

## *Neuropsychological and neuroimaging findings in traumatic brain injury and post-traumatic stress disorder*

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*Advances in imaging technology, coupled with military personnel returning home from Iraq and Afghanistan with traumatic brain injury (TBI) and/or post-traumatic stress disorder (PTSD), have increased interest in the neuropsychology and neurobiology of these two conditions. There has been a particular focus on differential diagnosis. This paper provides an overview of findings regarding the neuropsychological and neurobiological underpinnings of TBI and/or PTSD. A specific focus is on assessment using neuropsychological measures and imaging techniques. Challenges associated with the assessment of individuals with one or both conditions are also discussed. Although use of neuropsychological and neuroimaging test results may assist with diagnosis and treatment planning, further work is needed to identify objective biomarkers for each condition. Such advances would be expected to facilitate differential diagnosis and implementation of best treatment practices.*

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The goal of this publication is to briefly summarize neuropsychological and neuroimaging findings among adults with traumatic brain injury (TBI) and/or post-traumatic stress disorder (PTSD), and highlight current thinking in the field. Tables have been used to consolidate evidence. The existing data is vast, and complete discussion is outside the purview of this paper. Readers are encouraged to review publications noted for further discussion of specific areas of interest.

### Traumatic brain injury (TBI)

Diagnostically, to have suffered a TBI one must have experienced an event (eg, motor vehicle accident, fall) which resulted in a structural injury to the brain or a physiological disruption of brain function (eg, alteration of consciousness [AOC], loss of consciousness [LOC]). TBI severity is classified according to the extent of injury to the brain or altered consciousness post-injury, not to the severity of sequelae reported or observed. See *Table 1* for further information regarding classification of TBI severity. Secondary to a cascade of cellular and molecular events, primary neurological injury associated with a traumatic event can also cause progressive tissue atrophy and related neurological dysfunction. Ultimately, such processes can result in neuronal cell death (secondary brain damage).<sup>1</sup> Cellular mechanisms that modulate pathophysiological and neuroprotective processes appear to contribute to the nature and extent of damage post-injury.<sup>2</sup> Diffuse axonal injury (DAI), preferential multifo-

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## Selected abbreviations and acronyms

<b>ACC</b>	<i>anterior cingulate cortex</i>
<b>AOC</b>	<i>alteration of consciousness</i>
<b>LOC</b>	<i>loss of consciousness</i>
<b>MRI</b>	<i>magnetic resonance imaging</i>
<b>OEF</b>	<i>Operation Enduring Freedom</i>
<b>OIF</b>	<i>Operation Iraqi Freedom</i>
<b>PCS</b>	<i>postconcussive symptoms</i>
<b>PTS</b>	<i>post-traumatic symptoms</i>
<b>PTSD</b>	<i>post-traumatic stress disorder</i>
<b>TBI</b>	<i>traumatic brain injury</i>

cal involvement of myelinated tracks, often occurs and can be related to the primary injury or secondary brain damage. As the severity of the injury increases, so do findings noted on imaging and neuropsychological measures.<sup>3</sup> According to the Centers for Disease Control and Prevention, approximately 1.7 million people per year in the United States sustain a TBI.<sup>4</sup> Most injuries incurred by civilians and military personnel are mild in nature.<sup>4,5</sup> That is, the associated AOC immediately following the injury is limited (eg, LOC less than 30 minutes). Individuals serving in Iraq and Afghanistan are sustaining TBIs secondary to blast exposure.<sup>5</sup> Reported estimates of TBI vary between 8% and 23%.<sup>5,6</sup> Blast exposure can result in TBI via multiple mechanisms including: (i) primary blast—injury caused by the overpressurization wave; (ii) secondary blast—injury secondary to object being thrown by the blast towards the person; and (iii) tertiary blast—when individuals are thrown and strike objects. Additionally, some explosions are accompanied by electromagnetic perturbations which result in “small” and “brief” radiofrequency impulses.<sup>7</sup> The physiological implications of these impulses is unclear.<sup>7</sup> In terms of the overpressurized wave and brain injury, the primary means by which blast energy transduction occurs

remains a topic of debate. Potential hypotheses include: (i) transcranial propagation; (ii) the vascular system; and (iii) cerebrospinal fluid entering the foramen magnum.<sup>7</sup> Injuries noted post-blast exposure include edema, contusion, DAI, hematoma, and hemorrhage.<sup>7,8</sup>

Clear evidence exists regarding the relationship between injury severity, impairment (eg, cognitive) and functional status.<sup>9,10</sup> In comparing postinjury neuropsychological test performance among individuals with moderate and severe TBI, Bercaw et al<sup>11</sup> identified a pattern of performance which suggested that scores at 1 year post-rehabilitation predicted functional outcomes at year 2. Whereas most individuals with a mild TBI return to baseline functioning within one year, between 7% and 33% report persistent symptoms.<sup>12</sup> Regardless of injury severity, one of the most frequently reported symptoms post-TBI is cognitive dysfunction (eg, memory problems).<sup>5,10</sup> Particularly among those with mild TBI and persistent post-acute symptoms, there is often a disconnect between subjective (eg, self-report) and objective markers (eg, neuropsychological test performance) of such dysfunction. Nevertheless, among those with mild to severe TBI, observed cognitive disturbances have been linked to poorer psychosocial functioning (eg, return to work).<sup>13</sup>

## Post-traumatic stress disorder (PTSD)

Postdeployment, military personnel are also reporting post-traumatic symptoms.<sup>14</sup> To meet criteria for PTSD an individual must be exposed to a psychologically traumatic event which facilitates the onset of persistent symptoms. These symptoms must also cause significant distress or impact functioning. The *Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (DSM-IV)*<sup>15</sup> defines a “traumatic event” as one in which “(i) the per-

Criteria	TBI severity		
	Mild	Moderate	Severe
Structural imaging	Normal	Normal or abnormal	Normal or abnormal
Loss of consciousness	0-30 minutes	> 30 minutes and < 24 hours	> 24 hours
Alteration of consciousness/mental state**	A moment up to 24 hours	> 24 hours; severity based on other criteria	
Post-traumatic amnesia	0-1 day	>1 day and < 7 days	> 7 days
Glasgow Coma Score (best available score in first 24 hours)	13 to 15	9 to 12	<9

**Table 1.** Departments of Defense and Veterans Affairs consensus-based classification of closed traumatic brain injury (TBI) severity.<sup>63</sup> \*\*Alteration of mental status must be immediately related to the trauma to the head. Typical symptoms would be looking and feeling dazed and uncertain of what is happening, confusion, difficulty thinking clearly or responding appropriately to mental status questions, and being unable to describe events immediately before or after the trauma event.

son experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury or a threat to the physical integrity of self or others; and (ii) the person's response involved intense fear, helplessness, or horror” (p 467). PTSD symptoms are clustered into three categories including re-experiencing of the traumatic event, avoidance of trauma-related stimuli and/or emotional numbing, and hyperarousal. PTSD has been conceptualized as a disorder of fear in which the individual has exaggerated fear responses or the inability to control fear responses.<sup>16</sup> It has also been described as a disorder of memory, in which individuals suffering from PTSD seem to “relive their trauma in the form of involuntary recollection,” (p 271).<sup>17</sup> In addition to demonstrating enhanced recall for traumatic memories, distressing recollections for those with PTSD are often “vivid” and “long-lasting.”<sup>18</sup>

