Mild traumatic brain injury and posttraumatic stress disorder in returning veterans: Perspectives from cognitive neuroscience

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ABSTRACT

A significant proportion of military personnel deployed in support of Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) has been exposed to war-zone events potentially associated with traumatic brain injury (TBI) and posttraumatic stress disorder (PTSD). There has been significant controversy regarding healthcare policy for those service members and military veterans who returned from OEF/OIF deployments with both mild TBI and PTSD. There is currently little empirical evidence available to address these controversies. This review uses a cognitive neuroscience framework to address the potential impact of mild TBI on the development, course, and clinical management of PTSD. The field would benefit from research efforts that take into consideration the potential differential impact of mild TBI with versus without persistent cognitive deficits, longitudinal work examining the trajectory of PTSD symptoms when index trauma events involve TBI, randomized clinical trials designed to examine the impact of mild TBI on response to existing PTSD treatment interventions, and development and examination of potential treatment augmentation strategies.

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Improved protective equipment and emergency medical care innovations characterize contemporary war zones, saving lives from injuries that likely would have proven fatal in past wars. With increased survival, however, military personnel deployed to contemporary war zones are more likely to return with physical injuries. Traumatic brain injury (TBI) has been of particular concern, reflecting high rates of head and neck injuries among Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) veterans (Xydakis, Fravell, Nasser, & Casler, 2005). The preponderance of head injuries stems in part from the nature of the warfare, including the frequent use by enemy combatants of improvised explosive devices (IEDs), which have been reported as the most common cause of TBI among OEF/OIF veterans (Galarneau, 2008; Owens et al., 2008).

Concurrently, war-zone veterans are returning from OEF/OIF deployments with elevated rates of psychiatric symptoms, including posttraumatic stress disorder (PTSD) (Hoge et al., 2004; Smith et al., 2008; Tanielian & Jaycox, 2008). Not surprisingly, given that combat intensity elevates risk of both physical and psychological injuries (Hoge et al., 2004; Hoge et al., 2008), many of the veterans who express symptoms of PTSD also report exposure to events potentially associated with TBI. The co-occurrence of TBI and PTSD in returning veterans and the symptom overlap between the two disorders have fueled controversies regarding how the care of returning veterans should best be provided (Hoge, Goldberg, & Castro, 2009). Such controversies encompass the implementation of population-based screening in DoD and VA healthcare facilities, the optimal context for healthcare delivery (e.g., primary care, mental health and rehabilitation specialty clinics, polytrauma settings), treatment priorities, and compensation and pension issues. Especially at lower levels of TBI severity, the sequelae of TBI and psychological trauma exposure may be difficult to distinguish (Hill, Mobo, & Cullen, 2009). In addition to clouding diagnostic decisions, shared attributes and associated features potentially complicate the course and clinical management of each disorder. For example, TBI sequelae and PTSD may each be associated with elevated risk of substance abuse and suicidal behavior, as well as with symptoms of irritability, anxiety, depression, cognitive impairment, and sleep disturbance (Lew et al., 2008; Stein & McAllister, 2009). Associated pain syndromes may further complicate the recovery of each (Lew et al., 2008).

In keeping with this Special Issue's focus on PTSD in returning war-zone veterans, the article is written from a "PTSD centric" viewpoint, emphasizing how mTBI potentially affects the presentation, course, and clinical management of PTSD in veterans of OEF/OIF. In doing so, we take a cognitive neuroscience perspective, centering on core neuropsychological, cognitive, and neural aspects of TBI and PTSD. Although there are many possible vantages from which to view TBI and PTSD, a cognitive neuroscience perspective may prove useful because of (a) the centrality of cognitive processes to PTSD and its treatments; (b) the involvement of the brain in influencing these processes; and (c) the overlapping neural substrates that characterize TBI and PTSD. Because mild TBI (mTBI) is thought to be more common than moderate and severe TBI among returning OEF/OIF veterans (Hoge et al., 2008) and because theoretical questions regarding the potential overlap of TBI with PTSD have greater applicability to milder injuries, the review focuses primarily on mTBI. The review is organized to address several key issues: the epidemiology of mTBI in OEF/OIF veterans, the development and expression of PTSD when accompanied by TBI, overlap in the neuropsychological and neuroanatomical substrates of mTBI and PTSD, and implications of mTBI for the clinical management and treatment of PTSD. We begin first, however, with a brief description and definition of mTBI.

1. mTBI: a brief description and definition

TBI implies that a mechanical (e.g., blunt trauma) or biomechanical (e.g., blast injury) force sufficient to result in at least temporary neural insult has been applied to the brain. Brain injury (versus head injury without damage to the brain) is typically inferred by a sign or symptom at the time of the injury (e.g., alteration or loss of consciousness, visual disturbances), although in rare cases of slowly developing secondary damage, the injury does not manifest until later. Computed tomography (CT) and conventional magnetic resonance imaging (MRI) techniques typically do not reveal pathophysiological alterations associated with mild injury, but may allow visualization of neural changes in cases with more extensive injury. The development of uniform case definitions for mTBI has been particularly challenging, and TBI classification systems vary in their severity criteria. However, most case definitions of mTBI specify alteration or loss of consciousness of up to 30 min and no more than a 24 hour period of posttraumatic amnesia (Ruff, 2005).

Most overt symptoms associated with mTBI resolve within days or weeks of the injury (Bigler, 2008), and recovery is substantial in most individuals (Iverson, Zasler, & Lange, 2007). However, 10–20% of mTBI victims report continued problems (Ruff, Camenzuli, & Mueller, 1996; Rutherford, Merrett, & McDonald, 1979; Wood, 2004), with recent estimates suggesting that as many as 44–50% of mTBI patients experience three or more symptoms at one-year post-injury (S. Dikman, personal communication, June 7, 2009). Such lingering sequelae, often referred to as persistent post-concussive syndrome (PPCS; Bigler, 2008; Iverson, Brooks, Lovell, & Collins, 2006), include psychological symptoms, subjective cognitive impairments, and somatic complaints. The non-specific nature of many of these symptoms has contributed to controversies regarding the status of PPCS as a diagnostic entity and how lingering symptoms should be conceptualized in relation to war-zone TBI. For example, in a UK sample of war-zone veterans, PPCS-type symptoms were as likely to occur with certain war-zone experiences not associated with blast exposure, such as aiding the wounded, as they were with war-zone exposure to blast (Fear et al., 2008). Nonetheless, when occurring in the context of brain injury, persistent symptoms have been associated with observable pathophysiological abnormalities using newer neuroimaging techniques (e.g., Huang et al., 2009; Kraus et al., 2007; Lipton et al., in press; Lipton et al., 2008; Lo, Shifteh, Gold, Bello, & Lipton, 2009; Niogi et al., 2008) and on post-mortem examination (Bigler, 2004), providing compelling evidence of a neural basis for persistent symptoms (Bigler, 2008).

