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Review

Functional magnetic resonance imaging of mild traumatic brain injury

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ABSTRACT

Functional magnetic resonance imaging (fMRI) offers great promise for elucidating the neuropathology associated with a single or repetitive mild traumatic brain injury (mTBI). The current review discusses the physiological underpinnings of the blood-oxygen level dependent response and how trauma affects the signal. Methodological challenges associated with fMRI data analyses are considered next, followed by a review of current mTBI findings. The majority of evoked studies have examined working memory and attentional functioning, with results suggesting a complex relationship between cognitive load/attentional demand and neuronal activation. Researchers have more recently investigated how brain trauma affects functional connectivity, and the benefits/drawbacks of evoked and functional connectivity studies are also discussed. The review concludes by discussing the major clinical challenges associated with fMRI studies of brain-injured patients, including patient heterogeneity and variations in scan-time post-injury.

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1. Introduction

Recently, there has been a dramatic change in thought regarding the physiological consequences of concussion, also referred to as mild traumatic brain injury (mTBI). It was initially believed that mTBI resulted in limited behavioral and no long-term neurological consequences (Pellman et al., 2004), except for in a small percentage of patients with pre-existing psychiatric conditions. Standard clinical neuroimaging methods (computed tomography scans; T_1- and T_2-weighted images) are typically negative for the majority of concussed patients (Hughes et al., 2004; Iverson, 2006), which helped propagate the view that mTBI did not lead to frank neuronal pathology. However, more recent studies suggest that the life-long effects of concussion, especially when repetitive, may be more severe than initially believed, predominantly a result of the dramatic increase in the diagnoses of chronic traumatic encephalopathy (CTE) amongst recently deceased athletes (McKee et al., 2013). A proliferation of neuroimaging studies of mTBI has also occurred, with different imaging modalities finding that neuronal pathology may be present long after traditional outcome measures (e.g., balance and neuropsychological testing) have returned to pre-morbid levels of functioning (Belanger et al., 2007; Bigler, 2013; Bigler and Maxwell, 2012; Mayer et al., 2011). However, a more realistic assessment of the field suggests a nascent understanding of the neuronal and behavioral consequences of both single and repetitive mTBIs in humans, with several key challenges remaining to be resolved.

The goals of the current review are to provide the reader with a more thorough appreciation for the challenges of conducting functional magnetic resonance imaging (fMRI) studies in mTBI. We begin with a discussion of the physiological underpinnings of the blood-oxygen level dependent (BOLD) response, how mTBI may alter it, and the analytic strategies through which researchers attempt to non-invasively capture the effects of neuronal injury. The mTBI literature using both task-based (i.e., evoked) paradigms as well as resting state measurements (i.e., functional connectivity) is reviewed next. Finally, the many methodological challenges associated with fMRI studies of brain-injured patients are discussed from a clinical perspective. Although some groups have made a distinction between the terms concussion and mTBI based on injury severity (reviewed in Harmon et al., 2013), for the purpose of the current paper these terms are used inter-changeably.

2. fMRI physiology and putative effects of trauma

The relation between neuronal activity and the resultant hemodynamic response (i.e., neurovascular coupling) remains a topic of active investigation. The cerebral metabolic rate of glucose (CMR_{glu}), the cerebral metabolic rate of oxygen ($CMRO_2$) and cerebral blood flow (CBF) are tightly coupled in the absence of evoked neuronal activity. There is an increase in metabolic demands/energy requirements following excitatory neuronal transmission, and excess glutamate must be rapidly removed from the synaptic cleft (Attwell et al., 2010; Logothetis, 2008). Astrocytes convert excess glutamate into glutamine and release vasoactive agents, with neurons concurrently releasing nitric oxide (Attwell et al., 2010). These events all contribute to vasodilation and an increase in CBF, followed by a concomitant decoupling between CBF and oxidative metabolism. All of these events ultimately culminate in an excess of oxygenated blood, a decrease in the ratio of deoxyhemoglobin relative to oxyhemoglobin, and a subsequent increase in MR signal due to differences in magnetic properties between the two forms of hemoglobin. Thus, the BOLD response during normal neurovascular coupling represents an amalgamation of signals derived primarily from the ratio of oxy- to deoxyhemoglobin, with contributions from CBF and cerebral blood volume (CBV).

The resultant shape of the BOLD response is similarly complex in nature. The canonical hemodynamic response function (HRF) consists of two primary components, a positive signal change that peaks approximately 4–6 s after stimulus onset, and a post-stimulus undershoot (PSU) that reaches maximum 6–10 s after stimulus end. As previously discussed, the positive phase of the BOLD response has been associated with an increase in CBF, and the resultant change in the ratio of oxy- to deoxyhemoglobin intravascularly (Buxton et al., 2004). The biophysical origins of the PSU are less well established. An early model attributed the PSU to differences in timing of the return of CBF (earlier response) and CBV (delayed response) to baseline levels (Buxton et al., 2004). However, other work indicates that the duration of the PSU extends beyond the time when CBV returns to baseline, leading others to suggest increased demands for $CMRO_2$ as a contributing factor (Schroeter et al., 2006).

Thus, there are several different mechanisms, as well as interactions between mechanisms, through which head trauma can affect the BOLD response (Barkhoudarian et al., 2011). When discussing pre-clinical studies of trauma, it is critical to consider that animal models that accurately represent the mechanical forces experienced in milder forms of human mTBI have only been recently developed (Angoa-Pérez et al., 2014; Chen et al., 2012; Kane et al., 2012; Viano et al., 2009; Xiong et al., 2013). Specifically, most animal models frequently require invasive neurosurgical procedures (i.e., opposed to a true closed-head injury) and induce cortical contusions or other parenchymal alterations of sufficient severity that they are visible with MR, suggestive of more severe injuries in human TBI (Hughes et al., 2004). Critically, these models do not include the rapid acceleration/deceleration and loading factors on the brain that are more typical in human mTBI (Kane et al., 2012; Viano et al., 2009). In addition, non-specific effects of trauma (e.g., pain and fatigue), as well as the presence of prescribed medications (e.g., narcotics or sedatives), can also alter neurovascular coupling following mTBI in both human and animal models of injury.

