Chapter 14
Functional Magnetic Resonance Imaging in Mild Traumatic Brain Injury

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Abstract Patients with concussion (mild traumatic brain injury (mTBI)) frequently complain of both cognitive and emotional disturbances in the days to weeks after their injury, with a percentage of patients (5–20 %) remaining chronically symptomatic. Relative to other static neuroimaging techniques, functional MRI (fMRI) offers great promise for elucidating the underlying neuropathology associated with dynamic processes such as higher-order cognition. Not surprisingly, the majority of mTBI studies have focused on working memory and attention, with results suggesting a complex relationship between cognitive load/attentional demand and functional activation. More recently researchers have used functional connectivity analyses to investigate how injury may affect intrinsic neuronal activation. Several groups have reported that connectivity within the default-mode network is disrupted following injury, which may also contribute to patient reports of increased distractibility. The general benefits and drawbacks of the two methods (evoked versus connectivity studies) are discussed in the context of the injury literature. Mood disturbances are also prevalent following concussion, but fewer studies (evoked or connectivity) have been conducted to investigate the integrity of the emotional processing network. Finally, fMRI can also be used as a surrogate biomarker of

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pharmacological and cognitive rehabilitation treatment efficacy, although only preliminary work has been conducted in this area to date. The chapter also discusses the methodological challenges of performing and evaluating fMRI research with brain-injured patients, including clinical heterogeneity in patient selection criteria and variations in scan time post-injury. Finally, the chapter concludes with a discussion of the physiological underpinnings of the blood oxygen level-dependent (BOLD) response and the many ways in which trauma can affect this complex signal. We conclude that the fMRI signal represents a complex filter through which researchers can more directly measure the physiological correlates of concussive symptoms, an important goal for this burgeoning field.

Keywords Mild traumatic brain injury • Functional magnetic resonance imaging • Evoked activation • Functional connectivity • Confounds • Physiological basis

Introduction

Mild traumatic brain injury (mTBI) remains a poorly understood clinical phenomenon, despite lifetime incidence rates between 110 and 550 per 100,000 individuals [1]. This is primarily a result of the variable definitions of mTBI [2], which are entirely determined by clinical observations and self-reported symptomatology rather than objective markers. Findings from standard clinical neuroimaging sequences (CT scans; T_1 and T_2 weighted images) are typically negative for the majority of patients [3, 4], leading to a proliferation of studies that have attempted to define more objective imaging biomarkers of mTBI [5, 6]. Since the seminal studies of McAllister et al. [7, 8], there has been great interest in using functional magnetic resonance imaging (fMRI) to study mTBI given its ability to perform in vivo measurements during demanding cognitive tasks [9] and, more recently, to characterize intrinsic neuronal activity [10–12].

Single episode mTBI is characterized by subtle neurobehavioral deficits within the first few weeks of injury that typically resolve spontaneously within 3–6 months of injury in approximately 80–95 % of patients [5, 13–16]. Recent evidence suggests that the cumulative effects of multiple mTBIs result in a fourfold increase in neurodegenerative diseases [17] and a unique neuropathological syndrome involving tauopathies in periventricular spaces/deep cortical sulci with an overrepresentation of frontal and medial temporal pathology [18, 19]. Thus, although considerable challenges remain [20], mTBI offers a unique opportunity for examining both transient and permanent disruptions in cognitive and emotional functioning in human injury models. The chapter first provides a review of mTBI research using both evoked paradigms as well as functional connectivity, which have more recently been used to study the effects of brain trauma. Next, we focus on the considerable methodological challenges of performing fMRI research with brain-injured patients. Finally, a review of the physiological underpinnings of the blood oxygen level-dependent (BOLD) response, which represents a complex filter through which researchers attempt to noninvasively capture the effects of neuronal injury, is also provided.