It is in part these “reliving” experiences that take the form of nightmares, intrusive thoughts, and/or flashbacks, coupled with observed cognitive disturbances that have fostered interest regarding the neurobiological and neuropsychological underpinning of this condition. Despite knowledge that genetic variability, gender, and developmental history appear to impact neurobiological systems and responses to traumatic stimuli,<sup>19</sup> PTSD symptoms are believed to be related to an individual’s dysregulated biological response to stress.<sup>20</sup> *Table II* shows brain regions and neurochemical dysfunction often discussed in association with PTSD symptoms. During traumatically stressful situations, neurotransmitter systems and neuroendocrine axes are activated.<sup>20</sup> According to Langeland and Olf<sup>20</sup> research has primarily focused the hypothalamus-pituitary-adrenal (HPA) axis. The sympathetic-adrenomedullary (SAM) system

Hallmark PTSD symptom	(Over)activation	(Under)activation
<b>Re-experiencing</b>		
Brain region	Amygdala Insula	Prefrontal cortex Anterior cingulate cortex Inferior frontal cortex
Neurochemical	Cortisol Glutamate Norepinephrine	
<b>Hyperarousal</b>		
Brain region	Amygdala Thalamus	Prefrontal cortex
Neurochemical	Cortisol Dopamine Epinephrine Norepinephrine	Serotonin
<b>Avoidance/Numbing/Dissociation</b>		
Brain region	Prefrontal cortex Superior temporal cortex	Hippocampus Insula Prefrontal cortex Anterior cingulate cortex Superior temporal cortex Inferior frontal cortex
Neurochemical	Beta-endorphins Cortisol Dopamine Glutamate	

**Table II.** Brain regions and neurochemical dysfunction often discussed in association with post-traumatic stress disorder (PTSD) symptoms. Adapted from information presented in ref 66: Hopper JW, Frewen PA, van der Kolk BA, et al. Neural correlates of reexperiencing, avoidance, and dissociation in PTSD: Symptom dimensions and emotion dysregulation in responses to script-driven trauma injury. *J Trauma Stress.* 2007;20:713-725; Copyright © Wiley, 2007; ref 67: Weiss SJ. Neurobiological alterations associated with traumatic stress. *Perspect Psychiatric Care.* 2007; 43:114-122. Copyright © Wiley, 2007

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has also been implicated in that it releases epinephrine which facilitates the flight/fight response.<sup>21</sup> On the contrary, the contribution of the HPA axis, glucocorticoids, take time to produce. As such their impact, which is primarily on the brain, develops and continues over a longer period.<sup>21</sup> The SAM and HPA systems are regulated by “limbic brain circuits that involve the amygdala, hippocampus and orbital/medial prefrontal cortex” (p 150).<sup>21</sup> Neurobiological activation is thought to impact brain functioning and hypothesized to alter the structure of brain regions including the amygdala, hippocampus, locus coeruleus, dorsal raphe nucleus, and prefrontal cortex.<sup>22,23</sup> Although activation of these systems supports functioning, chronic activation seems to be problematic in terms of psychological and physical health.

At the same time, it has been suggested that neurobiological findings (eg, reduced hippocampal volumes) are instead premorbid characteristics that contribute to the development of PTSD.<sup>24</sup> For example, van Zuiden<sup>25</sup> and colleagues found that predeployment glucocorticoid receptor numbers were elevated in soldiers reporting higher PTSD symptoms postdeployment; thereby, highlighting the question of whether such biological differences are pre-existing characteristics, the result of the

PTSD, or a combination of the two. Much the same discussion has been had in terms of cognitive dysfunction often noted in those with PTSD.<sup>22</sup> A specific focus has been on whether lower intellectual functioning is a precursor of PTSD or a sequela of the condition.<sup>26,27</sup>

## TBI and PTSD co-occurring

Historically, some controversy has existed regarding whether PTSD and TBI can coexist; however, more recent work in this area suggests that they can. If the injury and psychiatrically traumatic event are co-occurring, those with a less severe AOC seem to be at greater risk for developing PTSD. As noted above, complaints are frequently shared between those with TBI and/or PTSD (eg, poor attention); thereby complicating differential diagnosis. This particularly true for those with mild TBI, and/or repeated exposure to trauma (physical, psychological). For example, work by Brenner et al,<sup>28</sup> suggested that in retuning soldiers with histories of physical injury, mild TBI and PTSD were independently associated with self-reported memory problems. Moreover, a combination of the conditions was found to be more strongly associated with memory problems than either

Brain Region	Function	PTSD and/or TBI
Amygdala	Generation and maintenance of emotional responses <sup>50</sup>	PTSD <sup>42</sup> ; TBI <sup>1</sup>
Cerebellum	Movement and motor coordination; processing fear memories <sup>49</sup>	PTSD <sup>48</sup> ; Chronic mild TBI <sup>51</sup>
Corona radiata	Attentional processes <sup>36</sup>	Chronic mild TBI <sup>55</sup>
Corpus colosum	Intrahemispheric communication <sup>68</sup>	Acute and chronic mTBI <sup>37</sup> ; Moderate to severe TBI <sup>70</sup> ; TBI <sup>1</sup>
Hippocampus	Explicit and declarative memory, working memory, episodic/autobiographical memory, contextual learning <sup>37,50</sup> ; control of stress responses and contextual aspects of fear conditioning <sup>19</sup>	PTSD <sup>48</sup> ; TBI <sup>1</sup>
Insula	Core affect, associated consciousness of subjective feelings, developing and updating motivational states, autobiographical memory, cognitive control, affective processing, pain, and conveyance of homeostatic information <sup>50</sup>	PTSD <sup>42</sup>
Internal capsule	Motor and sensory communication	Acute and chronic mTBI <sup>37</sup>
Medial temporal lobe	Declarative memory	Chronic mild TBI <sup>51</sup> ; TBI <sup>1</sup>
Parietal cortex	Volitional and avolitional allocation of attentional resources during the retrieval of episodic memories <sup>62</sup>	PTSD <sup>62</sup>
Prefrontal cortex	Manipulation of emotions and memories <sup>62</sup> ; extinguishing conditioned fear <sup>32</sup> ; inhibitory action on the amygdala <sup>16</sup>	PTSD <sup>32,42,47,61</sup> ; TBI <sup>1,69</sup>
Anterior cingulate cortex	Processing of cognitive and emotional interactions <sup>50</sup> including interference from emotional stimuli and performance monitoring, response selection, error detection, and decision making <sup>69</sup> ; conflict monitoring, attention and pain <sup>50</sup>	PTSD <sup>32,41,48</sup>
Uncinate fasciculus	Working memory <sup>37</sup>	Chronic mild TBI <sup>56</sup>

**Table III.** Brain regions and functions often discussed in relationship to post-traumatic stress disorder (PTSD) and/or traumatic brain injury (TBI). \*\*Acute mild, moderate, and severe

condition alone. In looking at post-traumatic symptoms (PTS) and postconcussive symptoms (PCS) (eg, slowed thinking, poor concentration) among returned Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) Veterans, Benge and colleagues<sup>29</sup> found that PTS and PTC were not independent variables, thereby suggesting that incorrect attribution of PCS to history of TBI may preclude referral to appropriate treatment.