Principally, trauma can cause frank neuronal dysfunction (e.g., alterations in synchronous excitatory neuronal activity), resulting in down-stream effects on BOLD-based activity through changes in the amount of glutamate in the synaptic cleft and the energetic needs of cells following neurotransmission. Reports of neuronal loss in animal models of fluid percussion injury (Lowenstein et al., 1992) and abnormal cell signaling (Alwis et al., 2012) directly support this hypothesis. Indirect support comes from magnetic resonance spectroscopy findings of altered glutamate and glutamine concentrations in the semi-acute stage (i.e., first few months of injury) of mTBI, as well as through more invasive measures during severe injury models (Hartley et al., 2008; Henry et al., 2011; Yeo et al., 2011).

The structural integrity of the microvasculature can also be directly affected by trauma. Fluid percussion studies in animal models indicate a semi-acute reduction in capillary number and diameter both at the injury site and distally (Park et al., 2009), with several other studies indicating a reduction in cerebral vascular reactivity (Metting et al., 2009). Similarly, hemosiderin depositions, secondary to microhemorrhages and inflammation, have been noted in human cases of mTBI using both non-invasive neuroimaging as well as at autopsy (Bigler and Maxwell, 2012). TBI also directly affects CBF transit time as well as cerebral perfusion (Soustiel and Sviri, 2007). Researchers may capitalize on TBI-related changes in CBF through the use of both static and dynamic arterial spin labeling (ASL). Static ASL can be used to both directly measure CBF and calibrate the BOLD signal for CBF changes (Liau and Liu, 2009), although the measurements must be made in a quantitative

fashion. Whereas, dynamic ASL can be used as a contrast mechanism for resting state fMRI (Zou et al., 2009) and would likely be complementary to more standard BOLD resting state techniques.

Even in the presence of normal perfusion, metabolic failure may occur after TBI (Vespa et al., 2007). Specifically both animal and human models suggest an initial decoupling between CBF and CMR_{glu}, followed by a generally reduced cerebral metabolism after injury (Giza and Hovda, 2001; Soustiel and Sviri, 2007). Alterations in CBF and CMR_{glu} may be the most long-lasting effects of concussion (Giza and Hovda, 2001), providing a physiological basis for a more prolonged impairment (i.e., days to weeks post-injury) of the BOLD response following injury. A challenge for reconciling findings from animal and human studies is the frequent recording of physiological states in the absence of evoked activity and in the presence of anesthesia. As previously noted, resting state activity is associated with differential dynamics between BOLD constituents (e.g., CBF, $CMRO_2$ and CMR_{glu}) relative to more dynamic states (evoked activity). Anesthesia also affects neuronal activity, neurovascular coupling and CBF. Although there has been an effort to reduce or eliminate anesthesia protocols in animal imaging (Liang et al., 2011), this model is only starting to be applied to pre-clinical models of trauma. Additional animal studies that specifically examine how mTBI affects both intrinsic and evoked activity will greatly improve our knowledge of the true bench-to-bedside capabilities of the technique in a more controlled environment.

3. Methodological challenges associated with analyses

Given the known complexity of the BOLD response, there are several analytic considerations in fMRI research of mTBI. Foremost, both region of interest (ROI) and voxel-wise analyses inherently assume that heterogeneous initial injury conditions (e.g. motor vehicle accidents, a blow to the left temple, or a blast in combat) result in a homogeneous pattern (i.e., high degree of spatial overlap) of gray matter abnormalities. Specifically, to survive group-wise statistics, traditional ROI and voxel-wise analyses assume that resulting BOLD disruptions occur in the similar neuronal regions across patients. Although the diencephalon, mid-brain, limbic circuit and prefrontal cortex represent common sites of injury (Bigler and Maxwell, 2012; McAllister and Stein, 2010), the basic premise of this spatial homogeneity assumption is likely to be flawed. Novel approaches for classifying heterogeneous lesion locations are increasingly being sought as necessary bases for performing mTBI imaging research, and have been used to identify voxel-wise abnormalities in diffusion tensor imaging (DTI) (Bazarian et al., 2012; Kim et al., 2013; Mayer et al., 2014b). However, this approach has not been applied to BOLD imaging data, and the underlying assumptions are likely to be dependent on the statistical properties (e.g., sample size, distribution properties and normalcy) of the data (Mayer et al., 2014b).

Secondly, the majority of fMRI studies in both mild and more severe forms of TBI have typically estimated only a single parameter (e.g., a beta coefficient) by convolving an assumed canonical hemodynamic response function (HRF) with known experimental conditions (e.g., onset of a particular trial) to derive a predictor function (e.g., regressor). fMRI studies typically use either a gamma variate or a double gamma variate function as the canonical HRF shape, with the double gamma variate function having the additional benefit of modeling the PSU (Mayer et al., 2014a; Palmer et al., 2010). These standard regression analyses assume that the relationship between the positive phase and PSU are largely unaffected by mTBI, and that a single parameter adequately captures resultant alterations in the HRF. However, only a few studies have explicitly examined the shape of the HRF in mild (Mayer et al., 2014a) and more severe TBI (Palmer et al., 2010). Palmer and colleagues reported no differences in the basic shape of the HRF following more severe TBI, with patients exhibiting an increased volume of activation within the visual cortex during visual stimulation. Mayer and colleagues reported differences in the shape of the HRF in semi-acute mTBI patients and HC within the bilateral primary/secondary visual cortex, right supramarginal gyrus and the right parahippocampal gyrus during a sensorimotor task (Mayer et al., 2014a). In contrast, the HRF within auditory, motor and other heteromodal cortical areas was similar across the two groups. These results suggest the need for additional fMRI studies that explicitly compare the different phases of the HRF in both human and animal models.