2. Epidemiology of TBI in OEF/OIF veterans

Although TBI has been labeled the "signature injury" of OEF/OIF (Okie, 2005; Warden, 2006), the actual prevalence of TBI among returning veterans has been difficult to estimate, with estimated prevalence rates ranging from 5 to 23% in larger studies using non-clinical samples. Several factors have likely contributed to wide variance in prevalence rates in non-clinical samples. First, difficulties estimating prevalence reflect in part the reliance on retrospective accounts of exposure, which can be subject to reporting biases (Wessely et al., 2003). This is especially problematic at milder levels of injury because, in the context of a war zone, such injuries are not necessarily treated or even documented at the time they occur. Second, the criteria upon which injury status was determined vary across studies. Finally, most studies have relied on convenience samples, making it difficult to generalize results to a population characterized by a broader array of war-zone geographic locations, duty assignments, and deployments at various stages of the military operations than any one convenience sample can portray. As would be expected, rates of TBI are typically higher in clinical populations, such as those receiving treatment for burn and explosion injuries (Gaylord et al., 2008), those presenting within VA polytrauma clinical settings (Sayer et al., 2008), and those receiving treatment for blast injuries in military medical settings (Warden, 2006).

Despite some variance in estimated TBI prevalence rates, research using non-clinical samples has generally revealed that deployed service members are at increased risk of TBI and that a sizable subset of returning veterans who screen positive for TBI also screen positive for PTSD. In a cross-sectional study of 2235 OEF/OIF veterans who had left combat theaters by September 2004 and who lived in the Mid-Atlantic region of the U.S. (Schneiderman, Braver, & Kang, 2008), approximately 12% reported a history consistent with mTBI on the 3-item Brief Traumatic Brain Injury Screen (Schwab et al., 2007), which requires alteration but not full loss of consciousness to meet criteria for TBI. With 11% of the sample screening positive for PTSD on the PCL (Weathers, Huska, & Keane, 1991), the strongest factor associated with post-concussive symptoms was PTSD, even after overlapping symptoms of TBI and PTSD were removed from the analyses. A study of 2525 Army soldiers selected from two combat infantry brigades who were assessed in 2006 after their return from Iraq revealed similar prevalence rates (10%) when TBI was defined as head injury with any alteration of mental state (Hoge et al., 2008). The prevalence of TBI was lower (approximately 5%), however, when TBI was defined as head injury with associated loss of consciousness. As in the Schneiderman et al. study, Hoge et al. (2008) found that PTSD and TBI frequently co-occurred. Of those soldiers reporting head injury with loss of consciousness, approximately 44% met screening criteria for PTSD as defined by a PCL score of 50 or greater and DSM-IV symptom congruency. To estimate TBI prevalence in a single brigade combat team of 3973 Army soldiers who had deployed to Iraq, Terrio et al. (2009) required a clinician-confirmed diagnosis and integrated collateral injury information from war-zone observers to determine TBI cases. Using these criteria, approximately 23% of the brigade combat team met criteria for TBI; however, because the study was limited to a single combat brigade team that saw extensive combat during their deployment, the results are difficult to generalize. Finally, in an attempt to obtain a more representative sample, RAND (2008) used a stratified random sampling protocol with weighted adjustments to estimate TBI prevalence in 1965 OEF/OIF veterans. This study reported an estimated TBI prevalence rate of 19% using the Brief Traumatic Brain Injury Screen and an estimated PTSD prevalence of 13% using the PCL scoring rule of DSM congruency, with the two disorders moderately ($r = 0.29$) correlated. Of those reporting TBI, over a third met screening criteria for either depression or PTSD.

3. PTSD development and manifestation following TBI

3.1. Can PTSD develop following TBI with loss of consciousness?

PTSD diagnosis, as defined by the *Diagnostic and Statistical Manual for Mental Disorders, 4th Edition* (DSM-IV-TR; American Psychiatric Association, 2000), requires exposure to a traumatic event resulting in fear, helpless, or horror; persistent re-experiencing of the event (e.g., intrusive thoughts); avoidance of stimuli associated with the event and numbing of general responsiveness; and, persistent symptoms of increased arousal. In addition, the symptoms must be present for at least one month and must result in clinically significant distress or functional impairment. It has been suggested that the development of PTSD is improbable if memory for the trauma event is compromised due to a neural insult (e.g., Boake, 1996; Sbordone & Liter, 1995). By this reasoning, amnesia for the event precludes several core aspects of PTSD including affective responses associated with the event, re-experiencing of trauma memories, and avoidance of trauma reminders after the event. However, as summarized by Harvey, Kopelman, and Brewin (2005), there are likely several mitigating factors that allow PTSD to develop in the context of amnesia for the event: (1) affective responses and sensory-perceptual experiences associated with the trauma may be encoded at an implicit (i.e., unconscious) level that influences subsequent physiological, behavioral, and emotional responses (Layton & Wardi-Zonna, 1995), even when the trauma is not explicitly (i.e., consciously) recalled; (2) amnesia may only be partial, with some aspects of the trauma preserved in conscious memory (King, 1997; McMillan, 1996); (3) reconstruction of memory from secondary sources such as family, friends, or other observers may influence the development of PTSD symptoms (Harvey & Bryant, 2001); and (4) the circumstances of the trauma and peri-traumatic events (e.g., subsequent medical procedures, sights at the scene of accident witnessed after consciousness was regained) are psychologically traumatic in and of themselves (McMillan, 1996) and therefore may lead to PTSD.

