests fell in the average to low average range, they may provide limited information in differentiating mTBI versus mTBI and PTSD in a clinical setting.

The limited deficits in cognitive performance overall, was consistent with prior studies of cognitive functioning among individuals with mTBI and PTSD. Specifically, within the current sample, the average time from injury to assessment was just under 4 years at 46.4 months. As such, the lack of significant cognitive deficits found in the mTBI group is consistent with the meta analysis of Frencham et al (2005). In this study, cognitive deficits trended toward zero with greater time since injury with an effect size that failed to remain significant when looking at the post-acute group only. Results of the current study indicating poorer performance on measures of memory and executive functioning in the combined group are consistent with previous research (Horner & Hamner, 2002; Golier & Yehuda, 2002) in which impairments were noted in these areas among individuals diagnosed with PTSD.

As mentioned previously, few studies have assessed the neuropsychological performance among individuals with co-occurring mTBI and PTSD. Brenner et al. (2010) found no significant differences between individuals with mTBI and those with co-occurring mTBI and PTSD across cognitive measures; though the authors pointed out that moderate effect sizes were noted across multiple executive tests which may have failed to reach statistical significance due to limited power. A study by Nelson et al. (2009) revealed poorer performance related to processing speed and response inhibition among veterans with co-occurring PTSD and mTBI when compared to the mTBI only group. It should be noted that significant impairment was not evident on neuropsychological measures in either group, only mild impairment on executive measures (Stroop Color and Stroop Word tests) in the co-occurring group. Similar to these studies, the current results suggest greater difficulty on executive tasks in the

combined group and additionally that executive and memory abilities differentiate individuals with and without PTSD post-mTBI.

By contrast, Gordon et al. (2011) found no differences among individuals with mTBI, mTBI and PTSD, or mTBI and other psychological disorders on any of the cognitive measures administered which included the CVLT-II and TMTB. The differences in these results and those from the current study may be at least partially explained by the differences in sample characteristics. Specifically, the Gordon et al. (2011) study included individuals from multiple conflicts (i.e. Desert Storm, Vietnam), individuals with other co-occurring diagnoses (ADHD, substance abuse), and individuals with possible neurological disorders (stroke, tumor, possible dementia). In addition, for most participants in this study brain injuries occurred outside of combat (89%), few were the result of blast explosion (9%), and occurred approximately 20 years prior to testing on average.

Finally, additional, exploratory analyses were conducted to investigate factors associated with blast injuries and in what way this mechanism of injury is related to mTBI and PTSD. Mann Whitney U tests were used to asses differences in cognitive variables previously discussed between individuals whose mTBI(s) resulted from an explosive blast versus those that were the result of other mechanisms. No significant differences were found between these groups on any of the cognitive variables mentioned. A significant binary logistic regression model that was composed of loss of consciousness, age, and race accounted for approximately 21% of the variance between blast and non-blast injury groups. The results of this analysis indicate that participants who reported a loss of consciousness were 81% more likely to have been injured as a

result of another (non-blast) mechanism. Also, for each additional year of age, individuals in this sample were 6% more likely to have an injury from a non-blast mechanism. Overall, individuals who experienced an injury as a result of a blast were younger at the time of injury and less likely to report loss of consciousness than those whose injuries resulted from other mechanisms. With regard to age, one hypothesis would be that among deployed soldiers, those who are younger (and perhaps lower in rank) may be exposed to more direct combat and/or severe danger resulting in a greater chance of blast exposure.

In the subset of individuals who experienced a blast injury, differences in variables of interest between the mTBI and combined group were assessed. Similar to the full sample, there were no significant differences between groups with regard to demographic variables. Also similar to the full sample, individuals who reported loss of consciousness were significantly more likely to be in the combined group. In this subset, the number of mTBIs also differed across groups with individuals in the combined group more likely to experience multiple injuries. It is unclear if multiple injuries and loss of consciousness leads to neurological changes that may promote PTSD as discussed previously, or if these factors are markers for the intensity of battle seen by these individuals making PTSD more likely.