Challenges associated with symptom attribution are at least in part related to the fact that common areas of the brain are implicated in both conditions (*Table III* shows brain regions and functions often discussed in relationship to PTSD and/or TBI). Whereas neuroimaging and neuropsychological findings have contributed to the understanding of each of these conditions, and are frequently employed in clinical practice, guidance regarding how to best use these diagnostics tools to inform practice with these populations is limited. Moreover, contextual and/or person-specific factors such as deployment to a combat zone, effort (eg, fatigue, distraction secondary to psychiatric condition) and potential secondary gains (eg, monetary compensation related to legal proceedings) impact performance on diagnostic tools in ways that further complicate interpretation. For example, among returning OIF Soldiers, Vasterling and colleagues<sup>6</sup> found increased reaction time, poor concentration, and short-term memory problems. Similarly, higher levels of combat intensity have been shown to be related to more efficient reaction time even 1 year post-deployment.<sup>30</sup>

Further complicating interpretation, for individuals with TBI and/or PTSD deficits in primary areas of cognitive functioning (eg, attention, processing speed) may undermine more complex processes (eg, executive functioning). For example, Nelson and colleagues<sup>31</sup> found that among OEF/OIF Veterans with TBI, processing speed contributed significantly to performance on measures of executive functioning. Challenges also exist in terms of using experimental findings to guide clinical practice. Research studies frequently discuss significant differences in test scores among those with and without PTSD; however, lower scores do not equal impairment (a score that is two standard deviations below the mean of the general population). McNally<sup>32</sup> highlights this point by suggesting that above-average intelligence be considered a protective factor against PTSD versus lower IQ being a risk factor for developing the disorder. A clinician evaluating an individual's performance on objective mea-

asures of functioning must note whether scores are actually impaired, or simply below personal expectations or previous levels of functioning. Making this determination can be particularly difficult if the premorbid data available for review is limited and/or anecdotal in nature.

## Cognitive functioning

Cognitive deficits associated with TBI, particularly mild TBI, generally diminish over time. Alternately, PTSD has been associated with enduring cognitive disturbances. Although the etiology of deficits differs between individuals with each of these conditions, significant areas of overlap exist both in terms of subjective complaints and objective findings (eg, attention). Below, the reader will be provided with summarized information regarding neuropsychological findings, clinical and experimental, among those with TBI (mild/moderate and severe) and PTSD. To augment this material readers are encouraged to review *Table IV*, the neuropsychological findings often discussed among those with TBI or PTSD.

### TBI (mild)

Although there appears to be general consensus regarding the presence of acute cognitive dysfunction in those with mild TBI,<sup>33,34</sup> findings regarding the overall effect of mild TBI on long-term neuropsychological test performance have been mixed. Frencham and colleagues<sup>35</sup> published a meta-analysis of neuropsychological studies post-mild TBI and found that measures of processing speed, working memory, attention, memory, and executive functioning were most impacted immediately postinjury.<sup>35</sup> Overall, their findings indicated that the effect of mild TBI on neuropsychological test performance was small, and that problems decreased as time since injury increased.<sup>36</sup> This assertion is supported by a recent study by Brenner and colleagues,<sup>28</sup> in which 45 soldiers post-mild TBI completed neuropsychological measures. Twenty-seven had enduring PCS, including cognitive complaints, and 18 did not. Mean time since injury was approximately 41 weeks. Presence of mild TBI symptoms did not impact test performance, and mean participant scores were overwhelmingly unimpaired. Alternately, it may be that neuropsychological measures frequently used in practice are not sophisticated enough to identify subtle postinjury impairments. Imaging studies may increase our understanding regard-

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ing neuropsychological test performance in those with mild TBI. For example, Van Boven and colleagues<sup>37</sup> suggested that those with mild TBI may require larger areas of cortex to complete tasks. In addition, the impact of injury on performance may grow as lifetime injury burden increases. This assertion is supported by the work of Belanger and colleagues<sup>38</sup> who found that a history of multiple self-reported TBI was associated with poorer performance on tests of delayed memory and executive functioning.

## TBI (moderate and severe )

Widespread and enduring cognitive deficits are often noted in those with moderate to severe TBI. Senthani-Raja and colleagues<sup>10</sup> compared the neuropsychological test performance of 112 individuals with complicated mild to severe injuries with matched controls and identified deficits in attention, processing speed, visual and verbal memory, executive functioning, and working

memory. These significantly worse scores were noted long postinjury. The performance of older individuals and long-term survivors was worse. Among a cohort that had been referred for rehabilitation, Draper and Ponsford<sup>39</sup> evaluated neuropsychological performance 10 years post-injury and found persisting deficits in processing speed, learning, and executive functioning. Level of impairment was associated with injury severity. Finally, Mathias and Wheaton<sup>40</sup> conducted a meta-analytic review regarding attention and information processing speed deficits post-severe TBI. Findings suggested large and significant deficits in the areas of information processing speed, attention span, focused/selective attention, sustained attention, and supervisory attentional control. In reviewing the literature on functioning post-severe TBI, Van Boven and colleagues<sup>37</sup> suggested that deficits such as those noted above may be related to difficulty adequately recruiting the cortical resources necessary to complete complex cognitive tasks.

Cognitive domain	Traumatic brain injury		Moderate to severe Publication	Post-traumatic stress disorder Publication
	Mild Acute/chronic	Publication		
Attention	Acute/chronic	Frencham et al <sup>35</sup> ;Peskind et al <sup>50</sup>	Mathias and Wheaton <sup>39</sup> ; Senathi-Raja et al <sup>10</sup>	Aupperle et al <sup>42</sup> ; Golier et al <sup>71</sup> ; Samuelson et al <sup>45</sup>
Sustained attention	Chronic	Kraus et al <sup>3</sup>	Mathias and Wheaton <sup>39</sup>	Vasterling et al <sup>72</sup> ; Vasterling et al <sup>27</sup>
Emotional processing				Halligan et al <sup>47</sup> ; Milad et al <sup>48</sup> ; McNally <sup>17</sup> ; McNally <sup>32</sup>
Executive dysfunction	Acute/chronic	Frencham et al <sup>35</sup> ;Peskind et al <sup>50</sup>	Mathias and Wheaton <sup>39</sup> ; Draper and Ponsford <sup>38</sup> ; Senathi-Raja et al <sup>10</sup>	Aupperle et al <sup>42</sup> ; Vasterling et al <sup>72</sup>
Working memory	Acute/chronic	Frencham et al <sup>35</sup> ; Peskind et al <sup>50</sup>	Senathi-Raja et al <sup>10</sup>	Aupperle et al <sup>42</sup> ;Moores et al <sup>46</sup> ; McNally <sup>32</sup> ; Samuelson et al <sup>45</sup> ; Vasterling et al <sup>27</sup>
Intelligence				Gilbertson et al <sup>26</sup> ; Vasterling et al <sup>27</sup>
Language and communication			Levin and Chapman <sup>73</sup>	McNally <sup>32</sup>
Learning	Acute	Frencham et al <sup>35</sup>	Draper and Ponsford <sup>38</sup> ; Vanderploeg et al <sup>74</sup>	Samuelson et al <sup>45</sup> ; Vasterling et al <sup>72</sup> ; Vasterling et al <sup>27</sup>
Processing speed	Acute/chronic	Frencham et al <sup>35</sup> ; Niogi et al <sup>56</sup> ; Peskind et al <sup>49</sup>	Draper and Ponsford <sup>39</sup> ; Mathias and Wheaton <sup>29</sup> ; Senathi-Raja et al <sup>10</sup> ; Willmott et al <sup>70</sup>	Nelson et al <sup>31</sup> ; Samuelson et al <sup>45</sup>
Verbal memory	Acute/chronic	Frencham et al <sup>35</sup>	Senathi-Raja et al <sup>10</sup> ; Lezak et al <sup>68</sup>	Golier; McNally <sup>32</sup> ; van Pragg
Visual memory	Acute	Frencham et al <sup>35</sup>	Senathi-Raja et al <sup>10</sup>	Marx et al <sup>41</sup>

**Table IV.** Neuropsychological findings often discussed among those with traumatic brain injury or post-traumatic stress disorder.