Review of Current Findings from the Literature

fMRI offers great promise for elucidating the underlying neuropathology associated with neurobehavioral sequelae following mTBI, especially when used in conjunction with tasks that dynamically tap into higher-order cognitive functioning [5, 21]. The seminal fMRI studies on mTBI focused on working memory paradigms, with results suggesting a complex relationship between cognitive load and functional activation. In a series of studies on semi-acute (within 1 month of injury) mTBI patients, McAllister et al. [7, 8] reported hyperactivation in right dorsolateral prefrontal cortex (DLPFC) and lateral parietal regions for mTBI patients compared to healthy controls (HC) for moderate processing loads (1-back to 2-back conditions), but hypoactivation for the lower loads (0-back to 1-back conditions). Additional studies by McAllister and colleagues indicated that mTBI patients exhibited frontoparietal hyperactivation in the 1-back to 2-back condition, but hypoactivation going from 2-back to 3-back. Other groups have reported a positive correlation 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, suggesting potential compensatory activation [22]. Using both fMRI and event-related potentials, Gosselin reported that mTBI patients had decreased BOLD signal changes in the left and right mid-dorsolateral prefrontal cortex (which correlated with symptom severity), the putamen, the body of the caudate nucleus, and the right thalamus, coupled with a reduced N350 ERP amplitude [23]. Others have not observed significant differences between a relatively large cohort of mTBI patients ($N=43$) and HC ($N=20$) on a similar n-back task, instead finding that length of post-traumatic amnesia (PTA) was related to hippocampal deactivation (0-back > 2-back) [24].

Demonstrating many of the methodological and interpretive challenges involved in imaging mTBI patients, results from fMRI studies of working memory using concussed athletes have been also been conflicting. In contrast to McAllister's findings of hyperactivation in the right DLPFC, athletes with persistent post-concussive symptoms (PCS) imaged while performing both verbal and visual design working memory tasks show hypoactivation of the right DLPFC [25, 26]. Chen et al. [25] also report both hypo- and hyperactivation in the left prefrontal cortex that was not related to PCS severity and, in general, more diffuse activation patterns in the PCS athlete group. Longitudinal imaging of one patient at 6 months with PCS symptoms and later at 9 months without PCS symptoms provided evidence for a negative correlation between right DLPFC activation and symptom severity but not between DLPFC activation and symptom duration. The correlation between PCS symptom severity and bilateral DLPFC hypoactivation was further supported using a whole brain analysis comparing nine low and nine high PCS severity patients in a verbal working memory task [27]. Importantly, multiple methodological differences exist between the McAllister findings and those of Chen and colleagues including auditory versus visual working memory, athletes versus emergency room patients, time–post-injury, and operational definitions of symptom severity.

There are additional examples of hyperactivation measured with fMRI during task. Using a pre- vs. post-injury design, Jantzen et al. showed hyperactivation of frontal regions post-injury even in the absence of cognitive performance differences [28] suggestive of a compensatory mechanism. The degree of abnormal activation (hyperactivation) may be indicative of a prolonged recovery profile in athletes, particularly when accompanied by more sparse and diffuse activation patterns [29]. Finally, recent fMRI data suggest that significant neuropathological changes can be missed if the focus of sports-related head injuries remains only on diagnosed concussions. Based on the high frequency of American-rules football-offensive lineman in postmortem neuropathological cases [18], it was proposed that sub-concussive hits also contribute to the development of chronic traumatic encephalopathy (CTE). To investigate the effects of sub-concussive hits, Talavage and colleagues scanned high school football athletes pre- and postseason with embedded sensors in the helmet to tally the number of head hits throughout the season. Results demonstrated 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 [30]. Interestingly, Talavage also showed that this pattern of decreased activity correlated with poorer working memory performance in non-concussed high school football players.

