

Cognitive Sequelae of Blast-Induced Traumatic Brain Injury: Recovery and Rehabilitation

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Received: 30 December 2011 / Accepted: 1 February 2012 / Published online: 17 February 2012
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Abstract Blast-related traumatic brain injury (bTBI) poses a significant concern for military personnel engaged in Operation Enduring Freedom and Operation Iraqi Freedom (OEF/OIF). Given the highly stressful context in which such injury occurs, psychiatric comorbidities are common. This paper provides an overview of mild bTBI and discusses the cognitive sequelae and course of recovery typical of mild TBI (mTBI). Complicating factors that arise in the context of co-morbid posttraumatic stress disorder (PTSD) are considered with regard to diagnosis and treatment. Relatively few studies have evaluated the efficacy of cognitive rehabilitation in civilian mTBI, but we discuss cognitive training approaches that hold promise for addressing mild impairments in executive function and memory, akin to those seen in OEF/OIF veterans with bTBI and PTSD. Further research is needed to address the patient and environmental characteristics associated with optimal treatment outcome.

Keywords Neurorehabilitation · Executive function · Memory · OEF/OIF · TBI · PTSD

Introduction

The nature of the current conflicts (Operation Enduring Freedom and Operation Iraqi Freedom; OEF/OIF) has

increased the risk of physical and psychological injuries in military personnel. Multiple tours of duty and high rates of exposure to blasts, as well as higher survival rates due to enhanced body armor, have likely contributed to elevated rates of traumatic brain injury (TBI) and stress-related health problems, such as posttraumatic stress disorder (PTSD) (Bruner 2006; King et al. 2008; Otis et al. 2011). Blast-related traumatic brain injury (bTBI) is one of the most common injuries in OEF/OIF, and according to statistics from Walter Reed Medical Center, an estimated 60% of all blast injuries result in TBI (Warden et al. 2005). Large surveys suggest that an estimated 15% to 23% of OEF/OIF personnel have experienced a TBI, with the majority being mild TBI (mTBI) (Terrio et al. 2009; Warden 2006). In one survey (Hoge et al. 2008), 15% of Army infantry soldiers reported mTBI after their return from a year-long deployment in Iraq. Another study (RAND 2008) estimated the incidence of TBI at 19.5%, with the likelihood of TBI directly linked to length of deployment.

There are other deployment-related factors that may complicate and extend the course of natural recovery in OEF/OIF returning veterans, such as prolonged stress exposure and related psychiatric sequelae (Hoge et al. 2004). The RAND study reported that of the 1.64 million individuals deployed in Afghanistan and Iraq, an estimated 300,000 veterans suffer from PTSD or depression (RAND 2008). A recent systematic review reported that estimated rates of PTSD among Iraq War veterans vary across studies from 1.4% to 31% (Sundin et al. 2010). Heterogeneity of study samples and methodological differences may account for the wide range of reported PTSD rates. In general, studies that use anonymous surveys report higher rates of PTSD than those that use on-the-record screening, reflecting possible concerns about stigmatization and confidentiality (see Sundin et al. 2010 for discussion). Prevalence rates also tend to increase

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in the 12 months following deployment. Among combat-deployed troops, a relatively consistent prevalence in the range of 10–17% is reported. The rate of PTSD in OEF/OIF veterans receiving health care at the Department of Veterans Affairs (VA), however, is higher (B. E. Cohen et al. 2010), and the highest rates of PTSD (33% to 39%) are reported among OEF/OIF soldiers with a history of mTBI (Carlson et al. 2011). There is emerging evidence that a history of mTBI increases the risk for PTSD in both civilian (Bryant et al. 2010; Fann et al. 2004) and military populations (Hoge et al. 2008). As we discuss below, the neuroanatomical overlap in neural circuits involved in mTBI and PTSD may mediate the interaction between mTBI and PTSD, as the same brain regions that are commonly affected in TBI are also involved in PTSD. While neurobiological mechanisms underlying the expression of PTSD in mTBI remain a subject of ongoing investigation, the increased risk for PTSD in association with mTBI is attributed to TBI-related neural damage that compromises the neural circuitry critical for regulation of fear following the trauma (Bryant 2008, 2011). Identification and early treatment of TBI-related symptoms and PTSD are critical for successful recovery in returning veterans (Kessler 2000).

There is a need for empirically based treatment protocols to address the multiple impairments in returning veterans with bTBI and PTSD. The VA Polytrauma System of Care, which includes Polytrauma Network Sites and Polytrauma Rehabilitation Centers, was developed to identify, diagnose and treat patients with multiple injuries. Local VAs and community-based Veteran Centers are equipped with mental health personnel trained to identify and manage mTBI and PTSD symptoms using current “standard of care” treatments specific for TBI or PTSD. However, it is unknown if evidence-based interventions specific for mTBI and PTSD are effective in comorbid mTBI/PTSD, as each condition may exacerbate symptoms and complicate treatment, ultimately affecting the course of the recovery. In a recent survey, providers treating patients with mTBI and co-occurring PTSD reported that each condition interfered with traditionally prescribed TBI or PTSD-specific treatment, with treatment adherence and symptom management among the most common problems (Sayer et al. 2009). Thus, there may be a need to adapt current approaches or to develop novel interventions specifically geared towards patients with mTBI/PTSD.

In this paper, we review the effects of bTBI on cognitive function and identify factors that may affect recovery of OEF/OIF military personnel. Next, we discuss current cognitive rehabilitation treatment options and provide updated practice guidelines and recommendations for this population. We also highlight current developments and ongoing research efforts in the field of cognitive rehabilitation, and discuss key issues to address in future research. This review is limited to mild TBI, as this is most common type of TBI among OEF/OIF military personnel.