## PTSD

In studying Vietnam combat veterans and their nonexposed identical twin brothers, Gilbertson and colleagues<sup>26</sup> found that performance on cognitive tasks (ie, intellectual, verbal memory, attention, executive functioning, and visuospatial skills) was more strongly associated with familial factors than PTSD. Patterns of vulnerability in terms of verbal memory and executive functioning were identified among both exposed and unexposed members of the twin pairs. Further study regarding learning, processing speed, intelligence, and visual recall have supported the theory that pretrauma performance on neuropsychological measures is related to PTSD symptom development.<sup>41,42</sup> In a recent publication, Aupperle and colleagues<sup>42</sup> summarized investigations regarding executive function and PTSD, and identified subtle impairments in response inhibition and attention regulation among those with PTSD. The authors described these areas of impairment as potentially predated PTSD, thereby acting as risk factors for the disorder. At the same time, they noted that impairments may be exacerbated by trauma exposure.<sup>42</sup> This is supported by the work of Vasterling and colleagues<sup>27</sup> which suggested that neurocognitive and intellectual performance deficits are independently associated with PTSD. Pretrauma deficits may exacerbate responses to trauma exposure thereby causing subtle impairments “to morph into significant symptoms” which are identifiable on neuropsychological measures and impact day-to-day functioning.<sup>41</sup> Although patterns of cognitive deficits have varied between cohorts with PTSD<sup>27,43</sup> difficulties in the areas of attention, learning, and memory, particularly verbal, have consistently been identified.<sup>27,41,44,45</sup> The impact of stress on neuropsychological functioning may in part be time-dependent. For example, in comparing performance on measures of sustained attention between Gulf War and Vietnam Veterans, Vasterling and colleagues<sup>27</sup> hypothesized that PTSD-related arousal dysregulation may change over time from a pattern of hyperarousal to disordered arousal. Moreover, recent work suggests that although absolute performance among those with PTSD may be normal, use of neuroimaging techniques allows for the exploration of systems and compensatory recruitment. This is evidenced by the work of Moores and colleagues<sup>46</sup> who found that individuals with PTSD must recruit larger areas of cortex to complete working memory tasks.

An additional focus has been on whether those with PTSD encode, process, experience, and/or express trauma-related information differently than individuals without this disorder. McNally<sup>17</sup> noted that those with PTSD selectively process trauma-relevant material. Emotional Stroop tasks in which individuals are asked to respond to emotionally loaded content are frequently used to assess such processing. Studies using the Stroop have consistently shown that those with PTSD take longer to name trauma-laden content. Halligan et al<sup>47</sup> conducted a study regarding assault victims and found that trauma memories were more disorganized in those with PTSD symptoms, and that the magnitude of disorganization predicted PTSD symptom severity. In addition, it has been demonstrated that those with war-related PTSD fail to retain extinction from learned fear.<sup>48</sup> This deficit was not identified in subject’s co-twins; thereby suggesting that it is acquired and related to PTSD versus a pre-existing vulnerability. Finally, Banich et al<sup>18</sup> discussed how attentional biases for threat in those with PTSD may be moderated by an individual’s tendency to dissociate. Dissociation appears to impact aspects of attention and cognitive control. Alterations in these cognitive control mechanisms can influence memories retrieved.

## Neuroimaging

To improve diagnosis and treatment of TBI and/or PTSD, identification of objective biomarkers is of significant clinical import. As evidenced by current advances, neuroimaging in certainly is a key tool in this process. *Table V* shows magnetic resonance imaging (MRI) neuroimaging techniques. Nevertheless, significant challenges exist in terms of summarizing existing findings and translating data to improve clinical practice. Studies often involve diverse cohorts (eg, mild TBI, combat veterans), and employ different paradigms (symptom provocation, cognitive activation) and modalities (eg, diffusion tensor imaging [DTI], functional magnetic resonance imaging [fMRI], single photon emission computed tomography [SPECT]).<sup>50</sup> As such, findings have varied. Peskind and colleagues noted that fluorodeoxyglucose positron emission tomography (FDG-PET) abnormalities in those with PTSD versus those without this disorder have been “limited and conflicting” (p 5).<sup>51</sup> In terms of validation, experiments supporting newer functional imaging techniques often rely on neuropsychological paradigms. For example, in response to

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findings regarding the positive relationship between DTI results and neuropsychological test performance among those with mild, moderate, and severe injuries, Kraus et al<sup>3</sup> suggested that white matter load may be a “useful index.” Much work is being conducted to support these new imaging techniques, and findings are increasing our knowledge regarding those with TBI and/or PTSD.

## TBI

Although newer techniques have begun to allow clinicians to explore questions regarding pathogenesis, natural history, neuroplasticity, and treatment response,<sup>52</sup> historically, neuroimaging has been used to identify and manage acute moderate-to-severe TBI. Less sophisticated structural imaging techniques such as computed tomography (CT) or MRI have been useful in identifying skull fractures or more severe injuries (eg contusion, intraparenchymal hemorrhage); however, they generally fail to adequately detect DAI or brain volume loss. Moreover, in combat or deployment settings these generally common diagnostic tools may not be available to the clinician.<sup>53</sup> Research among both Veteran and civilian populations suggests that use of CT and MRI has limited utility in confirming acute or post-acute mild TBI.<sup>54-56</sup> In looking at MRI results of veterans long post-TBI, Brenner and colleagues<sup>55</sup> found that those with moderate to severe TBI were significantly more likely

to have trauma-related findings (physical) than those with mild TBI. In specific, 11 out of 16 veterans with moderate to severe TBI versus 0 out of 16 with mild TBI had MRI findings.