In military combat, the context in which the TBI occurs is likely central to how PTSD develops. Specifically, war-zone stress exposures are not typically limited to a single trauma event but instead frequently involve a series of repeated and sometimes unremitting life threatening events. Thus, even if the specific trauma event associated with the TBI is not remembered, that event is often embedded within a larger context of psychological trauma exposure. Also of relevance, less severe levels of mTBI, which are the most prevalent among returning veterans reporting TBI, may entail only a brief episode of altered consciousness and rarely involve total amnesia for the event. Partial encoding may allow some aspects of the injury event to be preserved in conscious memory and therefore potentially re-experienced at a conscious level.

Other than the recent epidemiological reports from OEF/OIF described in the previous section, much of the empirical literature addressing the coexistence of TBI and PTSD have been conducted on individuals who experienced discrete events, most typically motor vehicle accidents. These studies generally indicate that both PTSD and acute stress disorder can coexist with TBI, even following a single incident in which the patient lost consciousness (see Harvey et al., 2005; Harvey, Brewin, Jones, & Kopelman, 2003 for reviews). PTSD has been documented in cases of moderate and severe TBI; however, of particular relevance to OEF/OIF veterans, several studies have suggested that PTSD is more likely to occur in the context of mild, as compared to severe, TBI (Joseph & Masterson, 1999; Glaesser, Neuner, Lütgehetmann, Schmidt & Elbert, 2004). The reason why milder injuries are more likely to result in PTSD is unknown, but a commonly invoked explanation holds that the limited encoding of the injury event associated with more severe injuries may be protective. Consistent with this notion, a recent longitudinal study of trauma center patients with mTBI documented an inverse relationship between the severity of select re-experiencing symptoms at 3-month follow-up and the duration of posttraumatic amnesia (Bryant et al., in press). The results of this study suggest that the strength with which trauma memories are encoded may in part determine whether PTSD develops, with clearer memories of the trauma associated with a greater likelihood of developing PTSD.

Taken as a whole, the literature suggests that PTSD and TBI can coexist and that PTSD is more likely to develop at milder levels of TBI. There is also evidence that PTSD may be inversely related to TBI severity and perhaps to the strength with which trauma memories are consolidated. If TBI severity is viewed as a continuum, with the absence of TBI anchoring the continuum as the point of lowest impact, a fully linear association between TBI severity and PTSD would imply that PTSD is more likely to occur after injuries that do not involve TBI. However, as described in the next section, a fully linear relationship between TBI severity and PTSD is not borne out by the data.

3.2. Does TBI confer additional risk of PTSD development or symptom exacerbation following psychological trauma exposure?

With much of the current debate centered on whether mTBI symptoms can be best explained by PTSD and other psychological phenomena, we chance overlooking one of the critical questions pertaining to the clinical management of comorbid TBI and PTSD: to what extent does neural insult complicate psychological recovery following exposure to traumatic stressors? Physical injury of any type, even if not involving the brain, is a risk factor for PTSD (Koren,

Norman, Cohen, Berman, & Klein, 2005). However, TBI may confer additional risk of adverse mental health outcomes, including PTSD, following psychological trauma exposure.

In OEF/OIF veterans, PTSD is more prevalent in those veterans who report mTBI, as compared both to veterans who suffered no injury (Hoge et al., 2008; Schneiderman et al., 2008) and to veterans who suffered injuries not involving the head (Hoge et al., 2008). In the Hoge et al. (2008) study, head injury with loss of consciousness was associated with PTSD and depression diagnoses, even after controlling statistically for shared variance attributable to combat severity, mechanism of injury, hospitalization, and demographic factors. In a study of Cambodian survivors of mass violence, Mollica, Henderson and Tor (2002) compared the relative impact of various trauma events on psychological outcomes and likewise found that psychologically traumatic events involving brain injury were significantly stronger predictors of depression and PTSD symptoms than psychologically traumatic events not involving brain injury. Previous research with military veterans of prior conflicts has likewise indicated that TBI is associated with greater depression (Vasterling, Constans, & Hanna-Pladdy, 2000) and PTSD (Chemtob et al., 1998) severity among combat-exposed veterans. Such findings are supported by a recent analysis of archived data collected in over 4000 Vietnam-era veterans enrolled in the Vietnam Experience Study, which revealed that the presence of mTBI (associated with being in a motor vehicle accident) increased the risk of current PTSD experienced an average of 16 years after their military discharge (Vanderploeg, Belanger, & Curtiss, 2009). In one of the only other longitudinal efforts to date, Bryant et al. (in press), referred to above, found that select PTSD re-experiencing symptoms at 3 months post-injury were more severe among trauma center patients with mTBI as compared to those with non-TBI injuries.

Most studies examining the effects of TBI on PTSD have been conducted with people who experienced closed head injury. The blast-induced injuries experienced by some OEF/OIF veterans are considered "closed" because there is typically no penetration of the brain. However, war-zone participation can also result in penetrating (i.e., "open") brain injuries, which involve penetration of the skull and dura matter (i.e., outermost layer of the brain) by a foreign object. In a study of penetrating focal brain injuries among Vietnam veterans who were also exposed to psychologically traumatic war-zone events, Koenigs et al. (2008) found that damage to two specific brain regions thought to be involved in the pathogenesis of PTSD (the amygdala and ventro-medial prefrontal cortex) was associated with less frequent occurrence of PTSD as compared to other lesion locations and to no brain damage. Although the study results are tentative due to the small sample size for certain lesion locations, this intriguing finding suggests that the nature and location of the brain damage possibly influence whether PTSD develops, with damage to certain areas potentially serving a protective role. It is plausible that these areas are among those critical to the seemingly protective effects against PTSD development observed in more severe and diffuse closed head injuries.

Interestingly, the relationship between neural insult and adverse psychological outcomes following exposure to psychological trauma might not be limited to TBI. For example, prisoners of war with captivity weight loss sufficiently extreme as to constitute neural risk reported more psychological distress decades after the exposure than those with no neural risk factors (Sutker & Allain, 1996). Likewise, the onset of cerebrovascular disease has been associated with the re-emergence of PTSD symptoms after years of relative freedom from PTSD symptoms (Cassiday & Lyons, 1992). These findings are also in keeping with studies suggesting that innate neural integrity, as reflected by pre-military cognitive and intellectual functioning, is inversely related to PTSD following subsequent trauma exposure (Breslau, Lucia, & Alvarado, 2006; Koenen et al. 2009; Kremen et al., 2007).