Blast Injury

According to the Department of Defense, more than 73% of OEF/OIF military casualties are caused by explosive weaponry, with the majority of deployment-related TBI resulting from IEDs (Galarneau et al. 2008). Although enhanced body armor has done much to protect service members from penetrating injuries, it does not protect against the damaging effects of explosions. Explosions generate a powerful blast wave of high pressure with associated blast wind, followed by reversal of wind back toward the blast and under-pressurization (DePalma et al. 2005; Wightman and Gladish 2001). These rapid pressure shifts affect air-filled organs (e.g. lungs) and air-fluid interfaces (e.g. eardrum), and can also affect the brain (Taber et al. 2006). In addition to these primary brain injuries, secondary injuries may occur, caused by objects accelerated by the blast wind that strike the victim; tertiary injuries occur when a victim’s body is displaced by explosive forces, resulting in contusions or other blunt trauma; and quaternary injuries result from radiation, burns, and toxin exposure from fires, explosions, or noxious fumes (DePalma et al. 2005; Wightman and Gladish 2001).

Evidence from animal studies indicates that explosions can exert detrimental effects on the brain, depending on the intensity and proximity of the blast and characteristics of the blast-wave (Bhattacharjee 2008; Cernak and Noble-Haeusslein 2010; Cernak et al. 2001a; Chafi et al. 2010; Taber et al. 2006). At least two mechanisms have been identified by which a blast wave can lead to neural injury: (1) when passing through the head, the blast wave and subsequent blast wind can directly interact with the head and cause acceleration and/or rotation of the head; and (2) kinetic energy from the blast wave can be transmitted to the nervous system through large blood vessels in the chest. The resulting blood surge dramatically increases cerebral perfusion pressure and causes damage to both tiny cerebral blood vessels and the blood–brain barrier (Chen and Huang 2011). These complex mechanisms of injury result in a cascade of responses at the level of the vascular system, autonomic nervous system, and local tissue (Cernak and Noble-Haeusslein 2010). While the pathobiology of blast-TBI is unique, secondary injury cascades are thought to be similar to those seen in non-blast TBI.

Animal studies suggest that damage to the brain caused by primary blast forces can lead to impairments on tests of coordination and balance, and can lead to persistent memory deficits (Cernak et al. 2001a; Moochhala et al. 2004; Saljo et al. 2008). There is evidence of neural injury (neuronal swelling, astroglial response, and myelin fragments) in the hippocampus and brainstem reticular formation (Cernak et al. 2001a, b), and biochemical changes have been observed that are suggestive of neurotoxicity (Cernak et al. 2001a). Other studies have reported changes suggestive of neural

degeneration in cerebral and cerebellar cortex (Kaur et al. 1995) and the pineal gland (Kaur et al. 1997). Additional brain injury, secondary to hypoxia or ischemia, can occur secondary to blast-induced cardiopulmonary events (Cernak 2005; DePalma et al. 2005).

The physiological and behavioral sequelae of blast exposure are the subject of ongoing investigation in both animal and human research, although it remains controversial whether in humans primary blast effects alone can cause TBI (Cernak and Noble-Haesslein 2010). In humans, secondary and tertiary injuries, as described above, are common, and the effects of these injuries are similar to those occurring in non-blast TBI. Impact mechanisms associated with secondary injury result primarily in cortical injury, affecting the anterior and inferolateral temporal lobes, orbitofrontal regions, and frontal poles. Acceleration and deceleration associated with tertiary injury lead to diffuse traumatic injury to white matter in the brain.

While to date, there are few studies of the effects of bTBI on cognition in humans (and even fewer on the effects of primary blast in isolation), outcome studies of non-blast TBI can provide a good model of recovery and can inform the development of treatment for bTBI.

Mild TBI

The American Congress of Rehabilitation Medicine (ACRM 1993) defines mTBI as an injury characterized by (1) alteration or loss of consciousness not greater than 30 min, and (2) a period posttraumatic amnesia that lasts at most 24 h. These patients have Glasgow Coma Scale scores of 13 to 15 (Teasdale and Jennett 1974). The acute symptoms of mTBI include physical (e.g., headaches, dizziness, sleep-wake disturbances), cognitive (e.g., poor concentration, memory problems), and emotional symptoms (e.g., irritability, anxiety, depression). Cognitive changes are apparent on tasks of working memory, executive function, processing speed and learning, and can be sufficiently severe to interfere with everyday activities (Alexander 1995). However, there is substantial recovery of function within the first few weeks to months post injury (Iverson et al. 2007; McCrea et al. 2009; Levin et al. 1987). While an estimated 10–44% of patients may still exhibit symptoms 3 months post injury (Dikmen et al. 2010; Ruff 2005), only a minority of patients are not fully recovered 12 months post mTBI, with estimates ranging from as low as 1–5% (McCrea 2008) to 10–15% of patients (Alexander 1995; Rutherford et al. 1979). The higher estimates, however, may be biased by the inclusion of convenience samples of mTBI patients who present to clinics with persistent complaints.

Little is known about the pattern of recovery following bTBI, but the available evidence suggests similarities in the

cognitive profile associated with blast and non-blast TBI. A study by Hoge et al. (2008) surveyed Army infantry soldiers 3–4 months post-deployment, and found that although soldiers with mTBI reported higher number of postconcussive symptoms than soldiers with other injuries, mTBI was no longer significantly associated with these symptoms after adjustment for PTSD and depression. Two other studies have compared the chronic effects of blast and non-blast TBI, and also suggest that the cognitive performance and reported symptoms are largely similar (Belanger et al. 2010; Lippa et al. 2010).

Cognitive domains that remain most frequently impaired are complex attention, executive function and memory (Bohnen et al. 1992; Ruff and Jurica 1999; Vanderploeg et al. 2005). Additionally, patients who report full recovery may continue to experience reduced mental efficiency under conditions of physical or psychological stress (Ewing et al. 1980). These residual deficits are thought to reflect a basic disorder in information processing capacity, either in terms of speed of processing or in terms of the amount of information that can be handled simultaneously (Stuss et al. 1985; Van Zomeren et al. 1984). A number of neurologic and somatic factors may contribute to these long-term impairments, but psychological factors are thought to play a major role in long-term outcome (Luis et al. 2003).

Of special relevance to the military context, it has been shown that a history of multiple concussions leads to worse cognitive outcomes, particularly in the domains of executive control and memory (Belanger et al. 2010). Military personnel may experience multiple TBI events during war-zone deployment and are frequently exposed to multiple blasts, even if at a sub-threshold level. Both of these may interfere with neuropsychological recovery (Guskiewicz et al. 2003) and increase risk for persistent neuropsychological impairment (Zillmer et al. 2006) and subsequent dementia syndromes (Gavett et al. 2011; Guskiewicz et al. 2005).