Finally, fMRI data is financially costly to accumulate and mTBI patients who meet strict inclusion criteria (homogeneous in both injury severity and scan-time post-injury with no pre-existing psychiatric history) are challenging to recruit. Not surprisingly, the combination of these two factors has resulted in the utilization of small sample sizes for most fMRI studies of mTBI despite the inherently low signal-to-noise ratio of the technique (Logothetis, 2008). Specifically, the majority of fMRI studies following mTBI have been conducted with sample sizes that are below commonly accepted recommendations (Desmond and Glover, 2002), producing results that are underpowered, suffer from low positive predictive power and/or provide poor estimates of true effect sizes. All of these factors, in conjunction with clinical design, may contribute to the conflicting findings of hypo- and hyperactivation observed across different fMRI studies (reviewed in the following section). To combat this problem of small sample sizes, funding agencies have recently begun to develop standard clinical definitions, common data elements and informational platforms for creating community-wide data sharing initiatives (e.g., Federal Interagency Traumatic Brain Injury Research; FITBIR). These efforts should accelerate research in this critical area by permitting the pooling of fMRI data for use in meta-analyses as has been done in a recent review (Eierud et al., 2014).

4. Evoked fMRI findings in mTBI

fMRI offers great promise for elucidating the underlying neuropathology associated with neurobehavioral sequelae following mTBI, especially in conjunction with tasks that dynamically tap into higher-order cognitive functioning (McDonald et al., 2012). The seminal fMRI studies of mTBI utilized working memory paradigms, with results suggesting a complex relationship between cognitive load and functional activation. Specifically, McAllister et al. (1999, 2001) reported hyperactivation in right dorsolateral prefrontal cortex (DLPFC) and lateral parietal regions for mTBI patients compared to healthy controls (HC) under moderate processing loads (1-back to 2-back conditions). Hypoactivation was observed for lower processing loads (0- to 1-back conditions). Additional studies confirmed that mTBI patients exhibited frontoparietal hyperactivation in the moderate load condition, but also found hypoactivation at higher processing loads (going from 2- to 3-back). Similar to McAllister's findings, concussed athletes showed increased bilateral DLPFC and inferior parietal lobe activation during the 2 minus 1 N-back contrast (Dettwiler et al., 2014). Positive correlations between self-report measures of symptom severity and increased activation both within the working memory network (e.g., dorsolateral and ventrolateral prefrontal cortex) and other regions have also been reported, suggesting potential compensatory activation (Smits et al., 2008). In addition, another study utilizing the N-back task reported that abnormal hyperactivation one-week post-injury may be indicative of a prolonged recovery profile in athletes (Lovell et al., 2007).

Other studies have reported hypoactivation during working memory tasks following mTBI. Gosselin reported decreased BOLD

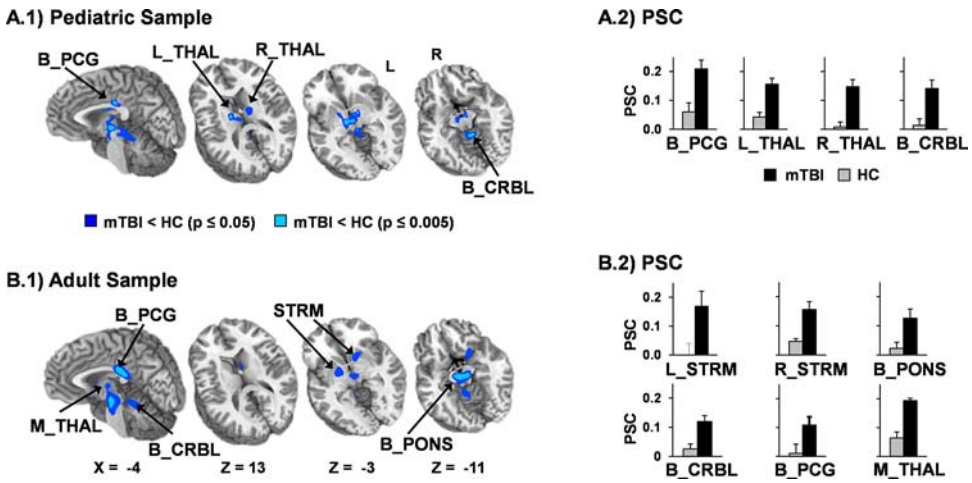

Fig. 1. This figure depicts regions of hypoactivation during an auditory orienting task across independent samples of pediatric and adult mild traumatic brain injury (mTBI) patients relative to age and education-matched healthy controls (HC). Panel A.1 presents regions showing significantly reduced activity for pediatric mTBI patients, with the magnitude of *p*-values denoted by either blue or cyan coloring. Locations of the sagittal (X) and axial (Z) slices are given according to the Talairach atlas (L = left and R = right) and are identical across both pediatric and adult samples. Panel A.2 exhibits percent signal change (PSC) data for selected regions for both patient (black bars) and control (gray bars) groups. Decreased activation for pediatric mTBI patients was observed within bilateral posterior cingulate gyrus (B_PCG), left and right thalamus extending into the basal ganglia (L_THAL and R_THAL), and bilateral cerebellum (B_CRBL). Data from adult mTBI patients and matched HC are presented in an identical scheme in Panels B.1 and B.2. Clusters of decreased activation for the adult mTBI sample included the posterior cingulate gyrus (B_PCG), right and left striatum (STRM), pons and midbrain nuclei (B_PONS), cerebellum (B_CRBL) and thalamus (M_THAL). Error bars correspond to the standard error of mean.

activation in the left and right mid-DLPFC (which correlated with symptom severity), the putamen, the body of the caudate nucleus, and the right thalamus, as well as a reduced N350 ERP amplitude following mTBI (Gosselin et al., 2011). Athletes with persistent post-concussive symptoms, imaged while performing both verbal and visual working memory tasks, also show hypoactivation in the DLPFC that was associated with the degree of symptomatology (Chen et al., 2004, 2007). Another study by Chen et al. (2008) reported that mTBI athletes with symptoms of depression showed bilateral DLPFC hypoactivation, as well as in striatum, and the severity of the depression symptoms correlated with activation in areas associated with major depression. Keightley et al. (2014) also reported hypoactivation in bilateral DLPFC, as well as in left premotor cortex, supplementary motor area, and left superior parietal lobule in concussed youths during verbal and nonverbal working memory task performance, with greater activities in bilateral DLPFC related to better performance.