In sum, most studies indicate that TBI, even as compared to non-TBI physical injury, confers additional risk of PTSD and associated psychological symptoms above and beyond that associated with the psychological trauma. These findings suggest that the inverse relationship between TBI severity and PTSD summarized in the previous section only holds when TBI is present. However, once an injury threshold is met, paradoxically, milder injuries confer greater risk of PTSD than more severe injuries. In the following sections, we describe the potential neuropsychological and functional neuroanatomical overlap between mTBI and PTSD with the aim of providing possible insights into the nature of the relationship between the two disorders.

4. TBI and PTSD: overlap in underlying neural substrates?

4.1. Neuropsychological features

Both mTBI and PTSD can be associated with mild neuropsychological impairment, with significant overlap in the neuropsychological domains potentially affected by each disorder (attention, learning and memory, and executive functioning). Although mTBI and PTSD may also differ subtly in the processes responsible for the involvement of each of these functional domains, their neuropsychological outcomes differ most notably in their recovery course. Meta-analytic studies have reliably indicated that most measurable neuropsychological deficits associated with mTBI resolve within a few weeks of the injury, returning to baseline within one to three months (Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005; Binder, Rohling, & Larrabee, 1997; Iverson, 2005; Schretlen & Shapiro, 2003; Levin, Mattis, & Ruff, 1987), although a recent re-analysis of data included in prior meta-analyses suggests that mild neuropsychological impairment endures more reliably than previously believed in a small subset of mTBI victims (Pertab, James, & Bigler, 2009). In contrast, PTSD symptoms and the neuropsychological deficits associated with PTSD more often persist years after psychological trauma exposure (e.g., Sutker, Vasterling, Brailey, & Allain, 1995; Yehuda et al., 2006). The potential transient nature of mTBI cognitive sequelae in most mTBI cases notwithstanding, the neuropsychological consequences of mTBI may nonetheless be relevant to PTSD for several reasons.

First, as summarized earlier, the recovery course among mTBI cases is not uniform (Binder, 1997), with as many 10 to 20% of mTBI patients still not fully recovered at 1 year post-injury (Ruff et al., 1996; Rutherford et al., 1979; Wood, 2004). The variability in recovery from mTBI may in part reflect heterogeneity in injury attributes across the cases that are classified as mTBI. Classification systems vary in their criteria and, even within a single classification system, "mild" TBI may encompass a relatively broad severity range. For example, several of the classification systems allow up to 24 h duration of posttraumatic amnesia within the mild category (e.g., American Congress of Rehabilitation Medicine, 1993; Holm, Cassiday, Carroll & Borg, 2005), but patients with posttraumatic amnesia exceeding 4–6 h may require months to years to fully recover (Alexander, 1995).

Overall, injury attributes may be less important in predicting recovery than the patient recruitment setting (e.g., treatment clinics, community settings, litigation) (Belanger et al., 2005), as well as a variety of individual difference characteristics (e.g., premorbid psychological factors, subsequent life stressors) (Ponsford et al., 2000). Genetic vulnerability is also being explored as a potential determinant of outcome (McAllister, Flashman, McDonald, & Saykin, 2006). It has been argued that PTSD and depression in particular increase risk of post-concussive symptoms following war-zone mTBI (Hoge et al., 2008). Interestingly, however, Vanderploeg et al.'s (2009) study of Vietnam-era veterans revealed that mTBI and PTSD contributed independently to variance in residual somatic, cognitive, and emotional complaints experienced years after injury/psychological trauma exposure, suggesting that the effects of mTBI and PTSD on post-concussive symptoms may be additive. Also of particular relevance to military personnel, who sometimes have several mTBI

exposures over the course of their lives and possibly within single deployments, recurrent brain injuries (even when mild) may interfere with neuropsychological recovery (Guskiewicz et al., 2003). This incomplete recovery increases the risk of both chronic neuropsychological impairment (Zillmer, Schneider, Tinker, & Kaminaris, 2006) and subsequent dementia syndromes (Guskiewicz et al., 2005), although the adverse effects of multiple concussions may be limited when there are only one or two previous concussions (Iverson et al., 2006).

Second, neuropsychological deficits associated with mTBI, even if transient, occur during a time relevant to the formation of trauma memories. TBI-related deficits are most likely to surface shortly after the event (Bigler, 2008). Because much of the initial binding process that allows for the formation of a memory trace (also called short-term consolidation) occurs within 24 h, this period is critical to the consolidation of the trauma memory and its integration into the larger autobiographical memory base (Dudai, 2004). If cognitive deficits occurring in the immediate aftermath of the event interfere with the formation of coherent and well-integrated trauma memories, these deficits could arguably affect the subsequent development of PTSD. Similarly, emotional responses to the psychological aspects of the event during and shortly after the exposure have been found to be among the strongest predictors of subsequent PTSD and may set the stage for the subsequent trajectory of emotional symptoms (Brewin, Andrews, & Valentine, 2000; Ozer, Best, Lipsey, & Weiss, 2003). Specifically, if the mTBI is associated with acute emotional dysregulation, whether due to altered cognitive processing of the event or as a direct result of limbic disruption, the subsequent course of psychological symptoms may be altered, even when the direct effects of the brain injury are transient.

Third, although residual cognitive performance deficits associated with mTBI typically do not fall within the normative range of clinical impairment, even "well recovered" patients may continue to experience reduced mental efficiency (Crawford, Knight, & Alsop, 2007; Stuss et al., 1985) and experience significant difficulty under conditions of physical or psychological stress (Ewing, McCarthy & Gronwall, 1980). These residual deficits are thought to reflect reduced information processing capacity, either in terms of speed of processing or in terms of the amount of information that can be handled simultaneously (De Monte et al., 2005; Stuss et al., 1985; Van Zomeren, Brouwer, & Deelman, 1984) and may affect the course of PTSD in subtle ways. It is noteworthy that, even in the absence of demonstrable residual cognitive deficits, mTBI may be associated with increased risk of developing anxiety and depression symptoms more generally (Iverson et al, 2006) especially in the context of multiple concussions (Guskiewicz et al., 2007).