Several groups have also examined attentional and memory functioning following mTBI. Smits et al. reported increased activation within the anterior cingulate gyrus, inferior frontal gyrus, insula, and posterior parietal areas during attention tasks with an increased incidence of post-concussive symptoms [22]. Previous results from our lab have indicated hypoactivation within several deep cortical, cerebellar, and subcortical sites during an auditory attention task in independent adult [31] and pediatric mTBI [32] cohorts, with within-group comparisons also indicating decreased cortical activation for mTBI patients during more attentionally demanding conditions [31]. Similarly, we have also seen decreased cortical activation during within-subject comparisons in mTBI relative to HC during a multimodal numeric Stroop task in conjunction with aberrant task-induced deactivation within the default-mode network (DMN) [33]. Witt and colleagues used a three-stimulus (standard, target, and novel stimuli) auditory oddball paradigm with low attentional demand [34]. An ROI analysis suggested that mTBI patients exhibited less activity in right DLPFC compared to HC while detecting target stimuli. In addition, during detection of novel stimuli, patients exhibited decreased activation in areas in the DMN and increased in right superior and inferior parietal areas. Finally, Slobounov and colleagues reported increased volumes of activity for recently concussed athletes within the DLPFC, parietal cortex, and hippocampus on a spatial memory task relative to non-concussed HC [35].

The effects of treatment on BOLD activity following mTBI have also recently been explored. McAllister and colleagues examined whether pharmacological challenges to the dopaminergic system may explain some of these brain abnormalities in working memory circuitry following mTBI. The authors reported that whereas HC performance improved during the *n*-back task following the administration of bromocriptine, compared to placebo, mTBI patients did not show any behavioral

improvement [36]. Moreover, HC in both drug conditions had higher activation in areas involved in working memory relative to patients, whereas mTBI patients on bromocriptine instead had higher activation in areas outside this working memory network. A similar complex pattern of activation was observed within the working memory circuitry when mTBI patients were placed on guanfacine, which indirectly affects dopamine transmission [37]. mTBI patients have also exhibited both increased and decreased activations following cognitive rehabilitation therapy on visually guided saccades and reading comprehension tasks in a relatively small sample of patients [38]. Although these findings are all in their preliminary stages, it suggests that BOLD-based activity may offer a mechanism for noninvasively measuring how treatment affects disrupted neurophysiology following mTBI.

In addition to evoked studies of BOLD activity, researchers are increasingly turning to measures of functional connectivity (fcMRI) to examine neuronal health following mTBI. Connectivity studies are based on intrinsic neuronal fluctuations that synchronously occur over spatially distributed networks in both humans and animals [39]. The majority (60–80 %) of the brain's energy resources is expended to maintain homeostasis [40, 41], and intrinsic neuronal activity likely contributes to this heavy metabolic load. Previous research indicates changes in baseline metabolism following TBI [42] as well as abnormal slow-wave electrophysiological activity during passive mental activity [43–45], providing the biological relevance for fcMRI as a biomarker of mTBI.

These intrinsic fluctuations in neuronal activity tend to alias to low frequency fluctuations (0.01–0.10 Hz) in BOLD signal, and therefore can be measured on any MRI scanner with a conventional echo-planar sequence. During these resting state scans, participants are simply asked to either fixate on a visual stimulus or close their eyes for a relatively brief period of time (approximately 5 min). As such, 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 in the scanner [46]. Similarly, mTBI participants do not perform difficult cognitive tasks during resting state scans, which are of greater clinical interest given that patients tend to report more difficulties under these conditions in everyday life [5, 21]. Finally, noise has a more direct influence on the correlation coefficient in fcMRI relative to evoked signals [47], which can further complicate interpretation of group-wise results.

However, resting state scans also have several advantages over more traditional evoked studies and may eliminate several potential confounds associated with cognitive tasks. Foremost, using a relatively simple task (i.e., passively maintaining fixation), it is possible to probe the neuronal integrity of the multiple sensory, motor, and cognitive networks that exist in the human brain. Specifically, Smith and colleagues demonstrated that intrinsic neuronal activity measured from 36 participants was organized into distinct networks that mirror activity evoked across a variety (30,000 archival data sets) of cognitive challenges [48]. Second, eliminating the complex requirements for presenting sensory stimuli and monitoring motor responses (e.g., interfacing with a computer, projecting stimuli, special nonferrous motor response devices) renders fcMRI more readily available for performing clinical scans.

Third, the passive nature of resting state scans (eyes closed or maintaining fixation) reduces some of the confounds associated with evoked studies due to lack of effort, effects of pain, and fatigue. Fourth, in the presence of task-based behavioral differences, it is difficult to disambiguate whether differences in BOLD-related activity directly result from behavioral performance differences, alterations in neurophysiology, or some combination of effects. Similarly, interpretation of evoked data is also frequently complicated by learning and/or practice effects, which are minimal during a passive task. Finally, as has already been demonstrated by several research groups [49–51], fcMRI can be used across the entire TBI spectrum (e.g., mildest injury to minimally conscious patients).