Other studies have not observed differences between a relatively large cohort of mTBI patients ($N = 43$) and HC ($N = 20$) on a similar working memory task (N-back), instead finding that length of post-traumatic amnesia (PTA) was related to deactivation of the hippocampus (0-back > 2-back) (Stulemeijer et al., 2010). Another study reported that asymptomatic high school and college athletes who sustained two or more concussions (mean time post-recovery = approximately 9 months) showed no differences in regional brain activation during the N-back task (Elbin et al., 2012). The multiple methodological differences across studies, including auditory versus visual working memory, athletes versus emergency room patients, time post-injury, age sustained trauma, and operational definitions of symptom severity, provide a challenging context for combining study findings. However, a recent meta-analysis reported hyperactivation during tasks that require continuous working memory and hypoactivation during tasks that require discrete periods of working memory following mTBI (Bryer et al., 2013), which may explain some of these discrepant results.

Several evoked fMRI studies have also examined attentional and memory functioning following mTBI. Increased activation during attention tasks within the anterior cingulate gyrus, inferior frontal gyrus, insula and posterior parietal areas with an increased incidence of post-concussive symptoms was reported by Smits et al. (2008). In contrast, results from our group (Fig. 1) have indicated hypoactivation within several deep cortical, cerebellar and subcortical sites during an auditory attention task in independent adult (Mayer et al., 2009) and pediatric mTBI (Yang et al., 2012) cohorts. Within-group comparisons also indicated decreased frontoparietal activation for mTBI patients during more attentionally demanding conditions (Mayer et al., 2009). Similarly, we have also observed aberrant task-induced deactivation within the default-mode network (DMN; Fig. 2A) (Mayer et al., 2012) in addition to decreased cortical activation (Fig. 2B) for mTBI patients (within-subject comparisons) during a multimodal numeric Stroop task (Mayer et al., 2012). During detection of novel stimuli in a three-stimulus (standard, target, and novel stimuli) auditory oddball paradigm with low attentional demand, mTBI patients in another study exhibited decreased activation in the DMN and increased activation in right superior and inferior parietal areas (Witt et al., 2010). Slobounov et al. (2010) found increased volumes of activity within the DLPFC, parietal cortex and hippocampus during performance of a spatial memory task in recently concussed athletes relative to non-concussed HC. During relational memory, Ford et al. (2013) reported that behavioral performance did not differ in former professional football players with low and high concussion histories. However, concussion history did negatively affect the recruitment of different brain regions in the relational memory network.

Evoked fMRI studies have also utilized a pre- vs. post-injury design in athletes. For example, the effect of "sub-concussive hits" was recently investigated in high school football athletes scanned both pre- and post-season. Embedded helmet sensors were used to tally the number and magnitude of head hits throughout the season. Findings suggested that prolonged exposure to sub-concussive hits resulted in hypoactivation within left middle and superior temporal gyri, left middle occipital gyrus, and bilateral cerebellum during an N-back working memory task (Talavage et al., 2014), which correlated with poorer working memory performance in the non-concussed high school football players. In another pre- vs. post-injury fMRI study that involved mathematical, memory and motor coordination tasks, Jantzen et al. (2004) showed hyperactivation of frontal regions post-injury even in the absence of cognitive