With regard to cognitive performance, the differences between groups were similar to that of the total sample, though in this subgroup nearly all of the CVLT-II subtests reached significance (see table 7). Interestingly, even though cognitive measures did not differ between the blast and non-blast groups, once the non-blast group was removed, the degree of difference between mTBI and combined groups on these

measures increased. Again due to a small mTBI sample, there was insufficient power to conduct a discriminant function analysis using these variables. However, given the increased differences between mTBI and combined groups on these cognitive measures in a more homogenous group (blast injury only), the CVLT-II may be more sensitive to the presence of PTSD in blast injured individuals.

Conclusions

Overall, several factors were predictive of a diagnosis of PTSD following mTBI. Among demographic factors, no variables were significantly different between groups, though race was significantly predictive of group differences in our model. IQ approached significance and may have been hampered by a relatively small sample size. In terms of injury related variables, reported loss of consciousness was strongly predictive of PTSD. The number of injuries consistent with mTBI differed significantly between outcome groups only when the sample consisted of individuals whose injuries were the result of an explosive blast.

As expected, individuals from the combined group were more likely to be involved in psychotherapy and be prescribed a greater number of meds than the mTBI group. However, it was not anticipated that depression would be more common in the combined group as well. As such, findings cannot be directly applied to the effects of PTSD without acknowledging a possible contribution from depression as well.

With regard to differentiating groups based on cognitive performance, specific subtests of the CVLT-II and TMTB combined to form a significant discriminant function. The utility of this function is limited due to the small variance between groups accounted for by this function and the over-classification of individuals into the combined group

even after accounting for differences in group size. The groups did differ significantly on several verbal memory measures from the CVLT-II and only the combined group exhibited performance on these measures and an executive functioning measure (TMTB) that approached significance. Overall, with regard to cognitive measures, poor performance appears to be related to psychiatric factors, particularly PTSD and possibly depression, rather than mTBI.

With regard to poor performance on the CVLT-II in the combined group, this may be partially explained by the nature of the test. Individuals with anxiety, may become overwhelmed by a task in which they are asked to memorize a long list of words and most likely fail on the first and possibly several subsequent trials. In addition, the combined group was more likely to be depressed which may have impacted the recognition of test items due to a negative response bias.

Finally, it was hypothesized that blast injuries may prove to have unique characteristics in the context of the variables available in this study. Blast injury was not predictive of PTSD following mTBI and no significant differences in variables of interest were found between individuals whose injuries resulted from a blast versus those from another mechanism. In sum, the results of this study suggest that individuals with mTBI and PTSD are likely to be Caucasian and report loss of consciousness. They may also perform worse on measures of verbal memory and executive functioning than others with mTBI, though performance is likely to remain in the average to low average range. While blast injury may lead to a different mechanism of neuronal damage, this was not reflected cognitively on the neuropsychological tests administered in this study.

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THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Institutional Review Board for Human Use

Form 4: IRB Approval Form
Identification and Certification of Research
Projects Involving Human Subjects

UAB's Institutional Review Boards for Human Use (IRBs) have an approved Federalwide Assurance with the Office for Human Research Protections (OHRP). The Assurance number is FWA00005960 and it expires on January 24, 2017. The UAB IRBs are also in compliance with 21 CFR Parts 50 and 56.

Principal Investigator:	LABBE, DONALD RAYMOND
Co-Investigator(s):	
Protocol Number:	**X110503006**
Protocol Title:	*Factors Associated with Post Traumatic Stress Disorder and Mild Traumatic Brain Injury in Veterans of Operations Iraqi Freedom and Enduring Freedom: The Role of Neuropsychological Assessment*

The IRB reviewed and approved the above named project on 6-22-12. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services. This Project will be subject to Annual continuing review as provided in that Assurance.

This project received EXPEDITED review.

IRB Approval Date: 6-22-12

Date IRB Approval Issued: 6-22-12

Marilyn Doss

Marilyn Doss, M.A.
Vice Chair of the Institutional Review
Board for Human Use (IRB)

Investigators please note:

The IRB approved consent form used in the study must contain the IRB approval date and expiration date.

IRB approval is given for one year unless otherwise noted. For projects subject to annual review research activities may not continue past the one year anniversary of the IRB approval date.

Any modifications in the study methodology, protocol and/or consent form must be submitted for review and approval to the IRB prior to implementation.

Adverse Events and/or unanticipated risks to subjects or others at UAB or other participating institutions must be reported promptly to the IRB.

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