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Functional MRI of mild traumatic brain injury (mTBI): progress and perspectives from the first decade of studies

Brenna C. McDonald,

IU Center for Neuroimaging, Department of Radiology and Imaging Sciences, Indiana University School of Medicine, 950 W. Walnut St., R2 E124, Indianapolis, IN 46202, USA. Section of Neuropsychiatry, Department of Psychiatry, Dartmouth Medical School, Lebanon, NH, USA

Andrew J. Saykin, and

IU Center for Neuroimaging, Department of Radiology and Imaging Sciences, Indiana University School of Medicine, 950 W. Walnut St., R2 E124, Indianapolis, IN 46202, USA. Section of Neuropsychiatry, Department of Psychiatry, Dartmouth Medical School, Lebanon, NH, USA

Thomas W. McAllister

Section of Neuropsychiatry, Department of Psychiatry, Dartmouth Medical School, Lebanon, NH, USA

Brenna C. McDonald: mcdonalb@iupui.edu; Andrew J. Saykin: asaykin@iupui.edu; Thomas W. McAllister: thomas.w.mcallister@dartmouth.edu

Abstract

Mild traumatic brain injury (mTBI) represents the great majority of traumatic brain injuries, and is a common medical problem affecting cognitive and vocational functioning as well as quality of life in some individuals. Functional MRI (fMRI) is an important research method for investigating the neuroanatomic substrates of cognitive disorders and their treatment. Surprisingly, however, relatively little research has utilized fMRI to examine alterations in brain functioning after mTBI. This article provides a critical overview of the published fMRI research on mTBI to date. These topics include examination of frontal lobe/ executive functions such as working memory, as well as episodic memory and resting state/functional connectivity. mTBI has also been investigated in military populations where studies have focused on effects of blast injury and comorbid conditions such as post-traumatic stress disorder and major depressive disorder. Finally, we address fMRI evaluations of response to behavioral or pharmacological challenges and interventions targeting cognitive and behavioral sequelae of mTBI. The review concludes with identification and discussion of gaps in current knowledge and future directions for fMRI studies of mTBI. The authors conclude that fMRI in combination with related methods can be expected to play an increasing role in research related to studies of pathophysiological mechanisms of the sequelae of mTBI as well as in diagnosis and treatment monitoring.

Keywords

Episodic memory; Frontal lobes; Functional connectivity; Functional MRI; Mild traumatic brain injury; Working memory

Introduction

The vast majority of traumatic brain injuries (TBIs) are mild by commonly used clinical criteria (Kay et al. 1993), with estimates indicating that 70–90 % of the more than 1.5 million TBIs suffered in the United States each year fall in this category (Cassidy et al. 2004; National Center for Injury Prevention and Control 2003; Rutland-Brown et al. 2006), including those typically labeled as concussions. Mild TBI (mTBI) is also a relatively common injury, with incidence estimates ranging from 100–300/100,000 to 600/100,000 population (Cassidy et al. 2004). While most individuals who experience mTBI recover fully from their injury within weeks to months (Belanger et al. 2005; McCrea et al. 2009), a subset of participants (estimated to be 10–15 %) report persistent symptoms, which can impair social and vocational functioning and quality of life (McAllister et al. 2006). Functional MRI (fMRI) has come into increasing use in the past 30 years to study a wide range of neuropsychiatric disorders. It is surprising, therefore, that relatively little fMRI research has examined the cognitive and behavioral sequelae of mTBI, their course over time, and their utility as a biomarker for potential treatment approaches. While attention to sports-related concussion has led to several recent fMRI studies regarding mTBI (concussion and subconcussive impacts) in athletes (Breedlove et al. 2012; Chen et al. 2004; Chen et al. 2007; 2008a, b; Jantzen et al. 2004; Johnson et al. 2012; Lovell et al. 2007; Pardini et al. 2010; Slobounov et al. 2011; Slobounov et al. 2010; Talavage et al. 2010; Zhang et al. 2010) (see also Slobounov et al. 2012 and Baugh et al. 2012), since the first published fMRI study of mTBI in 1999 (McAllister et al. 1999) fewer than 20 papers have investigated cognitive functioning after adult mTBI using fMRI (with even fewer examining pediatric mTBI); most of this work has been published since 2009. This literature has generally focused on examination of aspects of frontal lobe/executive functioning (e.g., working memory (WM), attentional functioning), as these are the cognitive processes found most likely to be affected after injury (McDonald et al. 2002). There has also been limited examination of alterations in episodic memory circuitry activation after mTBI. Other lines of investigation have included examination of mTBI in military populations, with a focus on blast injury and potential comorbid factors including post-traumatic stress disorder (PTSD) and major depressive disorder (MDD), study of resting state/ functional connectivity abnormalities after mTBI (see also Stevens et al. 2012), and evaluation of the effects of rehabilitative treatment or pharmacological challenges on brain activation patterns. Here we critically review these lines of research, and identify gaps in current knowledge that present opportunities for future investigation. For a summary listing of articles covered in this review, please see Table 1.