Research regarding newer functional imaging techniques (eg, FDG-PET, DTI, SPECT) suggests that in the future they may be of significant clinical utility, particularly in the context of mild TBI and/or post-acute injuries. For example, DTI findings can be used to create maps of regional connectivity within the brain, otherwise known as tractography, and as such may be a useful tool for highlighting white matter damage post-injury.<sup>6</sup> Recent studies using such techniques include work by Matthews et al<sup>57</sup> who used DTI and fMRI to examine the structural and functional neural correlates of major depressive disorder (MDD) in OEF/OIF war veterans with self-reported histories of mild TBI. Those with MDD showed greater activation in the amygdala and other emotional processing structures, lower activation in emotional control structures, and lower fractional anisotropy in several white matter tracts. Using FDG-PET and neuropsychological testing, Peskind and colleagues<sup>51</sup> compared results from 12 OIF veterans with mild TBI and/or PTSD to community volunteers. A decreased cerebral metabolic rate of glucose in the cerebellum, vermis, pons, and medial temporal lobe as well as subtle cognitive impairments (eg, verbal fluency, cognitive processing speed) were noted in the

Technique	What it measures	Applications
BOLD fMRI	Indirect measure of blood flow, BOLD signal changes originate in venules. BOLD fMRI takes advantage of susceptibility differences between oxygenated and deoxygenated blood.	Evaluate regional brain activity related to particular cognitive tasks or sensory/motor stimulation. Evaluate brain networks related to cognitive states. Evaluate brain “resting state” or “default” networks.
PW-MRI	Direct measure of blood flow, allows quantification of blood perfusion.	Assess brain perfusion or resting cerebral blood flow. Evaluate brain function in manner similar to fMRI.
DTI	Indirectly measures diffusion of water molecules. Mean diffusion, diffusion direction, and anisotropy white matter tracts.	Use diffusion anisotropy measures as marker of disease. Improved visualization of edema. Evaluate structural “connectivity” between brain regions.
MRS	Proton ( <sup>1</sup> H) MRI spectra typically contain signals from the metabolites N-acetylaspartate, creatine, Choline, glutamate/glutamine, and myo-inositol.	Evaluate changes in brain metabolites related to myelination, neuronal density, edema, etc.
SWI	MRI sequences that are especially sensitive to changes in magnetic susceptibility, in particular blood	Improved detection of hemorrhages. Improved imaging of blood vessels.

**Table V.** Magnetic resonance imaging (MRI) neuroimaging techniques. BOLD, blood oxygen level dependent; DTI, diffusion tensor imaging, fMRI, functional MRI; MRS, magnetic resonance spectroscopy; PW-MRI, perfusion weighted MRI; SWI, susceptibility-weighted imaging. Reproduced with permission from ref 37: Van Boven RW, Harrington GS, Hackney DB, et al. Advances in neuroimaging of traumatic brain injury and posttraumatic stress disorder. *J Rehabil Res Dev.* 2009;46:717-757. Copyright © Dept of Veterans’ Affairs 2009



veteran sample. Study limitations as described by the authors included the control group being 21 years older than the veteran group, and 10 out of the 12 veterans having a history of co-occurring PTSD. Readers are encouraged to review the following for more through discussions of functional imaging techniques and TBI: Belanger et al,<sup>54</sup> Niogi and Mukherjee,<sup>57</sup> Wortzel et al,<sup>59</sup> and Van Borgen et al.<sup>36</sup>

Newer techniques such as those described above are frequently unavailable to practitioners. Moreover, based upon the current state of knowledge regarding these measures, significant controversy exists regarding whether they can appropriately be used in clinical settings.<sup>59</sup> In a recent Letter to the Editor, Adinoff and Devous<sup>60</sup> suggested that at present there is an absence of empirical evidence to support using SPECT to diagnose and treat psychiatric illnesses. This assertion is consistent with opinions expressed by Niogi and Mukherjee<sup>57</sup> who stated that “because of substantial overlap in the range of DTI metrics between age-, gender-, and education matched controls and mild TBI patients, diagnostic interpretation in the individual patient relying solely on DTI results remains problematic” (p 251).

## PTSD

Garfield and Liberzon<sup>50</sup> elegantly summarize neuroimaging studies among those with PTSD, by highlighting the convergence of findings regarding the amygdala, anterior cingulate cortex (ACC), medial prefrontal cortex, insula, and hippocampus. The authors note that that findings “lend tentative support to a neurocircuitry model that emphasizes the role of dysregulation in threat-related processing” (p 379). A selection of specific structural and functional findings in support of this model are provided below.

In terms of structural imaging, findings suggest that PTSD is related to reduced hippocampal and ACC volumes.<sup>50</sup> Reported bilateral reductions in hippocampal volume have ranged from between 5% and 26%.<sup>62</sup> Gilbertson and colleagues<sup>24</sup> suggested that hippocampal volumes may represent a pre-existing, familial vulnerability to PTSD. Equivocal evidence in support of reduced bilateral amygdala volume, and limited findings regarding the insula have also been reported.<sup>50</sup> Recent work by Eckart and colleagues<sup>62</sup> noted reduced volume in the prefrontal and parietal regions of refugees with PTSD, and suggested that such disturbances along with

previously reported findings regarding the medial temporal region may highlight memory “disturbances” associated with PTSD.

Functional imaging studies in those with PTSD generally utilize symptom provocation or cognitive activation paradigms.<sup>50</sup> Symptom provocation entails the participant relating autobiographical information regarding their trauma history.<sup>50</sup> “Generally evocative” material may be also be used to elicit symptoms.<sup>50</sup> Cognitive activation paradigms are designed to assess dysfunction in “neural processes associated with PTSD” utilizing neuropsychological or neuroscience tasks (p 327).<sup>50</sup> Garfield and Liberzon<sup>50</sup> discuss the second strategy as being advantageous in that in that it generates a larger number of general or non-trauma-related responses without eliciting symptoms. Findings among those with PTSD demonstrated an exaggerated amygdala response, deficient prefrontal functioning, and decreased hippocampal activation.<sup>50</sup> The ACC and insula have been areas of focus, with repeated findings regarding reduced ACC activation among those with PTSD and emerging data regarding hyperactivation of the insula among anxious individuals.<sup>50</sup> Increased awareness of the interconnected nature of brain processes and the important role of receptors have further supported the use of functional imaging techniques among those with PTSD. Readers are encouraged to review the following publications for a more complete discussion of imaging and PTSD: Garfinkel and Liberzon,<sup>50</sup> Heim and Nemeroff,<sup>19</sup> Van Boven et al.<sup>37</sup>

## Co-occurring TBI and PTSD

As demonstrated above, TBI and PTSD are each individually complex conditions whose sequelae are contingent on a wide range of individual and systemic factors. Moreover, currently knowledge regarding the two conditions when they are co-occurring is limited. Recent studies suggest that the relationship between TBI and PTSD is complicated. In addition, to the above-noted challenges associated with differential diagnosis, there is mounting evidence that a history of TBI increases risk for developing PTSD.<sup>62</sup> Bryant and colleagues suggested that damage to the frontal regions of the brain may compromise neural networks which are required to regulate emotional experiences and as such predispose such patients to increased anxiety and depression.<sup>62</sup> Using functional imaging techniques Matthews and col-

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leagues<sup>57</sup> identified differences among OEF/OIF combat veterans with mild TBI and with and without MDD. The authors noted that significantly more subjects with MDD reported LOC, and suggested that this alteration in consciousness may uniquely contribute to the development of mental health conditions post-injury by exacerbating pre-existing vulnerabilities or independently increasing the probability of developing a mental health disorder such as depression or PTSD. Work conducted regarding cognitive processing during psychological trauma, such as the development of disorganized traumatic memories and PTSD, may be of use in increasing understanding regarding the increased rate of PTSD among those with TBI.<sup>47</sup> That is, alterations in consciousness associated with TBI may contribute to the development of disorganized traumatic memories and a subsequent increased risk for PTSD. Co-occurrence may also exacerbate existing symptoms. For example, frank neurological insult such as a TBI may exacerbate PTSD symptoms by creating an inability to self-regulate and inhibit behavioral responses.<sup>31</sup> Further study regarding the relationship between these two conditions is necessary to facilitate increased understanding and ultimately develop assessment and treatment strategies for those with co-occurring disorders.