The symptoms associated with mTBI suggest a disruption of functions mediated by frontal and temporal brain regions, which are the areas most affected in TBI (J. E. Kennedy et al. 2007). Although conventional neuroimaging modalities such as CT or MRI typically do not reveal neural abnormalities in patients with mTBI (reviewed in Belanger et al. 2007), the microscopic diffuse axonal injury associated with mTBI is apparent using newer neuroimaging techniques such as diffusion tensor imaging (DTI) (Mac Donald et al. 2011; Wilde et al. 2008). These abnormalities are particularly apparent in long white matter tracts that connect anterior and posterior regions of the brain (Kraus et al. 2007; Mayer et al. 2010; Messe et al. 2011). Further, functional neuroimaging studies show that even in patients with normal structural imaging alterations in neural activation can occur during performance of cognitive tasks (Mayer et al. 2011; McAllister et al. 2006).

Several studies have recently used DTI to examine the neural sequelae of bTBI. One study (Mac Donald et al. 2011) compared 63 military personnel with mild bTBI to 21 with blast exposure but without TBI. All participants had been evacuated for orthopedic or soft-tissue injury and were scanned in hospital, on average 2 weeks after the blast. There were marked abnormalities in the mTBI group in a number of white matter regions, consistent with axonal injury. Some tracts in which abnormalities were seen, such as the cingulum bundle, uncinata fasciculus, and anterior limb of the internal capsule, are also involved in non-blast TBI. Other regions, in contrast, such as the cerebellar peduncles and right orbitofrontal white matter, are not commonly associated with civilian mTBI, but were predicted to be vulnerable based on computational simulations of blast injury. At an individual level, however, there was substantial variability, and many individuals with bTBI showed no DTI abnormalities. Follow-up in a subset of individuals 6 to 12 months later showed persistent abnormalities at the group level, but there were changes in diffusivity consistent with evolution of injury. In a study of chronic bTBI (on average more than 2 years following exposure), Levin et al. (2010) found no difference in neural integrity between veterans with mild-to-moderate bTBI and veterans without blast exposure or TBI. This might reflect resolution of abnormalities over time. Alternatively, given the diffuse and heterogeneous nature of blast injury, it may be particularly difficult to pick up subtle chronic abnormalities using standard approaches that assess neural integrity in fixed regions of interest by averaging across individuals (Davenport et al. 2012). Consistent with the latter possibility, Davenport et al. (2012) found no evidence for disrupted neural integrity in veterans with mTBI 2–5 years post blast exposure using standard ROI approaches. However, individuals with bTBI showed a significantly greater number of voxels with low white matter integrity than individuals without blast exposure. These findings are consistent with subtle, diffuse neural disruption.

It should be noted that the above studies leave open the question as to the contribution of primary blast injury to the observed abnormalities, as many individuals with bTBI also had secondary injuries associated with the blast or had additionally been exposed to non-blast TBI. Two case studies, one of a service member exposed to a large explosion (Warden et al. 2009), and another to multiple blasts (Pannu-Hayes et al. *Forthcoming*) provide evidence that isolated blast injury can indeed disrupt white matter integrity.

While it is still unclear whether the immediate and long-term neurocognitive consequences of bTBI are identical to those of non-blast TBI, initial results suggest similar profiles of impairment in cognitive functioning (Belanger et al. 2010) and similar post-concussion symptoms (Belanger et al. 2011; Lippa et al. 2010). The most common impairments are cognitive deficits in the domain of executive functioning

(planning, goal setting, cognitive flexibility and behavioral control), complex attention, and learning and memory. With regard to the latter, impairments are particularly evident in delayed memory, and to a lesser extent in acquisition of information (Belanger et al. 2005, 2010). Functional and psychosocial disabilities are closely related to these cognitive deficits. Although the extent and cause of functional impairment in returning OEF/OIF veterans remains a matter of debate, the scope of the problem is clearly evident. MTBI can be associated with impairment in work productivity, social functioning and quality of life, and presents a costly personal and public health issue (McCrea 2008; NCIPC 2003). Providing timely rehabilitation treatment aimed at improving cognitive and psychosocial functioning is important for successful recovery in veterans with persistent mTBI symptoms.

Factors That Affect Functional Outcome in OEF/OIF Veterans with MTBI

Stress Exposure and PTSD Stress-related symptomatology is one of the most prevalent problems in OEF/OIF returning veterans, as military personnel with high rates of combat exposure are at increased risk for development of PTSD (Hoge et al. 2008; RAND 2008). PTSD is characterized by re-experiencing, avoidance, and hyperarousal symptoms in response to exposure to a life-threatening (or perceived to be life-threatening) traumatic event, such as the threat of death or serious injury (APA 1994). PTSD is also associated with cognitive inefficiencies in the domains of attention, executive function, and memory (Vasterling and Brailey 2005; Vasterling and Verfaellie 2009)—the very domains of cognition impacted by mTBI.

Neuroimaging studies have demonstrated anatomical and functional overlap between the neural areas implicated in PTSD and the areas most vulnerable to TBI (J. E. Kennedy et al. 2007; McAllister and Stain 2010; Vasterling et al. 2009). Specifically, areas of dysfunction in PTSD include the anterior cingulate and medial frontal gyri, as well as MTL regions including the hippocampus and amygdala. A key component of PTSD is thought to be inadequate regulation by prefrontal cortex of the amygdala, a structure central to the fear response and to the formation of fear associations (Bryant 2008, 2011). The hippocampus and medial prefrontal cortex are essential for appropriate contextual tagging of fear responses (Liberzon and Sripada 2008; Rauch et al. 2006). A failure to appropriately contextualize fear responses in PTSD may contribute to fear generalization and an inability to distinguish safe from unsafe environments.