To date, the majority of connectivity studies following TBI have focused on activation in the DMN. The primary nodes of the DMN include the rostral anterior cingulate gyrus (rACC), posterior cingulate gyrus (PCC), superior temporal/supramarginal gyrus (SMG), and ventromedial prefrontal cortex, with the rACC and PCC serving as central hubs [52]. The DMN is believed to mediate a variety of mental activities such as episodic memory review and future-oriented thought processes that occur during periods of unconstrained mental activity [53]. DMN activity parametrically varies with task difficulty [54] and is predictive of attentional lapses during cognitively demanding tasks [55, 56]. In addition, DMN BOLD signals are negatively (i.e., anticorrelated) correlated with activity in the lateral prefrontal cortex and inferior parietal lobes [57], suggesting that the two networks may act in conjunction to produce states of high (decreased DMN activity) or low (increased DMN activity) attentiveness to external events.

Early fcMRI studies focused on severely injured [58] or minimally conscious [49–51] TBI patients, with most studies reporting decreased DMN connectivity (but see [59]). In the semi-acute phase of mTBI, reduced connectivity has been reported within the DMN using a seed-based approach, with increased connectivity between the rACC and ventrolateral prefrontal cortex [11]. These abnormalities in DMN connectivity remained relatively stable approximately 4 months post-injury. Another study utilized independent component analysis (ICA) to examine DMN connectivity, reporting reduced connectivity in the posterior hubs (PCC and SMG) of the DMN in conjunction with increased connectivity within the ventromedial prefrontal cortex [60]. Similarly, Johnson and colleagues reported generally reduced connections across multiple nodes of the DMN 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 mTBI episodes [10]. 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 [61].

Others have reported disrupted interhemispheric fcMRI in the visual cortex, hippocampus, and DLPFC during task-based connectivity analyses [62], as well as decreased symmetry of connectivity based on thalamic seeds [63]. Another group also used ICA to investigate fcMRI [12], reporting decreased functional connectivity within the motor-striatal network and increased connectivity in the right fronto-parietal network. Finally, Stevens and colleagues reported disrupted (both increased and decreased) connectivity in 30 semi-acutely injured mTBI patients across 12

different sensory and cognitive networks [64]. On the basis of these studies, fcMRI appears to be well poised for interrogating connectivity within all major structures and networks of the brain following mTBI.

Overarching Issues in FMRI Research Following mTBI

As alluded to in the preceding paragraphs, there are several potential confounds that need to be carefully considered when performing and evaluating fMRI studies of mTBI. Some of the more common clinical confounds include injury-related pain (orthopedic), fatigue, poor effort, cognitive deficits, and the presence of other prescribed medications (e.g., narcotics or sedatives) that may alter neurovascular coupling [65–67]. Some of the nonspecific somatic confounds (e.g., pain and fatigue) and medication issues can be reduced or eliminated by recruiting orthopedically injured patients as control subjects, as has previously been done in the clinical literature [68, 69]. Confounds that can be controlled through careful experimental design include reducing heterogeneity in terms of both injury severity and post-injury scan time. For example, 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 can all be classified as having suffered from mTBI under current nosology [2]. However, the symptoms and recovery trajectories of these patients are likely to be very different [70, 71].

Developing methods for improving the nosology of mTBI and understanding of symptom trajectory will be critical for coalescing disparate neuroimaging findings. The temporal dynamics of mTBI has been elucidated using animal models, demonstrating a complex, multifaceted, and time-varying pathology that characterizes mTBI in the minutes to weeks following injury [72]. However, inclusion criteria for previous studies in human mTBI have ranged from days to years post-injury, with some studies focusing on chronically symptomatic patients. Several meta-analyses have documented that the majority of single-episode mTBI patients are expected to recover spontaneously from a neurobehavioral perspective within a few weeks to a few months post-injury [5, 13–16]. Understanding why a percentage of single episode mTBI patients remain chronically symptomatic is critical for the field. However, this cohort represents a subset of the larger mTBI population and findings from this sample may not generalize. Thus, while it is important to recognize the heterogeneity and chaos associated with mTBI [20], it is also important to foster studies based on homogeneous samples in clearly defined time-windows (acute, subacute, or chronic post-injury stages).