Below we summarize the most commonly occurring cognitive deficits associated with each disorder. It is worth noting that neuropsychological performance is typically multi-factorial in that one or more cognitive processes are necessary to perform a single task. Further, performance on many tasks is influenced not only by bottom-up processes (e.g., basic perceptual processes and simple attention influence learning) but also by top-down processes (e.g., executive functions influence the efficacy of memory retrieval). "Executive functioning" has proven to be a construct that is particularly difficult to define operationally, as it pertains to a variety of higher order control processes that are engaged in the performance of novel, non-routine or complex tasks. In this paper, we use "executive function" to refer to functions typically dependent on the frontal lobes and involving monitoring, self-regulation, planning, and mental flexibility.

4.1.1. PTSD

The most common cognitive deficits associated with PTSD involve attention, executive functions, and memory. Attention and executive deficits accompanying PTSD include impairment of working memory (i.e., the ability to maintain and manipulate information mentally in a temporary "buffer") (Brandes et al., 2002; Gilbertson, Gurvits, Lasko, Orr, & Pitman, 2001; Meewisse et al., 2005; Vasterling, Brailey,

Constans, & Sutker, 1998), difficulties in sustaining optimal levels of vigilance and attention over time (Jenkins, Langlais, Delis, & Cohen, 2000; McFarlane, Weber, & Clark, 1993; Vasterling et al., 2002; Veltmeyer et al., 2005), response disinhibition (Leskin & White, 2007; Vasterling et al., 1998), and impaired ability to gate, monitor, and regulate the flow of incoming information and environmental stimuli (McFarlane et al., 1993; Vasterling et al., 1998). Whereas these PTSD-related deficits are observed on tasks involving emotionally neutral information, additional attentional abnormalities occur when trauma-relevant stimuli are introduced. In particular, when confronted with trauma-relevant stimuli, trauma survivors with PTSD direct their attention to trauma-relevant information at the expense of attention to trauma-irrelevant information (Constans, 2005). The most replicable evidence for this "attentional bias" comes from the emotional Stroop task, a timed task that requires speeded naming the color of ink in which words of varying emotional content are printed. PTSD is associated with relatively slower response times for naming the color of ink of trauma-relevant words, as compared to non-trauma-relevant yet emotionally-valenced words and emotionally neutral words (Cassiday, McNally, & Zeitlin, 1992; Foa, Feske, Murdock, Kozak, & McCarthy, 1991; Kaspi, McNally, & Amir, 1995; McNally, Kaspi, Riemann, & Zeitlin, 1990; Williams, Mathews, & MacLeod, 1996).

Memory abnormalities are integral to the experience of PTSD. PTSD re-experiencing symptoms, for example, center on the inability to regulate intrusive trauma recollections, as well as the emotional and physiological responses that occur in response to reminders of the trauma event(s). Somewhat paradoxically, PTSD is also thought to be associated with unreliable access to trauma memories (e.g., Brewin, 2001; Ehlers & Clark, 2000). Moreover, a number of studies have documented associations between PTSD and deficits in learning and remembering new information unrelated to the trauma event. With respect to learning new information, impairments in PTSD have been documented using both verbal and visual–spatial tasks but are more pronounced when the information to be learned is verbal (Brewin, Kleiner, Vasterling, & Field, 2007). PTSD-related deficits have been observed variably at different stages of memory processing, including the initial registration of new information and, somewhat less commonly, in retaining the newly learned information over time (see Isaac, Cushway, & Jones, 2006; Verfaellie & Vasterling, 2009 for reviews). With respect to autobiographical memory recall, persons with PTSD tend to provide a paucity of specific details (e.g., McNally, Lasko, Macklin, & Pitman, 1995; Schönfeld & Ehlers, 2006; Schönfeld, Ehlers, Böllinghaus, & Rief, 2007), a phenomenon known as "overgeneral" memory. This tendency to recall personal life events in an overgeneral manner may be particularly pronounced for emotionally positive events. Whether trauma memories are encoded and recalled qualitatively differently from non-trauma autobiographical memories remains controversial (Zoellner & Bittenger, 2004). Regardless of the extent of their unique qualities, however, trauma memories are central to most cognitive conceptualizations of PTSD (c.f., Rubin, Berntsen, & Johansen, 2008).

4.1.2. TBI

Common neuropsychological deficits associated with TBI involve a range of deficits including attention/working memory, executive function, memory, motor skills, general intellectual skills, and problem solving; however, there appears to be a dose-response relationship in which milder injuries are associated with fewer residual deficits (Dikmen, Ross, Machamer, & Temkin, 1995). Nonetheless, in the acute stages following mTBI, cognitive deficits are of sufficient magnitude to interfere with everyday activities (Alexander, 1995) and are apparent on mental status examinations (Barr & McCrea, 2001) and neuropsychological tasks of working memory (McAllister et al., 2006), speed of information processing (Barrow, Collins & Britt, 2006; Barrow, Hough et al., 2006), executive function, supraspan list learning, and, in particular, delayed memory

and verbal fluency (Alexander, 1995; Belanger et al., 2005). Memory, complex attention/working memory, and executive function are the cognitive domains that most frequently remain impaired following mild TBI (Bohnen, Jolles, & Twijnstra, 1992; Ruff & Jurica, 1999; Vanderploeg, Curtiss, & Belanger, 2005). As summarized above, residual deficits in mental efficiency are likely due in part to underlying deficits in speed of information processing and processing capacity. Recent work in OEF/OIF veterans suggests that the presence of comorbid PTSD may exacerbate deficits in processing speed and response inhibition among returning veterans with mTBI (Nelson, Yoash-Gantz, Pickett, & Campbell, 2009). Specifically, as compared to veterans with history of mTBI without PTSD, those with PTSD showed less proficient performance on both the color naming condition and the color/word condition of the standard (non-emotional) Stroop task, but did not differ on other dimensions of executive functioning (e.g., cognitive flexibility).