As mentioned earlier, orbitofrontal and MTL regions are also commonly affected by TBI. Emotional dysregulation in

the acute aftermath of TBI may set the stage for the subsequent trajectory of emotional symptoms and the increased risk for PTSD (Bryant 2008, 2011). Likewise, fragmented encoding and impoverished consolidation of events and experiences in the immediate aftermath of the TBI may interfere with the creation of coherent, integrated trauma memories and could potentially affect the subsequent development of PTSD (Verfaellie et al. 2012). The presence of PTSD may in turn exacerbate cognitive symptoms of mTBI and compound functional difficulties (Carlson et al. 2011; Crowell et al. 2002; Polusny et al. 2011). Further, behavioral problems associated with PTSD can lead to social and occupational problems, such as loss of job, difficulties with interpersonal relationships, family and parenting issues, or substance use (Lew et al. 2008). These problems may in turn increase anxiety, depression and anger problems, and further complicate the course of natural recovery from mTBI and/or treatment adherence.

Even in the absence of PTSD, prolonged stress exposure may negatively impact on neuropsychological functioning (Vasterling and Proctor 2011; Vasterling et al. 2006). Vasterling et al. (2006) found that deployment itself (in the absence of TBI) was associated with mild but significant compromise on tasks of sustained attention and memory. Further, there is ample evidence that stress adversely impacts outcome following TBI. Patients under high levels of stress at the time of brain injury typically have worse recovery (Hannay et al. 2004), and the presence of stress-related symptomatology early following mTBI has been identified as an important predictor of poor long-term outcome (Friedland and Dawson 2001; Moore et al. 2006; Ponsford et al. 2000).

Sleep TBI sleep studies suggest that sleep is involved in the physiologic processes underlying neural recovery (Parcell et al. 2008) and plays an important role in functional outcome. Yet, sleep is often disturbed in patients with TBI (Castriotta et al. 2007). Based on analysis of sleep diaries, Parcell et al. (2006) reported an enhanced number of night-time awakenings and increased sleep-onset latencies in patients with mTBI. Reduced daytime vigilance and excessive sleepiness are also common symptoms. TBI patients with sleep disturbances perform worse on neuropsychological tests, especially on measures of sustained attention and short-term memory (Bloomfield et al. 2009).

Sleep disturbances, including repetitive nightmares and insomnia, are considered a core feature of PTSD. Results of actigraphy demonstrate that PTSD is associated with reduced sleep efficiency, increased sleep latency, and more restless sleep (Calhoun et al. 2007). Initial report of insomnia is also associated with future PTSD symptoms (McLay et al. 2010). Sleep disturbance is often resistant to treatment and independently contributes to poor daytime functioning

(Germain et al. 2008). Recent studies of sleep in OEF/OIF military personnel report that sleep complaints are extremely common among returning veterans with PTSD (Orr et al. 2010). Both sleep quality (self-reported trouble sleeping) and quantity (sleep duration) are affected, and these have been found to be significantly associated with mental health symptoms (Seelig et al. 2010). Despite the high rates of sleep disturbance in mTBI and PTSD, there is limited data on sleep architecture in mTBI/PTSD, and no studies have examined the effect of sleep disturbance on recovery and treatment outcome in this population.

Pain Patients with chronic pain often complain of forgetfulness, difficulty with attention and problems completing tasks, complaints similar to those seen in the post concussion syndrome (Iverson and McCracken 1997). They also show impairments on information processing tasks akin to those seen in patients with mTBI (Eccleston 1994). Chronic pain is commonplace in mTBI, and particularly in patients who have persistent post concussion syndrome (Dikmen et al. 1989). Thus, TBI patients with chronic pain can be expected to perform worse on cognitive tasks. It has been suggested that the combination of pain and head injury may cause additive disruption of cognitive-emotional regulation centers in the brain (Bigler 2003). Further, a number of studies have identified persistent pain as a significant predictor of poor outcome following mTBI (Ettlin et al. 1992; Mooney et al. 2005). The impact on cognitive and everyday functioning of pain in combination with mTBI and PTSD, and the implications for treatment and recovery, are poorly understood (see Otis et al. 2011, for an updated review and conceptualization).

Other Factors Many individuals who sustain bTBI concurrently sustain injuries to other parts of the body, but the impact of *extracranial injuries* on neuropsychological function is not well established. Patients with extracranial injuries generally take longer to recover and have worse functional outcome, presumably because of their physical limitations, but whether they fare worse cognitively is not clear. One study found more cognitive complaints in patients with extracranial injuries (Van Der Naalt et al. 1999), but several others did not (Savola and Hillbom 2003; Stulemeijer et al. 2006). It is possible that the moderating influence of other variables, such as pain and depression, accounts for these contradictory outcomes. It has been reported that *depression* exacerbates both the subjective complaints and objective cognitive deficits seen in mild to moderate TBI (Chamelian and Feinstein 2006; Rapoport et al. 2005). In particular, executive function, processing speed, and memory have been found to be lower in depressed than non-depressed TBI patients. Depression was also associated with significantly poorer recovery from mTBI (Mooney et al. 2005).

Another factor that has a detrimental effect on recovery is *alcohol use*. There is extensive evidence that alcohol has a damaging effect on cognitive functions, in particular, on executive function and memory (reviewed in Oscar-Berman and Marinkovic 2007). Alcohol use disorders are associated with significant cortical and subcortical volume reduction in the frontal lobes, limbic system, and cerebellum (Sullivan and Pfefferbaum 2005). Thus, alcohol abuse may increase the burden associated with mTBI and negatively affect recovery. Individuals with a premorbid history of alcohol abuse tend to have poorer outcomes, both in neuropsychological performance (Dikmen et al. 1993) and functional outcome (Ruff et al. 1990), and the severity of their impairment is directly linked to the level of alcohol use. Similarly, post-injury alcohol use negatively affects cognitive functioning and the potential for recovery (Gontkovsky et al. 2006). Treatment of substance use disorders in patients with TBI is especially important given that neuropsychological deficits associated with alcohol use can be improved with treatment (Rosenbloom et al. 2007), and that brain tissue recovery can occur following abstinence (Cardenas et al. 2007; Gazdzinski et al. 2010; Fortier et al. 2011).