It is notable that mTBI patients who meet strict inclusion criteria (homogeneous in both injury severity and scan-time post-injury) are challenging to enroll, and fMRI data is financially costly to accumulate. The combination of these factors has resulted in another methodological challenge: namely, the utilization of low sample sizes despite the inherently low signal-to-noise ratio of fMRI [73]. Specifically, the majority of fMRI studies following mTBI have been reported with sample sizes just

at or below commonly accepted recommendations. As a result, it is likely that these studies may be underpowered, suffering from low positive predictive power and providing poor estimates of the true effect size [74]. Therefore, conflicting findings from previously discussed working memory studies following mTBI may be the result of simple methodological differences (described above) and/or a result of the small sample sizes employed across the various studies. Importantly, fMRI studies of other cognitions (e.g., attentional and memory deficits) are not exempt from this critique, but independent replication attempts of these findings have been fewer. To combat the problem of small sample sizes, funding agencies have recently developed 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 data for meta-analyses.

A third methodological consideration relates to the self-reporting of symptoms. Importantly, symptom self-report may vary as a function of sample with sports-related populations underreporting neurobehavioral symptoms to return to play [75–77] whereas other mTBI populations may over-report symptoms [78, 79], especially in the presence of potential financial compensation. Multiple sociological barriers may account for the underreporting of concussive symptoms ranging from lack of education regarding the seriousness of concussion (parents, players, and coaches), hesitancy to report symptoms that do not result in significant pain, desire not to be removed from play, and stigmatization of concussion as a non-real injury [77, 80]. The peer pressure to continue play and not report injury is particularly important in vulnerable populations such as children who may not comprehend and underestimate the risks involved in continued participation, and in low socioeconomic areas where participation is perceived as a path to future benefit [81]. Additional pressures are on the coaching staffs who may feel pressured to win and underestimate the risk of returning a player to the field prematurely. Unfortunately, the rate of underreporting of concussion symptoms in high school football has been reported to be as high as 53 % [82].

Regardless of the sociological factors, underreporting of symptoms can lead to premature "return to play" decisions and put players at risk for exacerbated outcomes related to the occurrence of multiple sports-related concussions [83–86]. Repeat concussions (concussions occurring within the same sports season) increase the risk of long-term cognitive and psychiatric dysregulation by 1.5–3-fold relative to those with a single concussive incident [87]. A study of nearly 3,000 concussions in NCAA athletes clearly demonstrates that an initial concussion dramatically increases that player's risk of a repeat concussion [87, 88]. Athletes with a history of concussion are also more likely to report more baseline symptoms than are those with no history of concussion [85]. The increased risks of neuropathological incidence and behavioral decline associated with repeat concussions has been modeled in piglets and shows a worse neuropathological and neurobehavioral outcome for injuries that occur in temporal proximity [89]. Importantly, neuronal recovery may lag behind the recovery of behavioral and cognitive symptoms, emphasizing the need for objective biomarkers of when it is truly safe to return to play.

Psychiatric Sequelae and mTBI

Among the more challenging outcome measures to operationalize are psychiatric sequelae of TBI. Episodes of major depression are the most commonly diagnosed neuropsychiatric complication in TBI, regardless of injury severity [90–93]. The incidence of concussed high school and collegiate athletes reporting anxiety, depression, and irritability is reported to be range between 17 and 46 % [68, 94–96], whereas basal rates of self-reported mood disorders in collegiate athletes is equal to or slightly less (15–30 %) than the typical collegiate students [97–99]. Unfortunately, affective dysregulation resulting from sports-related concussion, at all ages, can linger for years in those diagnosed with post-concussion syndrome [100–105]. In pediatric and adolescent populations, TBI increases both rates of long-term depression and anxiety, dependent upon the lesion laterality and age at time of injury [106–108]. In addition, younger athletes reporting concussion-related mood sequelae have more prolonged depressive episodes [109, 110].