## Conclusions and implications for clinical practice

Among those with TBI and/or PTSD neuropsychological measures in the context of a comprehensive evaluation may help clarify an individual's strengths and weaknesses. However, the overlap of cognitive disruption noted by those with PTSD and/or TBI suggests that such measures are unlikely to assist in differential diagnosis. This is certainly in part related to the "the complex interplay of neurological, psychological, and physical factors in veterans with [mild] TBI" and/or PTSD, and highlights the need for "specialized evaluation" and management (p 271).<sup>29</sup> This stance is supported by best practices outlined in the Departments of Veterans Affairs and Defense updated mild TBI clinical practice guidelines.<sup>64</sup> The fact that brain regions of interest (eg, hippocampus) are involved in complex cognitive processes such as learning and memory, and as such require a high degree of plasticity, are capable of "life-long neurogenesis," and are vulnerable to physical and emotional insult have created significant challenges for those studying or working

with individuals who have PTSD and/or TBI.<sup>37</sup> To assist, resources are being deployed to develop biomarkers for both conditions. Identification of such laboratory biomarkers may assist in the early identification of each of these conditions, and as such facilitate timely intervention. However, until such biomarkers are identified, clinicians will be required to rely upon data (eg, clinical history, neuropsychological testing results, neuroimaging findings) which may or may not result in a definitive diagnosis.

The lack of definitive biomarkers can also place clinicians in the challenging position of determining how and when to use existing experimental data and/or employ newer imaging techniques in clinical practice. In terms of imaging, experts in the field would suggest that caution is warranted until our understanding and ability to integrate findings catches up with our ability to produce such data.<sup>58-60</sup> As our knowledge regarding individual risk factors, neural networks, genotypes, and gene expression patterns grows, so may our ability to effectively use both neuroimaging and neuropsychological findings in clinical practice. In the aim of benefiting those with TBI and/or PTSD, experts in the field (eg, clinicians and researchers) should be encouraged to work together to identify means of translating experimental findings to clinical practice. For those with PTSD, understanding may also be enhanced by continued exploration of the neurobiology and neuropsychology of specific symptoms or symptoms clusters versus PTSD on whole.<sup>65</sup> This focus may also allow for more individualized treatment approaches.

While awaiting the above-described advances, clinicians should be encouraged to include measures of functioning (eg, cognitive, psychosocial) when assessing the impact of a condition. Such measures are frequently employed in the TBI community, and may be of use when evaluating those with co-occurring psychiatric conditions or PTSD. Further study regarding such measures among those with mild TBI and/or PTSD is warranted. Clinicians are also encouraged to contact family members and friends to obtain collateral information regarding their clients' everyday functioning.

In summary, the recent advances in neuroimaging, coupled with the high number of United States military personnel returning from Iraq and Afghanistan with TBI and/or PTSD, have resulted in an increased focus on the neurobiological and neuropsychological underpinning of these two conditions. As data becomes available, so

must guidance regarding how to employ new findings in clinical practice. At present, use of neuroimaging and neuropsychological/psychological test results can certainly assist with diagnosis and treatment planning, par-

ticularly for those moderate to severe TBI. Nevertheless, further work is needed to identify objective biomarkers to facilitate this process among those with one or both of these conditions. □

### **Hallazgos neuropsicológicos y de neuroimágenes en el daño cerebral traumático y el trastorno por estrés postraumático**

*El aumento del interés en la neuropsicología y la neurobiología del daño cerebral traumático (DCT) y del trastorno por estrés postraumático (TEPT) se ha facilitado por los progresos en la tecnología de las imágenes y el retorno del personal militar, desde Irak y Afganistán, con una o ambas de estas condiciones. El diagnóstico diferencial ha constituido un foco de especial interés. Este artículo entrega una panorámica de los hallazgos relacionados con las bases neuropsicológicas y neurobiológicas del DCT y/o del TEPT. Se hace mención específica a la evaluación que emplea mediciones neuropsicológicas y técnicas de imágenes. También se discuten los desafíos asociados con la evaluación de sujetos con una o ambas condiciones. Aunque el empleo de resultados de las pruebas neuropsicológicas y de las neuroimágenes pueden ayudar con el diagnóstico y la planificación del tratamiento, se requiere de trabajos adicionales para identificar biomarcadores objetivos para cada patología. Es de esperar que tales avances faciliten el diagnóstico diferencial y la implementación de las mejores prácticas terapéuticas.*

### **Neuro-imagerie et neuropsychologie des lésions cérébrales traumatiques et du syndrome de stress post-traumatique**

*Les avancées en imagerie, associées au retour des militaires d'Irak et d'Afghanistan atteints de lésions cérébrales traumatiques (LCT) et/ou d'un état de stress post-traumatique (ESPT), ont entraîné un regain d'intérêt pour l'étude de la neuropsychologie et la neurobiologie de ces deux pathologies. Le diagnostic différentiel a été l'objet d'une attention particulière. Cet article propose une revue des connaissances actuelles concernant les anomalies neuropsychologiques et neurobiologiques sous-tendant les LCT et/ou les ESPT et en particulier de l'évaluation au moyen de mesures neuropsychologiques et de techniques d'imagerie. Nous analysons également les difficultés associées à l'évaluation des individus atteints d'une ou des deux pathologies. Bien que l'utilisation des résultats des tests de neuropsychologie et de neuro-imagerie puisse aider au diagnostic et à la mise en place du traitement, il faut encore travailler pour identifier des biomarqueurs objectifs de chaque pathologie. De tels progrès sont attendus pour permettre un diagnostic différentiel et la mise en œuvre de meilleurs traitements.*