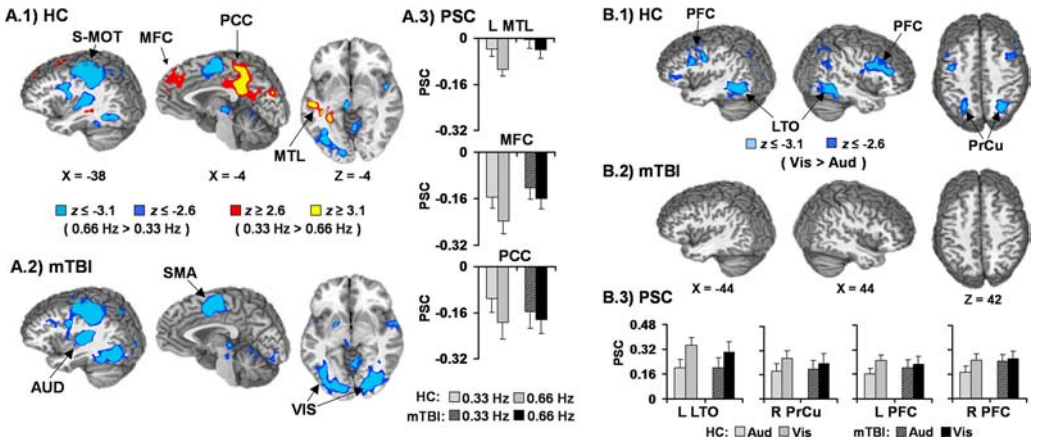

Fig. 2. This figure presents regions showing differential within-group activation between low (0.33 Hz) and high (0.66 Hz) frequency trials and between attend-visual (Vis) and attend-auditory (Aud) conditions for healthy controls (HC: Panels A.1 and B.1, respectively) and adult mild traumatic brain injury patients (mTBI: Panels A.2 and B.2, respectively). The overall task involved a multisensory Stroop task during which congruent and incongruent stimuli (auditory and visual numbers) were presented at low or high frequencies. The main effect of frequency (Panels A.1 and A.2) indicated increased activation during high frequency (blue/cyan coloring) trials for both groups within the bilateral primary and secondary auditory cortex (AUD), visual cortex (VIS), bilateral supplemental motor area (SMA), and bilateral sensorimotor cortex (S-MOT). In contrast, only HC demonstrated significantly greater deactivation within the default-mode network for high compared to low frequency (red/yellow coloring) trials. The regions included the left medial temporal lobes (L MTL), bilateral medial frontal cortex (MFC), and bilateral posterior cingulate gyrus (PCC), with percent signal change data (PSC) presented in Panel A.3 (mTBI patients (black bars) and HC (gray bars) during low (striped bars) and high (solid bars) frequency trials). Importantly, PSC for regions of interest were determined solely based on the unique areas of deactivation from HC in statistical parametric maps (Panel A.1 red/yellow colored regions). Increased activation for HC (Panel B.1) but not mTBI patients (Panel B.2) was observed in the bilateral prefrontal cortex (PFC), "what" (lateral temporal-occipital cortex; LTO) and "where" (precuneus/cuneus; PrCu) visual pathways during the attend-visual (Vis) relative to attend-auditory (Aud) conditions. Percent signal change (PSC) values for selected regions are presented in Panel B.3 for both mTBI (black bars) and HC (gray bars) during Aud (striped bars) and Vis (solid bars) conditions based on selected regions from Panel B.1 (HC group only). The magnitudes of z-scores are color-coded for all comparisons across all maps, with the locations of sagittal (X) and axial (Z) slices provided according to the Talairach atlas. Error bars in Panels A.3 and B.3 correspond to the standard error of mean.

performance differences on a variety of neurocognitive tests, suggestive of a compensatory mechanism.

Mild TBI represents a "signature wound" for military combatants in Operations Iraqi (OIF) and Enduring (OEF) Freedom (Hoge et al., 2008), and is one of the primary drivers behind the recent increase in public awareness for mTBI. Several task-based fMRI studies have also been conducted in military populations. One such study used event-related fMRI during a stimulus-response compatibility task (Scheibel et al., 2012), reporting that patients exhibited greater activation in the anterior cingulate gyrus, medial frontal cortex, and posterior cerebral areas involved in visual function relative to controls. A similar study was conducted to compare differences in response inhibition after combat blast-induced mild to moderate TBI relative to civilian injuries (Fischer et al., 2014). Results from this study indicated that the military TBI group evidenced increased activation in bilateral inferior temporal, left superior temporal, caudate, and cerebellar regions during inhibitory failures relative to a military control group. In contrast, the civilian impact-related TBI group exhibited hypoactivation in these same areas relative to a civilian control group, suggesting different neuropathology for blast relative to more traditional acceleration/deceleration or blunt-force trauma injuries. A recent study combined DTI and fMRI to examine differences in amygdala activation in response to emotional faces in concussed veterans of OEF/OIF with and without major depressive disorder (Matthews et al., 2011a,b). fMRI results demonstrated decreased activity in the amygdala in veterans with depression, which was associated with lower fractional anisotropy in several white matter tracts. The authors suggest that functional disruption may be the direct result of white matter pathology. This same group (Matthews et al., 2011a,b) examined the effects of brief loss vs. alteration of consciousness on inhibitory processing (a stop task) after blast-induced mTBI in OEF/OIF veterans. The patients who had loss of consciousness showed decreased activation in the ventromedial prefrontal cortex during easy trials, which related to less severe somatic symptoms, possibly due to a deficit in self-awareness.

A few studies have examined how treatment affects BOLD activity following mTBI. To investigate whether pharmacological challenges to the dopaminergic system may explain abnormalities in the working memory circuitry following mTBI, McAllister and colleagues examined performance during the N-back task following the administration of bromocriptine (a dopamine agonist) compared to placebo. They reported that mTBI patients did not show the same pattern of pharmacologically induced behavioral improvement seen in HC, with HC also exhibiting increased activation in the working memory circuitry relative to patients (McAllister et al., 2011a,b). In contrast, mTBI patients instead had higher activation in areas outside this working memory network when they were administered bromocriptine. When mTBI patients were placed on guanfacine, which indirectly affects dopamine transmission, a similar complex pattern of activations was observed within the working memory circuitry (McAllister et al., 2011a,b). Following cognitive rehabilitation therapy on visually guided saccades and reading comprehension tasks, others have demonstrated both increased and decreased activations in a relatively small sample of mTBI patients (Laatsch et al., 2004). Though in their preliminary stages, these studies suggest that BOLD-based activity may offer a mechanism for non-invasively measuring the effectiveness of treatment on the neurophysiological damage sustained from mTBI.

5. Intrinsic connectivity findings in mTBI

In addition to studies of evoked BOLD activity, researchers are increasingly turning to measures of intrinsic activity, or functional connectivity (fcMRI), to examine neuronal health following mTBI. Functional connectivity studies are based on neuronal fluctuations that occur synchronously over spatially distributed networks, and are found in both humans and animals. The majority (60–80%) of the brain's energy resources is expended to maintain homeostasis, with intrinsic neuronal activity likely contributing to this heavy metabolic load (Raichle and Mintun, 2006). Previous research

indicates that following TBI, changes in baseline metabolism occur, as well as abnormal slow-wave electrophysiological activity during passive mental activities (Huang et al., 2012; Lewine et al., 2007), providing biological relevance for fcMRI as a biomarker of mTBI.