Understanding and assessing the basis of mood dysregulation following mTBI is complicated by the possibility of having three potentially coexisting, yet distinct etiological mechanisms for depressed mood following mTBI. 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 depression [90, 111–113]. Second, psychiatric sequelae may result from the indirect effects of TBI secondary to psychosocial and psychosomatic consequences of the injury (somatoform depression). These include decreased the 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 [90, 91, 114–116].

A final primary etiological path for psychiatric sequelae is a biologically based disruption of the emotional processing neural network. Potential pathologies include direct damage to the network nodes and/or damage to white-matter connections within emotional processing networks. Secondary events such as neuroinflammation may also contribute by inducing “sickness behavior” [117–119], and are believed to be critically involved in CTE and post-concussive disorder [120, 121]. Further support for a pathophysiological mechanism of the depressive mood state following concussion is supported by the neuroinflammatory model of post-concussive state that mechanistically mimics the inflammatory model of major depressive disorder. Bellgowan and colleagues [122] demonstrated increased levels of the inflammatory marker IL-1B negatively correlate with connectivity within the subgenual ACC and other regions of the medial emotional network [123]. Regardless of the etiology, all processes result in negative affect that increases stress and interferes with the hypothalamic-pituitary-adrenal (HPA) axis [124–126], resulting in further dysregulation of emotional processing networks [127, 128].

The increased incidence of mood disturbances observed in retired boxers and professional football players with a history of concussion provides prognostic evidence for the neuropathological etiology of concussion-related mood dysregulation [18, 19].

Of particular concern in those that have been diagnosed with CTE is the high rate of suicidality [18, 129, 130]. Suicide rates for concussed persons who are at risk for mood disorder or have a diagnostic history of mood disorder are also significantly elevated [131, 132]. Though the mood disturbances reported in retired players and diagnosed CTE cases were obtained retrospectively and lack prior psychiatric history, others [84] have demonstrated that the later life diagnosis of clinical depression is correlated with concussion history [84].

fMRI Physiology and Trauma

The exact linkage between neuronal transmission and resultant hemodynamic activity (neurovascular coupling) remains an active area of investigation. During intrinsic activity (at rest), a tight coupling exists between the cerebral metabolic rate of glucose (CMR_{glu}), the cerebral metabolic rate of oxygen ($CMRO_2$) and cerebral blood flow (CBF) to maintain homeostasis [133]. Following excitatory neuronal transmission, energy (glucose) is required to reverse ionic influx and excess glutamate needs to be rapidly removed from the synaptic cleft [134–136]. Excess glutamate is taken up by astrocytes and converted to glutamine, nitric oxide is released co-temporally by neurons and vasoactive agents are released by astrocytes [134], all of which likely contribute to vasodilation and a concomitant increase in CBF. Importantly, there is a decoupling between CBF and oxidative metabolism [137] following neuronal activation, which leads to an excess in oxygenated blood, a decrease in the ratio of deoxyhemoglobin relative to oxyhemoglobin, and a subsequent increase in signal.

As such, it has long been recognized that the BOLD response represents an amalgamation of signals derived from the ratio of oxy- to deoxyhemoglobin (primary), CBF, and cerebral blood volume (CBV) [73, 138, 139]. The shape of the BOLD response is also complex in nature, with the canonical hemodynamic response function (HRF) consisting of two primary components, a positive signal change that peaks approximately 4–6 s post-stimulus onset, and a post-stimulus undershoot (PSU) that peaks 6–10 s after the stimulus ends [138, 140]. As previously discussed, the positive phase of the BOLD response has been associated with an increase in CBF, and subsequent change in the ratio of oxy- to deoxyhemoglobin intravascularly [138]. The biophysical origins of the PSU remain more controversial. An early model attributed the PSU to temporal delays between when CBF (earlier response) and CBV (delayed response) returned to baseline levels [138, 141]. However, more recent work suggests that the duration of the PSU extends beyond even when CBV returns to baseline [142], leading others to suggest that increased metabolic demands ($CMRO_2$) following cellular signaling may contribute to the PSU [142, 143].