Management and Treatment of Cognitive Difficulties in MTBI

Current practice guidelines state that treatments for mTBI should be symptom-focused and evidence-based (VA Consensus Conference 2010), but the evidence-base for intervention in mTBI is very limited. Standard clinical management of mTBI is typically focused on “prevention through education”. This approach aims to facilitate expectations of complete recovery and to prevent secondary injuries; it also focuses on specialized medical treatment to reduce associated symptoms (such as headache, mood, and sleep problems) that may adversely impact on cognitive functioning (DCOE and DVBIC 2009; Comper et al. 2005). While a number of studies support the efficacy of educational interventions in mTBI (Mittenberg et al. 1996; Paniak et al. 2000; Ponsford et al. 2001; Wade et al. 1997), one recent study showed no impact (Heskestad et al. 2010). Thus, further evidence is needed, and federally funded clinical trials evaluating the efficacy of educational interventions in mTBI are underway. An additional question of importance to OEF/OIF veterans with mTBI, who commonly present for care only months after suffering their injury, is whether educational interventions can still be beneficial beyond the acute stage. At present, there is only anecdotal evidence for this possibility (Ryan et al. 2011).

The majority of interventions for TBI are designed for rehabilitation of patients with moderate to severe injuries

and there is only limited evidence that these approaches are useful for treating patients with mTBI (Cicerone et al. 2005, 2011). Nonetheless, some preliminary evidence points to their efficacy in individuals with mild cognitive impairment subsequent to mTBI and possible other co-morbidities, as well as in elderly individuals with mild impairments in executive function and memory, the domains most commonly affected in mTBI. Before reviewing this limited evidence, we briefly discuss the nature and goals of cognitive rehabilitation more broadly.

Cognitive Rehabilitation

The Brain Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine (ACRM, BI-ISIG) defines cognitive rehabilitation as comprehensive, interdisciplinary rehabilitation interventions aimed at restoring, reorganizing, or compensating for impaired function through new cognitive patterns or external devices (Harley et al. 1992). “The overall goal may be restoring function in a cognitive domain or set of domains or teaching compensatory strategies to overcome domain specific problems, improving performance of a specific activity, or generalizing to multiple activities” (Katz et al. 2006). While the specific goals and course of an intervention may depend on underlying theoretical conceptions, the basic rationale for cognitive rehabilitation rests on the premise that patients experiencing loss of cognitive function require help and training in selecting, learning and implementing new adaptive strategies to improve their cognitive function (Stuss et al. 2007). A Consensus Conference sponsored by the National Institute of Health (Rose 1999) outlined the characteristics thought to define effective cognitive interventions in TBI: they are structured, systematic, goal-directed and individualized, and involve learning, practice, social contact and a relevant context.

The Cognitive Rehabilitation Task Force (ACRM, BI-ISIG) has conducted a systematic review of cognitive rehabilitation after TBI, and has provided updated evidence-based practice recommendations (Cicerone et al. 2011). Speaking to the full spectrum of TBI severity, the report recommends the use of attention, problem solving, and memory training during postacute rehabilitation of individuals with TBI. Emphasis is placed on the use in training of metacognitive strategies that increase awareness of anticipated difficulties and help develop online monitoring and self-regulation skills. Such skills are necessary to promote the generalization of newly acquired compensatory strategies to real-world tasks (Cicerone et al. 2011).

As outlined above, the cognitive domains most commonly affected in mTBI are complex attention, executive function, and memory. Because to date, there is virtually no evidence for the efficacy of attention training in mTBI

(IOM 2011), in what follows, we focus specifically on the rehabilitation of executive functioning and memory. The basic assumption is that although the capacity for organization and planning may be compromised in mTBI, patients are capable of learning and implementing new strategies aimed at enhancing executive functioning and memory, which in turn can improve daily functioning. Once new strategies become incorporated and used more frequently in real life situations, their implementation becomes less effortful; gradually, the use of such strategies generalizes and becomes integrated into patients' daily lives.

Executive Function Rehabilitation A number of studies have demonstrated the effectiveness of training of executive functioning and problem solving in patients with a range of injury severities (Knight et al. 2002; Levine et al. 2000; Medd and Tate 2000; Novakovic-Agopian et al. 2011; Ownsworth et al. 2000; Schlund 1999; Stablum et al. 2000; Stuss et al. 2007; Tham et al. 2001), but studies examining its effect in patients mild cognitive impairment are more limited. Nonetheless, problem-solving interventions have been used successfully to improve functioning in patients with mild to moderate TBI (Levine et al. 2000; Novakovic-Agopian et al. 2011) and in elderly with mild cognitive deficits (Levine et al. 2007). These interventions were based on goal management training, a theory-driven rehabilitation protocol developed by Robertson (1996). This group-based training focuses on monitoring of executive problems and training to compensate for these problems. The main elements of the program include training in specific strategies that help to establish and reach a goal, and recognizing and inhibiting distractions that interfere with accomplishing the goal. These strategies are taught and illustrated by way of interactive discussions, with reinforcement and facilitation of learned skills through homework assignments.

In a mixed group of patients with executive impairment, Chen and colleagues (2011) assessed the neural basis of goal management training by assessing changes in fMRI pre- to post-intervention during a selective attention/working memory task. They found enhanced frontal modulation of processing in extrastriate cortex associated with goals training. This was reflected by the fact that the relative balance of neural activation associated with relevant compared to non-relevant information was enhanced. Additionally, activation in dorsolateral frontal cortex at baseline was predictive of the shift in activation in that region associated with training. Although preliminary, these results suggest the possibility of identifying neural markers of interindividual differences to treatment response.

We are aware of one pilot study that used a similar kind of cognitive strategy training in OEF/OIF veterans with mild cognitive impairment and a history of TBI (Huckans et al.

2010). The study entailed a 6- to 8-week group-based program that provided training in a variety of compensatory cognitive strategies, including organizational skills, goal planning, and problem solving strategies. The weekly treatment sessions consisted of didactic presentations, discussions, and exercise activities, followed by the homework assignments. Following the intervention, participants reported enhanced use of cognitive strategies, improved mood, and reduced cognitive symptoms. Although based on a limited study sample, these results are encouraging, and suggest that further studies of executive function interventions in veterans with bTBI are warranted.