Existing knowledge about the sequelae of mTBI largely stems from studies of individuals who suffered motor vehicle accidents or sports-related concussion. Given the possibility that the mechanisms of injury associated with blast TBI differ from mechanisms associated with non-blast TBI (Bhattacharjee, 2008), the question arises whether blast injury leads to different neuropsychological outcomes than those observed in previous mTBI research. To date, only one study has directly compared the performance of patients with blast TBI and non-blast TBI (Belanger, Kretzmer, Yoash-Gantz, Pickett, & Tupler, 2009). The findings revealed that, after controlling for PTSD symptom severity, patients with non-blast mTBI performed less proficiently on a visual memory task than patients with blast mTBI. No group differences emerged in verbal memory or on tasks of cognitive speed/flexibility. It should be noted, however, that the approach of using covariance in situations in which the two variables (blast and PTSD) may be related to both a common risk source (i.e., intensive combat) and a common outcome (i.e., neuropsychological performance) has been questioned (Miller & Chapman, 2001). Of relevance to the potential increased risk of PTSD among veterans with mTBI, a non-significant trend suggested that blast TBI was associated with more severe PTSD symptoms than non-blast TBI, and both injury types were associated with increased PTSD symptoms as a function of time since injury. Injuries experienced more distally were associated with increased PTSD symptoms, a relationship reflective of the general trend among the broader population of returning veterans who have demonstrated increasing PTSD symptoms with the passage of time since their return from the war-zone (Milliken, Auchterlonie, & Hoge, 2007).

4.2. Functional neuroanatomical features

4.2.1. PTSD

Neurocircuitry models of PTSD focus on several key frontal and limbic structures, including the prefrontal cortex (especially its medial, ventro-medial, and orbital aspects), the amygdala, and the hippocampus. These models purport that a key component of the disorder is inadequate frontal inhibition of the amygdala, a limbic structure thought to be central to the fear response and the formation of fear associations (e.g., Liberzon, Britton, & Phan, 2003; Pitman, Shin, & Rauch, 2001; Rauch, Shin, & Phelps, 2006). The resultant exaggerated amygdala response is thought to lead to heightened responsivity to potential threat. Learned fear responses may be further complicated by problems with contextualization, leading to difficulties distinguishing "safe" from "unsafe" stimuli and environments. Both the hippocampus (Rauch et al., 2006) and medial prefrontal cortex (Liberzon & Sripada, 2008) are thought to be critical for appropriate contextual tagging of fear responses.

A converging body of neuroimaging data supports such models, indicating that PTSD involves exaggerated responsivity of the amygdala with concurrent dampening of activation within the prefrontal cortex and hippocampus, especially during fear processing (Rauch et al., 2006). A number of functional imaging studies have demonstrated heightened amygdala responsivity and deactivation or decreased activation in the hippocampus, anterior cingulate, and orbital frontal cortex in response to symptom provocation (e.g., Bremner, Narayan et al., 1999; Bremner, Staib et al., 1999; Driessen et al., 2004; Lanius et al., 2001; Liberzon et al., 2003; Liberzon et al., 1999; Rauch et al., 1996; Shin et al., 2004) and during encoding and retrieval of threat-relevant stimuli (Bremner et al., 2003b; Dickie, Brunet, Akerib, & Armony, 2008; Rauch et al., 2000; Shin et al., 2001; Shin et al., 2005). Likewise, PTSD has been associated with structural abnormalities, primarily evidenced as reduced volume, in the frontal cortex (Carrion et al., 2001; De Bellis, Baum et al., 1999; Fennema-Notestine, Stein, Kennedy, Archibald, & Jernigan, 2002; Geuze et al., 2008), including medial prefrontal cortex structures (Kasai et al., 2008; Rauch et al., 2003; Woodward et al., 2006; Yamasue et al., 2003), as well as in the hippocampus (e.g., Bremner Innis et al., 1997; Bremner et al., 2003a; Gilbertson et al., 2002; Gurvits et al., 1996; Karl, Schaefer et al., 2006; Kitayama, Vaccarino, Kutner, Weiss, & Bremner, 2005; Stein, Koverola, Hanna, Torchia, & McClarty, 1997) and amygdala (Karl, Malta & Maercker, 2006). These findings, however, have not been uniformly replicated (Bonne et al., 2001; Bremner Innis et al., 1997; Carrion et al., 2001; De Bellis, Baum et al., 1999; Gurvits et al., 1996; Schuff et al., 2001), especially when samples with more recent trauma exposure have been examined (Bonne et al., 2001; Carrion et al., 2001; De Bellis, Keshavan et al., 1999).

4.2.2. TBI

Despite the favorable recovery often associated with mTBI, enduring pathophysiological effects are nonetheless evident (see Bigler (2008), for a review). These are often not visible with conventional CT and MRI but, as reviewed in a previous section, can be seen with diffusion tensor imaging, which measures the functional integrity of white matter, and on post-mortem brain studies. The primary pathology associated with mTBI is traumatic axonal injury, caused by shearing and tensile forces that result from sudden deceleration and rotation of the head (Bigler, 2004; Povlishock, 1993). Shearing effects may lead to the tearing and disconnection of axons (diffuse axonal injury) and primarily affect deep frontal white matter and subcortical structures with white matter projections to frontal cortex (Cicerone, Levin, Malec, Stuss, & Whyte, 2006). Shearing may also disrupt small veins, resulting in microhemorrhagic lesions in frontal and temporal regions (Bigler 2004). Tensile effects are thought to occur more commonly than shearing effects and result in the stretching of axons (Buki & Povlishock, 2006). The hippocampus is also especially vulnerable to axonal damage (Povlishock, 1993), and may be affected indirectly by the damaging effects of trauma-induced release of excitatory neurotransmitters (Hicks, Smith, Lowenstein, Saint Marie, & McIntosh, 1993; Santhakumar, Ratzliff, Jeng, Toth, & Soltesz, 2001). In some cases, MRI may show focal damage to the anterior and inferior surfaces of the frontal and temporal lobes that reflect where the brain was impacted by bony protrusions of the skull (Hayes, Povlishock, & Singha, 1992). Finally, focal injury may occur as a result of coup and contrecoup forces, when the victim has been hit by an object or has struck the head against an object.

The pathophysiological effects associated with blast TBI are still poorly understood, but animal studies have documented neural changes comparable to those seen in non-blast TBI (Cernak, Wang, Jiang, Bian, & Savic, 2001a,b; Moochhala, Lu, Teng, & Greengrass, 2004), as well as changes that may be unique to blast TBI (Kaur, Singh, Lim, Ng, & Ling, 1997; Kaur et al., 1995). Proposed vascular models of blast injury (Bhattacharjee, 2008) likewise imply damage to the hippocampus and frontal regions. Further, primary blast effects are often associated with secondary injury similar to that associated with non-blast TBI, such as falls, being thrown with force, and projectiles hitting the head. Thus, regardless of mechanism of injury, there is evidence that both blast and non-blast mTBI are associated with damage to the same brain regions found to show functional and structural abnormalities in PTSD.