## REFERENCES

1. Kaplan G B, Vasterling JJ, Vedak PC. Brain-derived neurotrophic factor in traumatic brain injury, post-traumatic stress disorder, and their comorbid conditions: role in pathogenesis and treatment. *Behav Pharmacol*. 2010;21:427-437.
2. Redell JB, Zhao J, Dash PK. Altered expression of miRNA-21 and its targets in the hippocampus after traumatic brain injury. *J Neurosci Res*. 2011;89:212-221.
3. Kraus MF, Susmaras T, Caughlin BP, et al. White matter integrity and cognition in chronic traumatic brain injury: a diffusion tensor imaging study. *Brain*. 2007;130(Pt 10):2508-2519.
4. Traumatic Brain Injury (2010). Available at: <http://www.cdc.gov/traumaticbraininjury>. Atlanta, Ga: Centers for Disease Control and Prevention. Accessed March 12, 2011.
5. Terrio H, Brenner L A, Ivins BJ, et al. Traumatic brain injury screening: preliminary findings in a U.S. Army brigade combat team. *J Head Trauma Rehab*. 2009;24:14-23.
6. Vasterling JJ, Proctor SP, Amoroso P, Kane R, Heeren T, White RF. Neuropsychological outcomes of army personnel following deployment to the Iraq war. *JAMA*. 2006;296:519-529.
7. Hicks RR, Fertig SK, Desrocher RE, Koroshetz WJ, Pancrazio JJ. Neurological effects of blast injury. *J Trauma*. 2010; 65:1257-1263.
8. Levi L, Borovich B, Guilburd JN, et al. Wartime neurosurgical experiences in Lebanon, 1982-1985. II: Closed craniocerebral injuries. *Isr J Med Sci*. 1990;10:555-558.
9. Bush BA, Novack TA, Malec JF, et al. Validation of a model for evaluating outcome after traumatic brain injury. *Arch Phys Med Rehabil*. 2003;84:1803-1807.
10. Senathi-Raja D, Ponsford J, Schönberger M. Impact of age on long-term cognitive function after traumatic brain injury. *Neuropsychology*. 2010;24:336-344.
11. Bercaw EL, Hanks RA, Millis SR, et al. Changes in neuropsychological performance after traumatic brain injury from inpatient rehabilitation to 1-year follow-up in predicting 2-year functional outcomes. *Clin Neuropsychol*. 2011;25:72-89.

# Clinical research

12. Belanger HG, Curtiss G, Demery JA, Lebowitz BK, Vanderploeg RD. Factors moderating neuropsychological outcomes following mild traumatic brain injury: a meta-analysis. *J Int Neuropsychol Soc.* 2005;11:215-227.
13. Benedictus MR, Spikman JM, van der Naalt J. Cognitive and behavioral impairment in traumatic brain injury related to outcome and return to work. *Arch Phys Med Rehabil.* 2010;91:1436-1441.
14. Newsletter. Available at: <http://pascrell.house.gov/work/TBI%20Newsletter%202010.pdf>. Congressional Brain Injury Task Force (2010). Washington, DC: Accessed December 22, 2010.
15. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed, Text Revision. Washington, DC: American Psychiatric Association; 2000.
16. Jovanovic T, Ressler KJ. How the neurocircuitry and genetics of fear inhibition may inform our understanding of PTSD. *Am J Psychiatry.* 2010;167:648-662.
17. McNally RJ. Experimental approaches to cognitive abnormality in post-traumatic stress disorder. *Clin Psychol Rev.* 1998;18, 971-982.
18. Banich MT, Mackiewicz KL, Depue BE, et al. Cognitive control mechanisms, emotion and memory: a neural perspective with implications for psychopathology. *Neurosci Biobehav Rev.* 2009;33:613-630.
19. Heim C, Nemeroff CB. Neurobiology of posttraumatic stress disorder. *CNS Spectr.* 2009;14(suppl):13-24.
20. Langeland W, Olff M. Psychobiology of posttraumatic stress disorder in pediatric injury patients: a review of the literature. *Neurosci Biobehav Rev.* 2008;32:161-174.
21. Gunnar M, Quevedo K. The neurobiology of stress and development. *Annu Rev Psychol.* 2007;58:145-173.
22. Vasterling JJ, Proctor SP. Understanding the neuropsychological consequences of deployment stress: a public health framework. *J Int Neuropsychol Soc.* 2011;17:1-6.
23. Southwick SM, Davis LL, Aikins DE, Rasmuson A, Barron J, Morgan CA. Neurobiological alterations associated with PTSD. In: Friedman MJ, Keane TJ, Resick PA, eds. *Handbook of PTSD: Science and Practice*. New York, NY: Guilford Press; 2007:166-189.
24. Gilbertson MW, Shenton ME, Ciszewski A, et al. Smaller hippocampal volume predicts pathological vulnerability to psychological trauma. *Nat Neurosci.* 2002;5:1242-1247.
25. van Zuiden M, Geuze E, Willems HL, et al. Pre-existing high glucocorticoid receptor number predicting development of posttraumatic stress symptoms after military deployment. *Am J Psychiatry.* 2011;168:89-96.
26. Gilbertson MW, Paulus LA, Williston SK, et al. Neurocognitive function in monozygotic twins discordant for combat exposure: relationship to post-traumatic stress disorder. *J Abnorm Psychol.* 2006;115:484-495.
27. Vasterling JJ, Duke LM, Brailey K, et al. Attention, learning, and memory performances and intellectual resources in Vietnam veterans: PTSD and no disorder comparisons. *Neuropsychology.* 2002;16:5-14.
28. Brenner LA, Ivins BJ, Schwab K, et al. Traumatic brain injury, posttraumatic stress disorder, and postconcussive symptom reporting among troops returning from Iraq. *J Head Trauma Rehabil.* 2010;25:307-312.
29. Benge JF, Pastorek NJ, Thornton G M. Post concussive symptoms in OEF/OIF veterans: Factor structure and impact of posttraumatic stress. *Rehabil Psychol.* 2009;54:270-278.
30. Marx BP, Brailey K, Proctor SP, et al. Association of time since deployment, combat intensity, and posttraumatic stress symptoms with neuropsychological outcomes following Iraq war deployment. *Arch Gen Psychiatry.* 2009;66:996-1004.
31. Nelson LA, Yoash-Gantz RE, Pickett TC, Campbell TA. Relationship between processing speed and executive functioning performance among OEF/OIF veterans: implications for postdeployment rehabilitation. *J Head Trauma Rehabil.* 2009;24:32-40.
32. McNally R. Cognitive abnormalities in post-traumatic stress disorder. *Trends Cogn Sci.* 2006;10:271-277.
33. McRea MA. *Mild Traumatic Brain Injury and Post Concussive Syndrome: the New Evidence Base for Diagnosis and Treatment*. USA: Oxford University Press; 2007.
34. McRea MA, Guskiewicz KM, Marshall SW, et al. Acute effects and recovery time following concussion in collegiate football players: the NCAA Concussion Study. *JAMA.* 2003; 290:2556-2563.
35. Frencham KA, Fox AM, Mayberry MT. Neuropsychological studies of mild traumatic brain injury: A meta-analytic review of research since 1995. *J Clin Exp Neuropsychol.* 2005;27:334-351.
36. Brenner LA, Terrio H, Homaifar BY, et al. Neuropsychological test performance in soldiers with blast-related mild TBI. *Neuropsychology.* 2010;24:160-167.
37. Van Boven RW, Harrington GS, Hackney DB, et al. Advances in neuroimaging of traumatic brain injury and posttraumatic stress disorder. *J Rehabil Res Dev.* 2009;46:717-757.
38. Belanger HG, Spiegel E, Vanderploeg RD. Neuropsychological performance following a history of multiple self-reported concussions: a meta-analysis. *J Int Neuropsychol Soc.* 2010;16:262-267.
39. Draper K, Ponsford J. Cognitive functioning ten years following traumatic brain injury and rehabilitation. *Neuropsychology.* 2008;22:618-625. <http://psycnet.apa.org/journals/neu/22/5/618/>. Accessed February 28, 2011.
40. Mathias JL, Wheaton P. Changes in attention and information-processing speed following severe traumatic brain injury: a meta-analytic review. *Neuropsychology.* 2007;21:212-223.
41. Marx BP, Doron-Lamarca S, Proctor SP, Vasterling JJ. The influence of pre-deployment neurocognitive functioning on post-deployment PTSD symptom outcomes among Iraq-deployed Army soldiers. *J Int Neuropsychol Soc.* 2009;15:840-852.
42. Aupperle RL, Melrose AJ, Stein MB, et al. Executive function and PTSD: Disengaging from trauma. *Neuropharmacology.* doi10.1016/j.neuropharm.2011.02.008.
43. Twamley EW, Hami S, Stein MB. Neuropsychological function in college students with and without posttraumatic stress disorder. *Psychiatry Res.* 2004;126:265-274.
44. Bremner JD, Randall P, Scott TM, et al. Deficits in short-term memory in adult survivors of childhood abuse. *Psychiatry Res.* 1995;59:97-107.
45. Samuelson KW, Neylan TC, Metzler TJ, et al. Neuropsychological functioning in posttraumatic stress disorder and alcohol abuse. *Neuropsychology.* 2006;20:716-726.
46. Moores KA, Clark CR, McFarlane AC, et al. Abnormal recruitment of working memory updating networks during maintenance of trauma-neutral information in post-traumatic stress disorder. *Psychiatry Res.* 2008;163:156-170.
47. Halligan SL, Michael T, Clark DM, et al. Posttraumatic stress disorder following assault: the role of cognitive processing, trauma memory, and appraisals. *J Consult Clin Psychol.* 2003;71:419-431.
48. Milad MR, Orr SP, Lasko NB, Chang Y, Rauch SL, Pitman PK. Presence and acquired origin of reduced recall for fear extinction in PTSD: results of a twin study. *J Psychiatr Res.* 2008;42:515-520.
49. Milad MR, Pitman RK, Ellis CB, et al. Neurobiological basis of failure to recall extinction memory in posttraumatic stress disorder. *Biol Psychiatry.* 2009;66:1075-1082.
50. Garfinkel SN, Liverzon I. Neurobiology of PTSD: A review of neuroimaging findings. *Psychiatric Annals.* 2009;39:370-372, 376-381.
51. Peskind ER, Petrie EC, Cross DJ, et al. Cerebrocerebellar hypometabolism associated with repetitive blast exposure mild traumatic brain injury in 12 Iraq war Veterans with persistent post-concussive symptoms. *Neuroimage.* 2011;54(suppl 1):S76-S82.
52. Duckworth JL, Stevens RD. Imaging brain. *Curr Opin Crit Care.* 2010;16:92-97.
53. Rosenfeld J V, Ford N L. Bomb blast, mild traumatic brain injury and psychiatric morbidity: a review. *Injury.* 2009;41:437-443.
54. Belanger HG, Vanderploeg RD, Curtiss G, et al. Recent neuroimaging techniques in mild traumatic brain injury. *J Neuropsychiatry Clin Neurosci.* 2007;19:5-20.
55. Brenner LA, Ladley-O'Brien SE, Harwood JE, et al. An exploratory study of neuroimaging, neurologic, and neuropsychological findings in veterans with traumatic brain injury and/or posttraumatic stress disorder. *Mil Med.* 2009;174:347-352.
56. Niogi SN, Mukherjee P, Ghajar J, et al. Extent of microstructural white matter injury in postconcussive syndrome correlates with impaired cognitive reaction time: a 3T diffusion tensor imaging study of mild traumatic brain injury. *Am J Neuroradiol.* 2008;29:967-973.