Memory Rehabilitation The ACRM, BI-ISIG recommends as a practice guideline the remediation of mild memory deficits following TBI by means of compensatory and self-monitoring strategies that can be directly applied to functional activities (Cicerone et al. 2005). Compensatory strategies may include internal strategies, such as visual imagery and various encoding strategies, as well as external memory aids, such as use of a notebook or organizer. Self-monitoring strategies require patients to predict and self-evaluate their performance, and involve specific techniques, such as task management and error monitoring (Cicerone et al. 2011). There is evidence that training in the use of internal strategies and self-monitoring techniques improves the use, maintenance, and helpfulness of external memory aids (Ownsworth and McFarland 1999).

Several recent studies suggest that such strategies may be useful in patients with mild memory impairment. Stringer (2011) focused on the use of internal strategies—specifically writing, organizing, picturing and rehearsing material—in patients with mild to severe brain injury of various etiologies, and found improved performance at all levels of severity on memory tasks that simulated everyday memory demands. Another study evaluated internal strategy training combined with self-monitoring techniques in patients with mild to severe TBI, and reported improved memory performance, with most benefit associated with mild to moderate TBI (O'Neil-Pirozzi et al. 2010). Finally, a 4-week training program for older adults with subjective memory complaints, that incorporated both internal and external strategies, demonstrated lasting gains in episodic memory, which were particularly apparent on tasks with high demands on strategic encoding and retrieval (Craik et al. 2007). These studies motivate the use of similar approaches in patients with mTBI and PTSD, but randomized studies including longer follow-ups and ecologically relevant measures are needed to further evaluate the value of memory training for this population.

Seeking to identify variables that predict memory rehabilitation outcome in a group of patients with self-reported memory difficulty as a consequence of TBI of variable

severity, Strangman et al. (2008) obtained fMRI during a verbal encoding task prior to training of internal memory strategies. They found that activation in left ventrolateral prefrontal cortex predicted rehabilitation success. The association reflected an inverted U function, such that both extreme under- and over-activation were associated with less successful learning after training. The authors interpreted their findings as reflecting the fact that there is likely an optimal level and/or type of strategic processing that is associated with a level of activation in the midrange, and with performance success. Future studies that examine differences between individuals who show over- and under-activation may help differentiate reasons for poor rehabilitation outcomes.

Multimodal Rehabilitation

One of the key issues currently debated in the field of cognitive rehabilitation is whether holistic or multimodal rehabilitation is more effective than specifically targeted rehabilitation interventions (Cicerone et al. 2006; Gordon et al. 2006b). There is growing evidence for the effectiveness of holistic, multimodal rehabilitation programs that provide integrated treatment of cognitive and neuropsychiatric problems, as well as interpersonal and practical skills training (Ben-Yishay 1985; Cicerone et al. 2006, 2008; Gordon et al. 2006a; Kaschel et al. 2002; Sohlberg et al. 2000; Wilson et al. 2005). Current practice standards recommend providing comprehensive-holistic neuropsychological rehabilitation to reduce cognitive and functional disability for persons with moderate or severe TBI (Cicerone et al. 2011). However, theoretically-driven multimodal and holistic interventions may also be well-suited to address the complexity of cognitive and neuropsychiatric problems in OEF/OIF veterans with comorbid mTBI and PTSD (DCOE and DVBIC 2009). In an attempt to develop an integrative system of care for veterans with symptoms of chronic mTBI, PTSD, and pain, Walker et al. (2010) proposed a multidisciplinary program focusing on education and symptom management to maximize recovery and prevent symptom exacerbation. Future research will need to evaluate the effectiveness of targeted and multimodal integrated interventions in this population.

The Cognitive Rehabilitation Consensus Conference convened in 2009 by the Defense Centers of Excellence (DCOE) for Psychological Health and Traumatic Brain Injury and the Defense and Veterans Brain Injury Center (DVBIC) highlighted the limitations of existing treatment options and issued specific recommendations for cognitive rehabilitation programs in mTBI (DCOE and DVBIC 2009). Recommended core elements of cognitive rehabilitation programs in the Military Health System include: (1) comprehensive assessment by an interdisciplinary group of

mental health care providers to evaluate current level of function and to assist in the development of rehabilitation goals; (2) identification of individualized cognitive rehabilitation goals that target symptom reduction through restoration and compensation, functional improvements, and therapeutic alliance; (3) development of an interdisciplinary individualized treatment plan that addresses concurrent conditions, current operational demands, occupational status and psychosocial stress; (4) recurrent cognitive reassessment and review of goals, and update of the clinical and re-integration plans; and (5) development of an individually tailored discharge plan, as well as community re-integration and follow-up plans.

Given the increased risk of neuropsychiatric disorders associated with mTBI in the military context, it was also recommended that cognitive assessment and rehabilitation occur in combination with a complete mental health assessment, and mental health treatment as indicated. Among other recommendations were incorporation of multidisciplinary case management conferences, treatment goals review, and coordination of care with the patient's family, other medical providers, and the unit chain of command (for service members). Underlying these recommendations is an emphasis on the importance of interdisciplinary and coordinated care to ensure optimal delivery of cognitive rehabilitation programs and quality care for service members with mTBI and associated comorbidities (DCOE and DVBIC 2009).

While larger medical centers may have the resources to provide such integrated care, smaller treatment settings and community clinics that lack the necessary multidisciplinary teams may need additional resources, in the form of teleconsultation or manualized treatment protocols that providers can be trained to administer. An additional challenge may be the delivery of integrated care to veterans in rural areas, where treatment accessibility may be limited. The use of telehealth technology is promising in this regard, but more evidence is needed to determine its clinical efficacy. A recent consensus study concluded that there is limited evidence for the use of telehealth technologies in cognitive rehabilitation to date. The study committee suggested that telehealth technologies, integrated into a broader cognitive rehabilitation program, can facilitate successful outpatient treatment programs for some patients who otherwise might require inpatient programs (IOM 2011).