During "resting state" scans, participants are asked to either close their eyes for a relatively brief period of time (approximately 5 min) or fixate on a visual stimulus. As a consequence of the simplicity of these instructions, resting state paradigms have been criticized based on the general lack of control over participant's mental activities and the inability to specify what cognitive tasks the participant actually performed during data collection. Similarly, the analyses of resting state data can be influenced by the various analytic approaches (e.g., seed-based analysis vs. independent component analysis (ICA) vs. graph theory metrics) that are used to parse network activation (Mannell et al., 2010). Noise also has a more direct influence on fcMRI relative to evoked studies due to the lack of independent predictor variables (Saad et al., 2012).

Advantages of resting state scans over more traditional evoked activation studies include the elimination of several confounds associated with task (e.g., poor effort, fatigue, differences in behavioral performance, learning effects, etc.), the ability to assay the neuronal integrity of multiple sensory, motor and cognitive networks in a relatively short period of time (Smith et al., 2009), and the ability to compare results across the entire TBI (e.g., mildest injury to minimally conscious patients) spectrum (Sharp et al., 2014). Some of the advantages of fcMRI may be larger during the acute to semi-acute stage of injury when cognitive deficits and neurobehavioral symptoms are expected to be the greatest. Most importantly, fcMRI eliminates the complex requirements for presenting sensory stimuli and monitoring motor responses (e.g., interfacing with a computer, projecting stimuli, special non-ferrous motor response devices), making it more feasible to perform fcMRI in clinical settings in a relatively short period of time.

To date, several fcMRI studies conducted in mTBI patients have focused on the connectivity within DMN, and between the DMN and other intrinsic connectivity networks (ICN). The DMN is characterized by nodes in the rostral anterior cingulate gyrus/ventromedial prefrontal cortex (rACC), posterior cingulate gyrus (PCC) and superior temporal/supramarginal gyrus (SMG), with the rACC and PCC serving as central hubs (Buckner et al., 2008; Sharp et al., 2014). The DMN mediates a variety of mental activities such as episodic memory review and future-oriented thought processes (Andrews-Hanna et al., 2010), and acts in conjunction with frontoparietal networks to produce states of high (decreased DMN/increased frontoparietal activity) or low (increased DMN/decreased frontoparietal activity) attentiveness to external events (Eichele et al., 2008; Hellyer et al., 2014).

In mTBI patients, reduced connectivity has been reported within the DMN in the semi-acute phase using a seed-based approach, with additional findings of increased connectivity between the rACC and ventrolateral prefrontal cortex (Mayer et al., 2011). These connectivity abnormalities remained relatively stable when retested approximately 4 months post-injury, in spite of normal recovery on neuropsychological evaluations and reduced self-reported symptoms. Another study utilizing ICA reported reduced connectivity in the posterior hubs (PCC and SMG) of the DMN in conjunction with increased connectivity within the ventromedial prefrontal cortex (Zhou et al., 2012). Similarly, generally reduced connections across multiple nodes of the DMN have been reported in recently concussed athletes relative to HC, as well as a larger departure from typical DMN connectivity as a function of the number of previous concussions (Johnson et al., 2012). However, a subsequent study by the same group did not find any significant differences within DMN connectivity unless a physical stress challenge was presented to recently concussed athletes (Zhang et al., 2012).

Functional connectivity studies have revealed abnormalities in other networks aside from the DMN following mTBI. Disrupted interhemispheric fcMRI has been reported in the visual cortex, hippocampus and DLPFC during task-based connectivity analyses (Slobounov et al., 2011), as well as decreased symmetry of connectivity based on thalamic seeds (Tang et al., 2011). Thalamic seed-based functional connectivity has also been used during both motor task and resting state, finding decreased thalamo-thalamo, thalamo-frontal, and thalamo-temporal connectivity during resting state and a lack of thalamo-motor connectivity during the motor task in mTBI (Zhou et al., 2014). This study also reported that the amplitude of low frequency fluctuations, defined as the total power in the lower end of the BOLD frequency range, was also affected in patients with mTBI (Zhou et al., 2014). Others report decreased functional connectivity within the motor-striatal network and increased connectivity in the right frontoparietal network during ICA analyses of mTBI (Shumskaya et al., 2012). Disrupted (both increased and decreased) connectivity in 30 semi-acutely injured mTBI patients across 12 different sensory and cognitive networks has been observed in persistent post-concussive syndrome (Stevens et al., 2012). In addition, abnormal fcMRI between the DMN, the task positive network (or the executive network), and the salience network has been found after mTBI injury (Sharp et al., 2014; Sours et al., 2013). Using ICA to examine resting-state fcMRI in blast-induced mTBI patients, Vakhtin et al. (2013) found weaker functional connections within six network pairs (DMN-basal ganglia, attention-sensorimotor, frontal-DMN, attention-sensorimotor, attention-frontal, and sensorimotor-sensorimotor).

Longitudinal changes in connectivity have also been described in some but not all studies. In mTBI patients with post-concussion syndrome, increased connectivity in temporal regions was seen at the subacute stage of injury, while decreased connectivity in frontal regions was seen at the chronic phase (Messe et al., 2013). Han et al. (2014) used module-based graph theoretic analysis in military personnel after blast-related mTBI and found abnormal modular organization of cortical functional connectivity in the semi-acute phase, yet found mixed findings in follow-up data during the chronic phase. Finally, others have reported relatively stable functional connectivity abnormalities over a 4 month period post-injury (Mayer et al., 2011). The variety of target networks investigated in the literature thus far support the view that fcMRI is well poised for interrogating connectivity following mTBI.