4.3. Summary

PTSD and mTBI share a number of neuropsychological and functional neuroanatomical characteristics (see also Kennedy et al. (2007); Stein & McAllister (2009)). In regard to neuropsychological functioning, there is overlap within the domains of attention, working memory, executive functioning, and episodic memory. Correspondingly, imaging studies implicate abnormalities in prefrontal and temporal brain regions in both disorders. As summarized in previous sections, PTSD is more prevalent among returning veterans who report mTBI. The potential overlay of mTBI-related neural and neuropsychological compromise onto similar abnormalities thought to play a role in perpetuating PTSD may offer clues as to why mTBI is associated with increased risk of PTSD. In the next section, we discuss potential mechanisms by which mTBI could complicate the manifestation and treatment of PTSD.

5. Clinical implications

5.1. Implications for the development and expression of PTSD

Despite the clear evidence that mTBI is associated with increased risk of PTSD and mood disturbances following psychological trauma exposure, there is little direct empirical evidence addressing the specific mechanisms that might account for the additional risk of PTSD apparently conferred by mTBI. In this section, we present neurocognitive, biological, and psychosocial factors that may all play some role in compounding PTSD when mTBI is present.

From a neurocognitive perspective, there is increasing evidence that impaired monitoring and inhibition are associated with PTSD-related behavioral disturbances such as re-experiencing (Leskin & White, 2007; Vasterling et al., 1998). Executive functions, including inhibitory control, working memory, and monitoring, are thought be integral to autobiographical memory retrieval (Conway, 2005; Conway & Pleydell-Pearce, 2000; Williams et al., 2007). If mTBI exacerbates executive deficits associated with PTSD, it could be reasoned that the individual's control over the recall of emotionally-charged trauma memories would be further degraded and therefore less amenable to effective self-management of emotional responses to the memory. Unregulated recall of the trauma event may be particularly problematic if intrusive memories and associated emotional and physiological responses lead to the incorporation of new contextual elements into the trauma memory, thereby expanding the potential "triggers" that elicit emotional distress (Verfaellie & Vasterling, 2009). Moreover, some theorists suggest that controlled access to trauma memories is necessary to reconstruct memories with sufficient cohesion to allow full emotional resolution (Brewin, 2005, 2007; Ehlers & Clark, 2000). This may be particularly challenging when encoding and consolidation of the memory was piecemeal due to alterations in consciousness at the time of the injury. If mTBI impairs executive functions supporting the regulation of trauma memories, mTBI may lead to less desirable PTSD outcomes than would occur either in the context of no injury or, at the other end of the spectrum, more severe injuries associated with full amnesia for the event. This hypothesis is consistent with findings indicating that whereas mTBI increases risk of PTSD compared to no injury, the probability of PTSD decreases as TBI severity increases.

Neuropsychological deficits associated with mTBI may likewise more generally affect how individuals cope with PTSD. For example, as suggested by Bryant (2008), intact cognitive resources are necessary to engage in adaptive appraisals of the trauma event and resulting symptoms. For example, one longitudinal study that found that maladaptive cognitive processes (e.g., rumination, negative appraisals) measured two weeks after a motor vehicle accident were significantly associated with subsequent PTSD and depression severities, even after accounting for initial symptom levels (Ehring, Ehlers, & Glucksman,

2008). If cognitive resources are compromised by mTBI, it may be more likely that the individual cannot detach from pessimistic rumination and other maladaptive appraisals. Similarly, diminished cognitive resources may make it less likely that the individual engages in other active coping strategies (e.g., problem solving) that have been demonstrated to be effective in coping with stress (Sharkansky et al., 2000; Wolfe, Keane, Kaloupek, Mora, & Wine, 1993). Finally, diminished cognitive resources associated with mTBI may exert indirect effects on PTSD and other psychological outcomes if the loss of cognitive efficiency adversely affects occupational performance or psychosocial functioning, thereby leading to additional stress.

In parallel, neurobiological abnormalities associated with mTBI may also complicate neural and biological abnormalities associated with PTSD. As summarized above, limbic structures, including the amygdala, are thought to be integral to emotions (e.g., anxiety) involved in the fear response and to the process of fear conditioning. As a "check" on the limbic system, the medial prefrontal cortex is thought to play a significant inhibitory role, allowing higher order cognitive functions to moderate less volitional limbic-based fear responses and the formation of associative fear cues. Because mTBI may involve damage to prefrontal cortical areas (Bigler, 2004; Cicerone et al., 2006), the additional loss of inhibitory control of the limbic system related to the TBI may therefore exacerbate PTSD symptoms and play a role in perpetuating the disorder. Hippocampal damage associated with TBI may further compound this problem because of its role in processing contextual cues, which allows determination of when an environment is related to the original conditioned fear response. It is also likely that more general neurotransmitter and neurohormonal alterations associated with mTBI (Kennedy et al., 2007) further dysregulate mood and exacerbate anxiety symptoms, and thus complicate the clinical presentation of PTSD.

Finally, although this paper emphasizes the possible impact of mTBI on PTSD from a cognitive neuroscience perspective, the associated psychosocial and psychiatric sequelae and vulnerabilities inherent to each disorder also warrant mention. Both disorders, for example, require exposure to an environmental event as part of their case definitions, but pre-existing psychiatric conditions appear to increase vulnerability to such exposures (e.g., Brewin et al., 2000; Ponsford et al., 2000). As summarized earlier, both also may be accompanied by, or lead to, psychiatric disorders, substance abuse, pain and other somatic conditions (see Lew et al., 2008; Stein & McAllister, in press), each of which in its own right may be associated with cognitive impairment (Alfano, 2006; Karp et al., 2006).