Thus, there are several different individual mechanisms as well as combinatory effects by which head trauma can alter the different phases of the BOLD response. Foremost, trauma can result in frank neuronal (e.g., alterations in synchronous

neuronal activity) dysfunction, causing downstream effects on BOLD-based activity by changing the amount of glutamate in the synaptic cleft and the energetic needs of cells following neurotransmission [73, 134]. Direct support for this hypothesis comes from reports of neuronal loss in animal models of fluid percussion injury [144] and abnormal cell signaling [145]. Indirect support for this hypothesis comes from findings of altered concentrations of glutamate and glutamine in the semi-acute stage of mTBI during magnetic resonance spectroscopy [146–148] as well as through more invasive measures during more severe injury models [149–152].

TBI has also been shown to directly reduce both CBF and metabolism, both of which would affect the BOLD response. CBF and transit time are reduced in human models of severe TBI [153], as well as cerebral perfusion [154]. Metabolic failure following TBI occurs even in the presence of normal perfusion [155], with an initial decoupling between CBF and CMR_{glu}, followed by a generally reduced cerebral metabolism [72, 154]. Animal models suggest that alterations in CBF and CMR_{glu} may be the most long-lasting physiological deficits of concussion [72], and thus the BOLD response should also be similarly affected for a longer duration following injury. Trauma may also directly affect the structural integrity of the microvasculature. Animal studies based on the fluid percussion model indicate a semi-acute reduction in capillary number and diameter both at the injury site and distally [156], with other studies suggesting that TBI also results in neurogenic damage within the perivascular nerve network [157]. Hemosiderin depositions, secondary to microhemorrhages and inflammation, have also been noted in the autopsy report of an mTBI patient who died 7 months post-injury [158].

At present, it would be unfeasible to draw conclusions about the relative importance of these different mechanisms as they pertain to previously reported finding of hypo- and hyperactivation in clinical samples of mTBI [9, 31]. Animal models of injury frequently make recordings during the baseline state (e.g., anesthetized animals), which is known to produce differential dynamics between BOLD constituents (e.g., CBF, $CMRO_2$, and CMR_{glu}) relative to more dynamic states (evoked activity). Several papers have recently examined fcMRI in animal models of neuronal injury [159, 160], with other studies [161] reducing/eliminating anesthesia protocols that can alter the neuronal response and/or neurovascular coupling. Future animal studies that specifically examine how mTBI affects both intrinsic and evoked BOLD-related activity will greatly improve our knowledge of the true bench-to-bedside capabilities of this technique in a more controlled environment.

Similarly, multimodal neuroimaging techniques can be used in conjunction with standard BOLD imaging techniques to potentially isolate physiological changes associated with neuropathophysiology. For example, spectroscopy can be used in conjunction with fMRI to get more direct measures of the level of excitatory neurotransmitters and measures of cellular energetics and death [146, 148, 162, 163]. Matthews and colleagues used combined DTI and fMRI methods to understand differences in amygdala activation to emotional faces in concussed Operation Enduring Freedom and Iraqi Freedom veterans with and without depressive symptoms [164]. fMRI results demonstrated abnormal amygdala activity in veterans with

depressive symptoms that was associated with lower fractional anisotropy (FA) in several white matter tracts, suggesting that functional disruption may be the direct results of structural pathology in white matter tracts. Similarly, we have examined the relationship between functional connectivity and FA within white matter tracts that connect the DMN and frontal areas during the semi-acute and more chronic stages of mTBI [11]. Finally, electroencephalography (EEG) and magnetoencephalography (MEG) both provide a more direct measure of neuronal activity at much higher temporal resolution [23, 43, 165, 166], eliminating some of the interpretative problems associated with fMRI. Importantly, EEG and fMRI can be acquired simultaneously within the scanner environment [167, 168], providing an unheralded access into brain pathology following mTBI that affords both high spatial and temporal fidelity.