6. Overarching clinical challenges in fMRI research following mTBI

The initial sections briefly introduced several clinical challenges for conducting fMRI studies following mTBI, which are reviewed in greater detail here. Perhaps the largest challenge facing the field are the various definitions for diagnosing mTBI and/or concussion (Ruff et al., 2009; West and Marion, 2013), and the fact that these terms are sometimes used synonymously and at other times denote different injuries. Under these current different diagnostic nosologies, patients who are only dazed following a blow to the head, patients who are unconscious for up to 30 min, and patients with large subdural hematomas are all given the same diagnosis. However, the underlying neuropathology, neurobehavioral sequelae and recovery trajectory are likely to be very different across these patient types (Kashluba et al., 2008). For example, meta-analyses (as reviewed in Bigler, 2008) and large N studies (McCrea et al., 2003, 2013) have documented that the majority of single-episode mTBI patients exhibit a rapid and spontaneous recovery

within the first few days to weeks post-injury *on traditional neurobehavioral measures* (see discussion below), with 80–95% of adult patients fully recovered at 3–6 months post-injury. In contrast, recent results from the multi-center Transforming Research and Clinical Knowledge (TRACK) in TBI study suggest a longer duration of symptomatology (McMahon et al., 2014), which is likely reflective of differences in sampling strategies (e.g., patients released from ER vs. admitted patients) and injury severity levels.

Similarly, recent evidence suggests that there are likely to be differences in the neuropathology and course of recovery (short and long-term) between patients who receive a single mTBI (e.g., an emergency room cohort) and patients who received temporally proximal, repetitive mTBIs (e.g., athletes and military personnel). Athletes with a history of concussion report more baseline symptoms than those with no history of concussion (Harmon et al., 2013). Repeat concussions within the same sports season increases the risk of long-term cognitive and psychiatric dysregulation by 1.5–3 fold relative to athletes with a single concussive incident, and an initial concussion dramatically increases player's risk for future concussions (Guskiewicz et al., 2003). Over the lifespan, the cumulative effects of repetitive mTBIs result in a four-fold increase in neurodegenerative disease (Lehman et al., 2012) and a unique neuropathological syndrome (CTE) involving tauopathies in periventricular spaces and deep cortical sulci (McKee et al., 2013). These neuropathies tend to aggregate within frontal and medial temporal lobes, and are frequently associated with behavioral disturbances. Animal studies have also confirmed the increased risks of neuropathological incidence and behavioral decline associated with repeat concussions (Friess et al., 2009), indicating that a detailed history of previous head trauma is critical for any imaging study.

In addition to being exposed to repetitive injuries in close temporal proximity, military mTBI also has other characteristics not frequently seen in the civilian sector (Graner et al., 2013; Kamnaksh et al., 2011; Levin et al., 2010). Foremost, the majority (~80%) of military mTBI occur in the context of blast rather than more traditional (acceleration/deceleration) injury mechanisms (Hoge et al., 2008; Owens et al., 2008). The putative neuropathology of blast is reviewed elsewhere (Magnuson et al., 2012) and actively debated, with clinical measures indicating few differences between blast and non-blast mTBI (Lange et al., 2012; Luethcke et al., 2011). Preclinical studies suggest that tertiary (i.e., acceleration/deceleration) rather than primary (overpressure) injury is the main driver of pathology (Goldstein et al., 2012). However, contrary evidence from evoked fMRI studies exists (Fischer et al., 2014), and additional research is required. For example, recent data suggests that blast exposure may be particularly detrimental for neurosensory dysfunction within auditory (Gallun et al., 2012; Oleksiak et al., 2012), visual (Capo-Aponte et al., 2012), and vestibular (Franke et al., 2012; Scherer and Schubert, 2009) systems. Finally, military mTBI often occurs in the context of chronic and extreme stress, and it is currently unknown how increased stress levels affect the expression of TBI (Kamnaksh et al., 2011; Kwon et al., 2011). Associations between military mTBI and post-traumatic stress disorder (PTSD) have been reported (Hoge et al., 2008; Schneiderman et al., 2008), making it difficult to interpret fMRI pathology without the inclusion of unique control groups (Roy et al., 2010).

Another major challenge facing the field of mTBI involves the considerable heterogeneity in time post-injury during which mTBI patients are recruited both within and across different fMRI studies, and the reliance on self-report as metrics of both injury and recovery. The temporal dynamics of TBI has been partially elucidated in animal models, demonstrating a complex, multifaceted and time-varying pattern of pathologies that occurs in the minutes to weeks following injury (Barkhoudarian et al., 2011; Giza and Hovda, 2001). Thus, the field must recognize that "recovery" may not represent a unitary concept, as it is currently conceptualized in most studies of mTBI. For example, an animal would be classified as "recovered" within the first minutes of injury based on abnormal glutamate levels secondary to excitotoxicity, whereas CBF is still typically abnormal up to one week post injury (Barkhoudarian et al., 2011; Giza and Hovda, 2001). Therefore, human mTBI studies with liberal time post-injury inclusion criteria (ranging from days to weeks to years post-injury) both increases measurement variability and potentially reduces the sensitivity of any given biomarker.

Studies that combine information across various neuroimaging modalities can both capture the multi-faceted pathology of mTBI as well as potentially isolate some of the physiological changes observed in BOLD imaging. For example, ASL provides additional information about the contribution of CBF to abnormal BOLD signals. DTI can be used to investigate functional/structural relationships in BOLD imaging as was recently done in concussed veterans with depressive symptoms (Matthews et al., 2011a,b), during working memory paradigms in sports-related injuries (Zhang et al., 2010) as well as in studies of functional/structural connectivity following mTBI (Mayer et al., 2011). Spectroscopy provides a more direct measure of excitatory neurotransmitter levels, cellular energetics and death (Govind et al., 2010; Henry et al., 2011; Vagnozzi et al., 2010; Yeo et al., 2011), all of which influence the BOLD signal. Of all imaging modalities, electroencephalography (EEG) and magnetoencephalography (MEG) may be the most complementary to BOLD imaging, providing a more direct measure of neuronal activity and superior temporal resolution (Gosselin et al., 2011; Huang et al., 2009; Lewine et al., 2007; Slobounov et al., 2009). The simultaneous acquisition of EEG and fMRI within the scanner environment (Laufs et al., 2006; Yuan et al., 2012) therefore provides maximal *in vivo* spatial and temporal resolution of underlying neurophysiology.