Special Considerations in Treatment of Cognitive Impairment in MTBI/PTSD

One of the well-recognized challenges in the care of OEF/OIF veterans with blast exposure concerns making a

diagnosis of mTBI, as the assessment often occurs months, and sometimes years, after the blast exposure, and depends on retrospective report by the patient, which is subject to distortion and reporting bias. Equally challenging is the determination as to whether symptoms and functional difficulties are due to mTBI, PTSD, or both (Sayer et al. 2009) especially in the military population. Deployment-related traumatic events occur in a high stress environment, and symptoms such as feeling dazed and not remembering the injury may represent either sequelae of mTBI or acute stress response (Harvey and Bryant 2002).

As discussed above, there is considerable overlap in the neuropsychological domains affected by mTBI and PTSD, but the time course of recovery differs markedly. A majority of mTBI symptoms resolve within weeks, while PTSD-related symptoms and associated neuropsychological deficits may intensify over time and persist years after the trauma. However, the distinctive trajectory of recovery associated with each disorder is frequently obscured when patients present for assessment months or years after deployment, and may have been exposed to multiple blasts or TBIs. Identification of PTSD-specific symptoms, such as hyperarousal and avoidance, which are typically not seen in civilian mTBI, can be helpful for differential diagnosis.

In light of the challenges associated with diagnosis, some have argued for a focus on symptoms and functional problems, rather than on the etiology of these symptoms (Walker et al. 2010). Such an approach is particularly sensible with regard to the treatment of mild cognitive impairments, as there is no evidence that different treatment strategies would be recommended depending on the etiology of the cognitive problems. Such a symptom-focused approach is exemplified in the study by Huckans et al. (2010) described above—to our knowledge the only cognitive treatment study that focuses specifically on OEF/OIF veterans with mTBI. That study included OEF/OIF veterans with current mild cognitive disorder diagnosis (DSM-IV 1994), whether due to a self-reported history of TBI (blast exposure, motor vehicle accidents, or falls) or other cognitive risk factors, including PTSD, depression, and sleep deprivation.

An important consideration in understanding the neuropsychological impairments seen in OEF/OIF veterans with mTBI relates to the possible contribution of poor effort. Two studies evaluating effort in OEF/OIF military personnel and veterans who screened positive on the Veterans Health Administration TBI screen reported failure rates on symptom validity measures of 17% (Whitney et al. 2009) and 58% (Armistead-Jehle 2010) respectively. The high rate in the latter study, however, may be attributable to the fact a large majority of participants were service connected and were receiving compensation for disability. Because disability status is reviewed on a scheduled basis, this may have created an external incentive to exaggerate cognitive

impairment. More broadly, however, it is important to keep in mind that poor effort need not reflect malingering, as there are many possible causes for poor effort (Iverson 2006).

There are also a number of challenges in regard to the treatment of cognitive problems in mTBI/PTSD patients, such as heterogeneity of cognitive difficulties, variability in PTSD symptomatology, and presence of other comorbidities (outlined above). Symptom management and adherence to a treatment regimen present significant challenges for veterans with mTBI/PTSD and their providers (Sayer et al. 2009). Treatment of TBI-related cognitive symptoms may be disrupted by PTSD symptoms, such as avoidance and emotional dysregulation. Conversely, managing PTSD symptoms depends on adequate cognitive resources, which may be compromised in mTBI (for further discussion, see Verfaellie et al. 2012). To assure effective treatment delivery and to facilitate treatment adherence, adjustments may need to be made to accommodate mTBI/PTSD patients. For instance, cognitive rehabilitation programs traditionally tailored for group treatment delivery may need to include additional PTSD-specific treatment components and techniques to help veterans with emotional regulation in a group treatment setting.

One of the key issues in treatment planning for mTBI/PTSD concerns the optimal timing for cognitive rehabilitation in relation to treatment of mental health issues. On the one hand, an argument for early treatment of cognitive dysfunction could be made, because residual cognitive deficits in mTBI may reduce treatment response to PTSD interventions, such as exposure and cognitive-behavioral therapy (Verfaellie et al. 2012). The limited evidence on this point, however, suggests that treatment for acute stress-related symptoms following psychological trauma can be applied successfully to patients with mTBI (Bryant et al. 2003). On the other hand, interventions for PTSD may need to take precedence, as problems with emotional regulation and impulse control may limit a patient's ability to participate in cognitive treatment (Bryant and Hopwood 2006). Furthermore, it is possible that trauma-focused psychotherapy in itself may help alleviate neuropsychological impairment in executive function (Walter et al. 2010), but this possibility requires further investigation.

An additional challenge with regard to integration of treatment approaches concerns treatment modality, given that cognitive rehabilitation programs are typically administered in a group setting, whereas trauma-focused psychotherapy is more likely to occur in an individual setting.

Another important issue to consider is the use of pharmacologic agents in the treatment of mTBI, PTSD and TBI/PTSD comorbidity. There is currently no evidence base for pharmacological interventions in the mTBI/PTSD population. While pharmacologic agents alone and in combination with cognitive treatments are commonly prescribed for

PTSD, careful consideration is required for treatment of comorbid TBI and PTSD, as some medications traditionally prescribed to treat PTSD symptoms may potentially exacerbate TBI-related cognitive symptoms, such as problems with attention, memory, and cognitive slowing (McAllister 2009). Further discussion of psychopharmacological issues in the treatment of mTBI and PTSD can be found in Chew and Zafonte (2009) and McAllister (2009).

Future Research Directions

A recent consensus study conducted by the Institute of Medicine (IOM), evaluated the effectiveness of cognitive rehabilitation treatment for TBI and provided recommendations to guide the use of cognitive rehabilitation for members of the military and veterans (IOM 2011). The IOM's report supports the ongoing use of cognitive rehabilitation treatment for people with TBI, and recommends "an investment in research to further define, standardize, and assess the outcomes of cognitive rehabilitation interventions". Among the committee's recommendations were the development of larger clinical trials, incorporation of a more comprehensive set of variables reflecting the heterogeneity of injuries and specific patient characteristics, and evaluation of the effectiveness of interventions for specific cognitive functions (IOM 2011).