57. Matthews SC, Strigo IA, Simmons AN, et al. A multimodal imaging study in U.S. veterans of Operations Iraqi and Enduring Freedom with and without major depression after blast-related. *Neuroimage*. 2011;54(suppl 1):S69-S75.
58. Niogi SN, Mukherjee P. Diffusion tensor imaging of mild traumatic brain injury. *J Head Trauma Rehabil*. 2010;25:241-255.
59. Wortzel H, Kraus MF, Filley CM, Andeson CA, Arciniegas DB. Forensic applications and single-subject use of diffusion tensor imaging in mild traumatic brain injury. *Amer Acad Psychiatry Law*. In press.
60. Adinoff B, Devous M. Scientifically unfounded claims in diagnosing and treating patients [letter]. *Am J Psychiatry*. 2010;167:598.
61. Shin LM, Shin PS, Heckers S, Krangel TS, et al. Hippocampal function in posttraumatic stress disorder. *Hippocampus*. 2004;14:292-300.
62. Eckart C, Stoppel C, Kaufmann J, et al. Structural alterations in lateral prefrontal, parietal and posterior midline regions of men with chronic post-traumatic stress disorder. *J Psychiatry Neurosci*. 2011;36:176-186.
63. Bryant RA, O'Donnell ML, Creamer M, McFarlane AC, Clark CR, Silove D. The psychiatric sequelae of traumatic injury. *Am J Psychiatry*. 2010;167:312-20.
64. Management of concussion. Department of Veterans Affairs/Department of Defense Evidence Based Practice (2009). Available at: [http://www.healthquality.va.gov/mtbi/concussion\\_mtbi\\_full\\_1\\_0.pdf](http://www.healthquality.va.gov/mtbi/concussion_mtbi_full_1_0.pdf). Washington, D.C.: Accessed on March 14, 2011.
65. Norrholm SD, Jovanovic T. Tailoring therapeutic strategies for treating posttraumatic stress disorder symptom clusters. *Neuropsychiatr Dis Treat*. 2010;6:517-532.
66. Hopper JW, Frewen PA, van der Kolk BA, et al. Neural correlates of reexperiencing, avoidance, and dissociation in PTSD: symptom dimensions and emotion dysregulation in responses to script-driven trauma injury. *J Trauma Stress*. 2007;20:713-725.
67. Weiss SJ. Neurobiological alterations associated with traumatic stress. *Perspect Psychiatric Care*. 2007;43:114-122.
68. Lezak MD, Howieson DB, Loring DW. *Neuropsychological Assessment*. New York, NY: Oxford University Press; 2004.
69. Shin LM, Lasko NB, Macklin ML, et al. Resting metabolic activity in the cingulate cortex and vulnerability to posttraumatic stress disorder. *Arch Gen Psychiatry*. 2006;66:1099-1107.
70. Willmott C, Ponsford J, Hocking C, et al. Factors contributing to attentional impairments after traumatic brain injury. *Neuropsychology*. 2009;23:424-432.
71. Golier J, Yehuda R. Neuropsychological processes in post-traumatic stress disorder. *Psychiatr Clin North Am*. 2002;25:295-315.
72. Vasterling JJ, Brailey K, Constans JI, et al. Attention and memory dysfunction in posttraumatic stress disorder. *Neuropsychology*. 1998;12:125-133.
73. Levin HS, Chapman SB. Aphasia after TBI. In: Sarno MT, ed. *Acquired Aphasia*. 3rd ed. San Diego, CA: Academic Press;1998;481-529.
74. Vanderploeg RD, Crowell TA, Curtiss G. Verbal learning and memory deficits in TBI: encoding, consolidation, and retrieval. *J Clin Exp Neuropsychology*. 2001;23:85-195.
75. van Praag HM. The cognitive paradox in posttraumatic stress disorder: a hypothesis. *Prog Neuropsychopharmacol Biol Psychiatry*. 2004;28:923-935.