5.2. Implications for PTSD treatment

There is currently no evidence as to whether or not mTBI in general, or mTBI associated with persistent neuropsychological deficits, complicates treatment. From a cognitive neuroscience perspective, it is plausible that cognitive deficits and neurobiological alterations associated with mTBI would adversely affect treatment outcomes. Of the many treatment approaches available, exposure-based and cognitive–behavioral interventions have been identified as the most efficacious in the treatment of PTSD, with exposure-based therapy named as the treatment of choice by the Institutes of Medicine. Both exposure-based and cognitive–behavioral interventions, however, depend on the successful engagement of cognitive resources. Exposure-based interventions, for example, require controlled retrieval of the trauma memory and subsequent modification of the memory and associated emotions. Cognitive–behavioral therapy (CBT) targets modification of negative or distorted thoughts attached to trauma experiences, with the goal of generating more realistic explanations and thoughts associated with the trauma and trauma experience. Such modifications require both the inhibition of maladaptive thoughts and sufficient cognitive flexibility to reappraise thoughts and memories. Thus, it is possible that mTBI, if associated with cognitive deficits involving executive or memory functions, may

reduce treatment responsivity to exposure-based and cognitive–behavioral interventions. Conversely, it could be argued that the residual cognitive deficits associated with mTBI do not reach a severity threshold sufficient to affect treatment outcome in a clinically meaningful manner. Moreover, cognitive behavioral interventions tend to be highly structured, which may be of particular benefit to patients who do have residual executive deficits (Soo & Tate, 2007).

In the only clinical trial addressing the efficacy of CBT in treating stress-related symptoms following mTBI, Bryant (2003) found that early provision of CBT for acute stress disorder after mTBI reduced development of PTSD post-treatment and at six months follow-up. Although the study targeted treatment of acute stress reactions to prevent, rather than treat, PTSD, Bryant's results hold promise that CBT may also be applied successfully to treat more enduring symptoms associated with PTSD in the context of mTBI. It is also possible, however, that PTSD interventions have attenuated impact for patients with mTBI, even when generally successful. Several recent studies linking neuro-cognitive and neural integrity with treatment response to CBT among otherwise healthy, non-TBI patients with PTSD potentially inform this question. The findings of these studies indicate that poor response to CBT treatment response is associated with less proficient pre-treatment verbal memory and narrative encoding (Wild & Gur, 2008), smaller volume of the rostral anterior cingulate cortex (Bryant, Felmingham, Whitford, et al., 2008), and increased activation bilaterally of the amygdala and ventral anterior cingulate (Bryant, Felmingham, Kemp, et al., 2008). Although none of these studies specifically examined the effects of mTBI on PTSD treatment response, their findings indicate that normal variation in brain functions and structures potentially altered by mTBI influences treatment response. If well-conducted clinical trials determine that mTBI, or the mTBI subset with persistent neuropsychological deficits, in fact attenuates PTSD treatment efficacy, an implication would be that existing PTSD interventions may benefit from supplemental cognitive enhancement strategies to minimize the influence of any cognitive deficits on treatment outcomes.

6. Conclusions

Predicting the ways in which mTBI affects the psychological outcomes of OEF/OIF veterans is far from straightforward. Even in the absence of mTBI, exposures to psychologically traumatic events affect individuals differently, leading to a range of outcomes. Some people will develop PTSD or other psychiatric disorders; others will emerge with few symptoms or even experience a sense of mastery and other psychological benefits. Likewise, brain injury leads to different outcomes across individuals. Further clouding the picture is the probability that recovery from mTBI and psychological trauma exposure is likely influenced by shared vulnerability factors and common associated features. The relationship between mTBI and PTSD is thus likely complicated, with mTBI and PTSD each potentially serving to hinder recovery from the other.

In this review, we focused on neuropsychological and neural features common to mTBI and PTSD. We further highlighted, from a cognitive neuroscience perspective, the ways in which mTBI may exacerbate PTSD, impede its recovery, and complicate its clinical management. There are many more questions than there are answers. Causal relationships between mTBI and PTSD remain poorly understood. Of even greater concern, however, is that there is virtually no empirical basis upon which to judge whether evidence-based treatments for PTSD are equally effective in the context of mTBI and, in particular, in mTBI with persistent neuropsychological compromise.

In our view, although there are a range of significant emotional, cognitive, social, and physiological factors that should be considered in conceptualizing the relationship between mTBI and PTSD, the cognitive neuroscience of the two disorders can be a useful framework from which to approach the task of better understanding the relationship between the two and of determining best clinical practices when mTBI and PTSD co-occur in returning veterans. As a first step, for example, it

will be necessary to determine whether mTBI affects recovery from PTSD. If so, it will be important to understand whether there are specific neural or neurocognitive mechanisms associated with mTBI that influence the formation and retrieval of traumatic memories, emotional regulation in response to the event or subsequent stressful war-zone events, or the ability to implement adaptive coping techniques. It will likewise be useful to understand where in the chronology of PTSD development mTBI exerts an impact. For example, it may be that the influence of mTBI on PTSD is evident during the later phase of adjustment to traumatic events, and is thus limited to the subset of mTBI cases with persistent neuropsychological sequelae. Alternatively, mTBI may affect the initial encoding of the trauma memory and the regulation of emotions in the immediate aftermath of the trauma, thus potentially setting into action an unfavorable PTSD symptom course outlasting any direct mTBI sequelae.

In terms of treatment, it is likewise unclear whether mTBI or specific characteristics (e.g., subtle neurocognitive deficits) influence response to PTSD treatments, whether psychosocial or psychopharmacological. It seems especially important to examine the influence of cognitive functioning on exposure-based and cognitive–behavioral interventions, which rely on the ability to retrieve and process the trauma event and to flexibly consider alternate appraisals of the event and its associated emotions. It may be that specific neuropsychological variables, for example, could be used to help predict treatment response and to determine which of several treatment options might be optimal for a particular patient. A related consideration would be whether augmentation strategies (e.g., cognitive rehabilitation techniques) can enhance treatment response in patients with mTBI undergoing treatment for PTSD, especially among those who are judged to be potentially refractory to conventional treatments.

These, and other, difficult questions will require carefully designed longitudinal studies and randomized clinical trials that acknowledge both the heterogeneity of outcomes associated with mTBI and the features of mTBI that stand to complicate PTSD recovery. In an area fraught with controversy, development of an adequate empirical base will be critical to both scientific and clinical progress.

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