Further, there is clearly a need for additional research to identify best practices for patients with comorbid mTBI and PTSD (VA Consensus Conference 2010). To address the needs of the growing population of veterans who have suffered physical and psychological trauma, interdisciplinary efforts need to be undertaken (IOM 2011). Primary areas of focus are the development and standardization of tools for differential diagnosis, individually tailored treatment planning, utilization of an interdisciplinary team approach for diagnosis and treatment, and development of new treatment protocols, combination treatments, and interdisciplinary/holistic programs. Additional challenges to consider are treatment delivery and accessibility. To assure consistent treatment delivery across different settings, manualized treatment protocols need to be developed and standardized. Efforts to develop manualized treatment protocols for TBI and mTBI are already underway, and several ongoing clinical trials utilize manualized interventions in their treatment programs. To accommodate veterans in rural locations, tele-rehabilitation protocols should be developed and implemented. It will be important to evaluate whether such protocols can improve adherence to treatment in this population.

An additional area of research concerns the development of methods and measures that allow prediction of outcomes following bTBI, so that cognitive rehabilitation can be prioritized for those individuals most in need. Similarly,

identification of predictors of success of cognitive rehabilitation is of great interest. There is currently much interest in potential biomarkers for the diagnosis, prognosis and evaluation of treatment efficacy in TBI (reviewed in Dash et al. 2010), but this research is still in its infancy. State-of-the-art neuroimaging techniques have great potential to facilitate diagnosis and treatment planning (Flanagan et al. 2008; Kinnunen et al. 2011), but multiple challenges, such as variations in clinical samples, study paradigms, and technical aspects of data collection, limit the clinical use and interpretation of current findings (Brenner 2011). Additional research is also needed to elucidate the neural bases of blast-induced neurocognitive and neuropsychiatric deficits, and the mechanisms of change associated with natural recovery and cognitive rehabilitation treatments (Cicerone et al. 2011; M. R. Kennedy et al. 2008; Levine et al. 2008).

Novel Treatment Paradigms

Novel therapeutic modalities, such as neuromodulation, that have shown promise for rehabilitation of stroke patients (Flanagan et al. 2008; Hummel et al. 2005; Khedr et al. 2005; Naeser et al. 2010), may also have potential for TBI rehabilitation. Utilizing transcranial magnetic stimulation (TMS) in combination with traditionally prescribed cognitive rehabilitation treatment options may provide an enhanced multi-pronged therapeutic approach, specifically tailored for individuals with TBI and psychiatric comorbidities. The therapeutic utility of TMS has been demonstrated in several psychiatric (depression, OCD, schizophrenia) and neurologic disorders (Parkinson's disease, epilepsy), as well as in cognitive rehabilitation (Rossi et al. 2009). A number of repetitive TMS studies have reported significant improvements in cognitive function, specifically in the domains of working memory and executive functioning (Demirtas-Tatlidede et al. 2011; Guse et al. 2010). There is also evidence to suggest that modulation of prefrontal activity with repetitive TMS may be beneficial in the treatment of PTSD (Boggio et al. 2010; H. Cohen et al. 2004; Grisaru et al. 1998; McCann et al. 1998; Watts et al. 2011). The combination of TMS with cognitive intervention may prove synergistic and may enable more successful treatment of patients with mTBI and comorbid PTSD.

Ecologically Valid Outcome Measures

Another key issue to address in future studies concerns the development and standardization of ecologically valid outcome measures. It is critical for both rehabilitation practice and research to identify functional outcome measures that enable monitoring of real-life changes associated with TBI and its treatment. Neuropsychological measures traditionally used to evaluate treatment outcome have functional and

ecological limitations (Wilson 2008), as they assess performance in a structured testing environment, and do not capture the real-life transfer of newly-acquired skills and strategies. The recent IOM report emphasized the importance of utilizing functional outcome measures as global indicators of how patients cope and recover from disability, and provided specific recommendations for outcome measures for cognitive rehabilitation. Outcome measures should include assessment of cognitive functioning in everyday activities, and the selection of measures should be guided by their ability to discern treatment effects that generalize across situations. Other recommended outcome measures are those that capture patient centered outcomes, such as functional status, quality of life, and community participation measures, including return to work and community integration (IOM 2011). Development of functional outcome measures specific for military personnel is of particular importance, as determining functional capacity in both acute and post-acute settings can be critical for deployment decisions.

Summary

A sizable subset of OEF/OIF military personnel returns from deployment with blast-related mTBI and co-occurring PTSD. The frequent co-occurrence of postconcussion symptoms, posttraumatic stress, and pain can significantly complicate the diagnosis of mTBI and influence the course of recovery and treatment outcome in this population. There is an increasing awareness that postconcussion symptoms are likely due to a combination of neuronal injury and psychological response to the trauma. Early identification and education, with an emphasis on expectation of recovery, can reduce postconcussion symptoms and promote successful recovery. Nonetheless, for some patients cognitive symptoms may persist and cognitive rehabilitation may be indicated. Integrating cognitive rehabilitation within a comprehensive system of care that addresses both medical and mental health issues requires collaboration between specialists in an interdisciplinary team of providers.

Rehabilitation of cognitive difficulties associated with blast-TBI is guided largely by treatment programs that have proven efficacious in the treatment of non-blast TBI. The overarching goal is to improve problem-solving and adaptive abilities by training new adaptive skills, which can carry over into everyday life and lead to improved functional capacity. As discussed above, however, the presence of psychiatric comorbidities can complicate treatment implementation and outcome. Controlled randomized clinical trials, as well as long-term follow-up studies utilizing ecologically valid outcome measures are needed to address the efficacy and generalizability of cognitive rehabilitation in veterans with bTBI and PTSD.

Although cognitive rehabilitation of OEF/OIF veterans poses unique challenges, it also provides a welcome impetus for more systematic research into innovative and multimodal interventions that specify objectively measurable functional goals. Further, identification of patient and environmental characteristics associated with optimal and lasting treatment outcome and standardization of outcome measures will benefit the evidence base and clinical implementation of rehabilitation well beyond the veteran population.

Acknowledgments This research was supported by the Clinical Science Research and Development and the Rehabilitation Research and Development Services of the Department of Veterans Affairs; the National Institutes of Health and Boston University Clinical and Translational Science Institute. We thank Dr. Jennifer J. Vasterling for her expert advice and helpful discussion, and Sarah M. Kark, B.S., for assistance with manuscript preparation. The authors have no conflicts of interest to disclose.

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