It is likely that different recovery trajectories may also characterize self-report and physiological biomarkers in human studies of mTBI. Specifically, self-report of recovery or normalization on cognitive scores does not necessarily equate to a return to baseline for physiological biomarkers. Intuitively, this concept is similar to other orthopedic injuries, during which the physical effects of an injury (e.g., scar tissue) are present long-after the patient ceases to report symptoms (e.g., pain). The possibility that neuronal recovery may lag behind the recovery of behavioral and cognitive symptoms (Mayer et al., 2011), further emphasizes the need for objective biomarkers of injury. Otherwise the field potentially risks premature "return to play" decisions, putting players at risk for exacerbated outcomes related to the occurrence of multiple sports-related mTBI (Guskiewicz et al., 2007; Harmon et al., 2013). Thus, multimodal studies that incorporate a longitudinal design are uniquely qualified to address the different recovery trajectories (e.g., faster or slower return to baseline levels) that have been shown to exist for injury biomarkers in animal models.

The lack of objective biomarkers represents a critical obstacle for the field, as imaging based metrics are frequently expected to correlate with patients' self-report from both diagnostic and prognostic perspectives. In addition to the potential for self-reported symptoms to recover more quickly than neurological injuries, the veracity of self-report may vary as a function of sample and/or due to individual differences. For example, sports-related populations may under-report neurobehavioral symptoms following concussion in order to return to play (Greenwald et al., 2012), with the rate of underreporting in high school football estimated to be as high as 53% (McCrea et al., 2004). Children with mTBI are less likely to accurately self-report symptoms and may underestimate the risks involved in continued sports participation (Gilbert and Johnson, 2011). In contrast, chronically symptomatic and litigation-seeking

patients may over-report symptoms (Bianchini et al., 2006), especially if there is the potential for financial gain.

7. Emotional sequelae following mTBI'

Of all of the challenges faced in mTBI research, operationalizing the psychiatric sequelae of injury may be the most challenging. Episodes of major depression are among the most commonly diagnosed neuropsychiatric complication of TBI across all levels of severity (Dikmen et al., 2004; Kreutzer et al., 2001; Mainwaring et al., 2004), and the diagnoses of mTBI and PTSD are highly comorbid in military populations (Hoge et al., 2008; Schneiderman et al., 2008). The incidence of anxiety, depression and irritability among concussed high school and collegiate athletes ranges between 17% and 46%, higher than the base rate of self-reported mood disorders in collegiate athletes (Covassin et al., 2012; Kontos et al., 2012; Schaal et al., 2011). Younger athletes with concussion-induced mood sequelae are more likely to report prolonged depressive episodes (Field et al., 2003), and affective dysregulation from sports-related concussion can persist for years across all ages (Konrad et al., 2011). This may be best typified by the increased incidence of mood disturbances observed in retired boxers and professional football players with a history of concussion (McKee et al., 2013).

Understanding and assessment of mood dysregulation following mTBI is complicated by the possibility of three potentially coexisting, yet distinct etiological mechanisms. First, predisposition for mood disorder, including family history of mood disorders, has been shown to be a strong factor in the presence and severity of post-concussive symptoms (Dikmen et al., 2004). As discussed in the introduction, this has helped promote a long-standing belief that only mTBI patients with previous psychiatric histories are likely to remain chronically symptomatic. A second etiological mechanism suggests that psychiatric sequelae are an indirect result of events associated with mTBI. These include secondary psychosocial and psychosomatic consequences of the injury (somatoform depression), including decreased ability to perform at a job, poor social functioning, perceived stigma of a non-visible injury and depression secondary to other injuries or losses (e.g., deceased spouse) sustained during the traumatic incident (Bay et al., 2004; Dikmen et al., 2004). A final primary etiological path for psychiatric sequelae is a biologically-based disruption of the emotional processing neural network, directly leading to emotional symptoms. Potential pathologies include damage to the network nodes and/or damage to white matter connections within emotional processing networks (Chen et al., 2008). Secondary events such as neuroinflammation may also contribute by inducing "sickness behavior," and may be critically involved in CTE and post-concussive disorder (Blaylock and Maroon, 2011). Regardless of etiological mechanism, all three pathways result in increased negative affect/stress and further dysregulation of emotional processing networks (Erickson et al., 2003).

Evidence of long-term affective changes in retired athletes (Didehbani et al., 2013) combined with neuroimaging results demonstrating that young concussed athletes with persistent depressive symptoms show decreased activity in emotional processing networks (Chen et al., 2008) provide an impetus for developing objective psychiatric metrics for determining neuropsychiatric recovery from concussion. fcMRI measures within the emotional processing networks may also be a potential method for assisting clinical judgment regarding neuropsychiatric recovery following concussion. *In vivo* characterization of depression is a top future priority for the field given the increased risk for suicide rates for concussed persons and athletes retrospectively diagnosed with CTE (Barnes et al., 2012; McKee et al., 2013).

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e.g., susceptibility weighted imaging, DTI). In addition, unlike other functional imaging techniques (electrophysiological and optical imaging), fMRI can be utilized to probe deep gray matter structures as well as more superficial cortical structures, a powerful advantage given that shear stresses are more likely to accumulate in these regions (Zhang et al., 2004). However, the BOLD signal represents an indirect measure of neuronal activity, resulting from a complex mixture of many underlying physiological processes that are affected by trauma (Mayer et al., 2009; McDonald et al., 2012). Thus, studies that incorporate multiple imaging modalities following mTBI are more likely to capture the true complexity of the underlying physiological response. Given the heterogeneity and "chaos" inherently associated with mTBI research (Rosenbaum and Lipton, 2012), both well-powered clinical studies with homogeneous inclusion criteria (time post-injury, injury severity and past history) as well as animal models that more accurately represent the kinematic forces associated with human mTBI (Kane et al., 2012) are critically needed to truly understand the underlying pathophysiology and natural course of recovery following mTBI.

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