As previously discussed, fMRI signals are critically linked to CBF, and the dysregulation of autonomic control of neurovascular coupling remains a challenge for future neuroimaging studies of mTBI. Arterial spin labeling measures of CBF have also been used to calibrate the BOLD signal [169, 170], although the measurements must be made in a quantitative fashion. Hypercapnic normalization is another frequently used technique that is achieved through the administration of CO_2, a voluntary breathhold scan or more regularized breathing [171, 172]. This method assumes that hypercapnia has a limited effect on neural activity and oxygen metabolism and thus primarily measures CBF [173, 174]. Previous results suggest that the hypercapnia method accounts for variability in subject vasculature and physiology differences during task performance, as well as changes in magnetic field strength [175–177]. A primary limitation of the method is that it requires the subjects to calmly hold their breath during an EPI acquisition and/or the administration of CO_2, both of which may increase the rate of anxiety in participants and subsequently affect subject motion.

fMRI Analyses

The final section of the chapter discusses several analytic considerations for performing fMRI research following mTBI. First, in spite of the known complexity of the BOLD response, previous research in both mild and more severe forms of TBI has typically estimated only a single parameter (typically a beta coefficient) by convolving an assumed canonical HRF (e.g., a gamma variate or a double gamma variate function) with known experimental conditions (e.g., onset of a particular trial) to derive a predictor function (e.g., regressor). Importantly, this assumes that the different phases of the hemodynamic response (positive phase and PSU) and their relationship to each other are largely unaffected by mTBI. To date, only a single study has explicitly examined the HRF in more severe TBI [178] reporting that although basic visual stimuli were associated with an increased volume of activation in the TBI group, there were no differences in the basic shape of the HRF.

More fMRI studies are needed in both human and animal models that explicitly compare the different aspects of the HRF as well as their individual sensitivity and specificity.

Investigators have also traditionally utilized region of interest (ROI) or voxel-wise analyses to directly compare the BOLD response between mTBI patients and healthy controls. However, both of these analytic methods are based on the implicit assumption that heterogeneous initial injury conditions (e.g., patients in a motor vehicle accidents versus patients who experienced a blow to the left temple) results in a homogenous (i.e., high degree of spatial overlap) pattern of grey matter abnormalities that would survive group-wise statistics. Although lesions tend to be more common in the diencephalon, mid-brain, limbic circuit, and prefrontal cortex [6, 179], the basic premise of the spatial homogeneity assumption is likely to be flawed. Therefore, it is increasingly being recognized that novel approaches for classifying heterogeneous lesion locations are necessary for performing mTBI imaging research [180–182]. For example, in diffusion tensor imaging studies of white matter injuries, variations on normative (i.e., *z*-scores) transformations [181–185] or bootstrapping [186] have been utilized to identify voxel-wise abnormalities on a patient-by-patient basis. While the logical appeal of these newer approaches is clearly superior, the underlying assumptions are likely to be dependent on the statistical properties of the data (e.g., sample size, distribution properties, and normalcy) and have not been thoroughly vetted in the context of typical neuroimaging data [180]. To our knowledge, these novel approaches have not yet been applied to BOLD imaging data to determine regions of anomalous activity on an individual subject level.

Conclusions

In summary, fMRI provides researchers with the ability to noninvasively measure the functional integrity of neuronal circuitry in both animal and human models of mTBI at relatively high spatial resolution. The ability to dynamically measure brain function during higher-order cognitive and emotive tasks represents a clear advantage relative to other imaging techniques that are only capable of measuring structural integrity (e.g., susceptibility weighted imaging, DTI). Moreover, unlike other functional techniques, fMRI is equally capable of probing deep grey structures as well as cortex. However, the dynamic nature of the BOLD signal also makes it more susceptible to nonspecific effects of trauma (e.g., pain, fatigue), behavioral performance, effort on testing, and normal day-to-day variations in human behavior. Moreover, the BOLD signal represents an indirect measure of neuronal activity that results from a complex mixture of many underlying physiological processes, all of which can be affected by trauma. Thus, clearly identifying the one, two, or multiple mechanistic causes of an "abnormal" BOLD signal will not be feasible when this technique is used in isolation.

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