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The role of biomarkers and MEG-based imaging markers in the diagnosis of post-traumatic stress disorder and blast-induced mild traumatic brain injury

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Summary
Background: Pervasive use of improvised explosive devices (IEDs), rocket-propelled grenades, and land mines in the recent conflicts in Iraq and Afghanistan has brought traumatic brain injury (TBI) and its impact on health outcomes into public awareness. Blast injuries have been deemed signature wounds of these wars. War-related TBI is not new, having become prevalent during WWI and remaining medically relevant in WWII and beyond. Medicine's past attempts to accurately diagnose and disentangle the pathophysiology of war-related TBI parallels current lines of inquiry and highlights limitations in methodology and attribution of symptom etiology, be it organic, psychological, or behavioral. New approaches and biomarkers are needed.
Preclinical: Serological biomarkers and biomarkers of injury obtained with imaging techniques represent cornerstones in the translation between experimental data and clinical observations. Experimental models for blast related TBI and PTSD can generate critical data on injury threshold, for example for white matter injury from acceleration. Carefully verified and validated models can be evaluated with gene expression arrays and proteomics to identify new candidates for serological biomarkers. Such models can also be analyzed with diffusion MRI and microscopy in order to identify criteria for detection of diffuse white matter injuries, such as DAI (diffuse axonal injury). The experimental models can also be analyzed with focus on injury outcome in brain stem regions, such as locus coeruleus or nucleus raphe magnus that can be involved in response to anxiety changes.

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Clinical: Mild (and some moderate) TBI can be difficult to diagnose because the injuries are often not detectable on conventional MRI or CT. There is accumulating evidence that injured brain tissues in TBI patients generate abnormal low-frequency magnetic activity (ALFMA, peaked at 1—4 Hz) that can be measured and localized by magnetoencephalography (MEG). MEG imaging detects TBI abnormalities at the rates of 87% for the mild TBI, group (blast-induced plus non-blast causes) and 100% for the moderate group. Among the mild TBI patients, the rates of abnormalities are 96% and 77% for the blast and non-blast TBI groups, respectively. There is emerging evidence based on fMRI and MEG studies showing hyper-activity in the amygdala and hypo-activity in prefrontal cortex in individuals with PTSD. MEG signal may serve as a sensitive imaging marker for mTBI, distinguishable from abnormalities generated in association with PTSD. More work is needed to fully describe physiological mechanisms of post-concussive symptoms.
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1. Background

Blast injuries are deemed the signature wounds of the first wars (Afghanistan and Iraq) of the 21st century (Lancet, 2007; Galarneau et al., 2008). According to a recent U.S. Department Veterans Affairs (DVA) and Defense (DoD) report, 12—23% of returning service members reported a TBI during deployment (O'Neil et al., 2013). Of these, the majority are in the ''mild'' range of severity (mTBI) (Centers for Disease Control and Prevention and National Center for Injury Prevention and Control 2003; Hoge et al., 2009; O'Neil et al., 2013). A review of the literature from 20th century wars (WWI, WWII, Vietnam) shows that current lines of scientific inquiry regarding the etiology of those symptoms parallel earlier attempts to disentangle the pathophysiology of post-concussive symptoms (PCS) from mental health symptoms, and to distinguish mTBI from war-related mental health syndromes, such as PTSD (Jones et al., 2007). Moreover this literature highlights limitations in methodology and attribution of symptom etiology, be it organic, psychological, or behavioral, that remain a focus of investigations today (Myers, 1915; Fulton, 1942; Jones et al., 2007; Rosenfeld et al., 2013).

A particular challenge in disentangling the symptoms and physiology has been establishing a quantitative, unassailable diagnostic methodology for defining mTBI, such a distinguishing blood or imaging biomarker signature. Most studies have relied on self-report of a concussive event, and have defined mTBI clinically, using symptom-based criteria. Brain changes that may accompany mTBI have been hard to visualize using standard imaging methods (Huang et al., 2012). While neurocognitive tests are used clinically and can be helpful, authors of the recent U.S. DVA Report observed that only a few studies among those reviewed found an association between mTBI and cognitive deficits (O'Neil et al., 2013). However, longitudinal follow-up of military personnel initially evacuated to Longstuhl with mTBI (self-report of war-related brain injury event) showed that rates of disability 6—12 months after evacuation were high and outcomes worse, overall in those service members with mTBI, comparable to those of civilian cohorts or polytrauma patients with mTBI (MacDonald et al., 2014). MacDonald et al. found no substantial differences in cognition between the evacuated personnel with and without a history of mTBI, however rates of PTSD and depression were higher in the mTBI group (MacDonald et al., 2014).

A substantial number of cross-sectional studies have shown higher (nearly double) rates of PTSD in individuals with mTBI, observed in both military (Hoge et al., 2008; Schneiderman et al., 2008; Luethcke et al., 2011; Vasterling et al., 2012; Rosenfeld et al., 2013) and civilian (Bryant et al., 2010; Mayou et al., 2000) settings. Moreover, these findings have been corroborated using prospective study designs in civilians (Roitman et al., 2013) and in active duty service members (Yurgil et al., 2014). In an 10 day and 8 month follow-up of civilians who presented to the emergency room as a result of motor vehicle accidents, some with mTBI (<30 min loss of consciousness) and some without, Roitman et al., showed that those with head injury and loss of consciousness (LOC) had higher levels of PTSD at follow-up. In the Marine Resiliency Study (MRS), a prospective, longitudinal study, of Marines and Sailors assessed at pre-deployment and again at 3—6 months after a 7-month deployment to Iraq or Afghanistan rates of reported prior TBI were 56.8% at the pre-deployment interview, and rates of deployment-related TBI were 19.8%; of the deployment-related TBIs approximately 87.2% were mild (Baker et al., 2012; Yurgil et al., 2014). As was observed in the civilian study, war-related mTBI significantly increased post-deployment PTSD symptom scores, either doubling or nearly doubling the PTSD rates in combatants who, prior to deployment, had been mentally healthy (Yurgil et al., 2014).

These two prospective studies provide accumulating evidence that mTBI is a robust prognostic indicator of subsequent PTSD development, raising the question as to the underlying cause. Whereas heightened emotional salience of traumatic events that involve blast/concussive injuries versus those without may, in part, provide an explanation for higher PTSD rates after mTBI, another likely, or perhaps even primary explanation may be that mTBI associated structural and functional brain changes increase vulnerability for development of mental disorders such as PTSD (Yurgil et al., 2014). Damage of the mTBI prefrontal cortical networks implicated in PTSD has been suggested as a possible cause of the increased vulnerability (Hoffman and Harrison, 2009; Yurgil et al., 2014).

Pre-clinical studies, as described below, focused on the pathophysiology and mechanisms of neurotrauma may contribute important information regarding mTBI associated brain changes that may contribute to PTSD development. These studies are needed to form a solid scientific basis