Executive/frontal lobe functioning after mTBI

In the earliest work using fMRI to examine cognitive changes after mTBI, McAllister and colleagues (McAllister et al. 1999; McAllister et al. 2001b) studied WM functioning within 1 month of injury using an auditory-verbal “N-back” task. As variations on this paradigm have been used extensively to study TBI across the spectrum of severity, including several studies of mTBI (e.g., McAllister et al. 2002; McAllister, McDonald et al. 2004; McAllister et al. 2006; McAllister, Flashman et al. 2011; McAllister, McDonald et al. 2011; Smits et al. 2009; Stulemeijer et al. 2010), a brief description of the task appears in order. In the version used by McAllister et al., during scanning participants hear a string of consonant letters. In initial work this blocked design task included 0-, 1-, and 2-back conditions, with subsequent studies adding a more challenging 3-back condition. For each letter, participants respond to signify whether the current letter is a match (i.e., is the same as the designated target or the letter presented 1, 2, or 3 back in the sequence) or a non-match (see Fig. 1). The experimental conditions are presented in pseudo-random order, preceded by instructions regarding which condition is active (e.g., “the match is one back”). Participants rehearse a

practice version of the task prior to scanning to ensure comprehension of task demands. This task reliably demonstrates robust activation of bilateral frontal, parietal, cerebellar, and basal ganglia circuitry, as demonstrated in a group of healthy controls in Fig. 2.

In their initial work McAllister et al. (McAllister et al. 1999) compared 12 mTBI patients to 11 healthy control participants. In both groups a pattern of bifrontal and biparietal activation was noted at the lowest WM load (i.e., 1-back>0-back contrast), consistent with the typical activation pattern seen for WM tasks. At increased WM load (2-back> 1-back contrast), controls showed minimal increase in brain activation, with greater activation only in right frontal regions. In contrast, mTBI patients showed notable increases in bifrontal and biparietal activation (right greater than left hemisphere) in response to increased WM load. In a subsequent study, this group (McAllister et al. 2001b) examined 18 mTBI patients and 12 controls using a task incorporating a more difficult 3-back condition, to examine the effect of mTBI on processing at higher WM load. Consistent with the prior study, mTBI patients showed relatively greater increases in activation in WM circuitry at moderate WM load (2-back>1-back contrast). However, at the highest WM load (3-back>2-back contrast), controls showed greater increases in activation than mTBI patients across multiple regions within typical WM circuitry (bilateral frontal and parietal regions). In both studies mTBI patients reported significantly more cognitive symptoms than controls, particularly difficulties with memory, but generally did not show impairment on objective neuropsychological testing. There were no between-group differences in N-back task performance in either study. The authors therefore interpreted these findings as potentially reflective of injury-related impairment in the ability to activate, modulate, or allocate processing resources effectively in response to WM load. As patients and controls did not differ across the majority of objective measures of cognitive functioning, but patients reported significantly more cognitive symptoms, the authors hypothesized that this presumed difficulty engaging WM circuitry might lead to a perception of cognitive impairment after mTBI (i.e., patients feeling as though they are having to “work harder” to perform cognitive tasks).

In one of the few longitudinal studies of mTBI, McAllister et al. (McAllister et al. 2002; McAllister et al. 2006) scanned a subgroup of participants (11 mTBI patients, six controls) from the above study again 1 year after injury to evaluate changes in brain activation patterns over time. While the mTBI group no longer reported significant post-concussive symptoms (PCS) at the one-year follow-up, they continued to show mildly depressed reaction speed relative to controls. In addition, mTBI patients showed greater increases in task-related right frontal activation for the highest WM load relative to controls from 1 month to 1 year post-injury. Across both groups, increased 3-back performance over time was correlated with increased left prefrontal activation. These findings suggest the possibility of persistent abnormalities in brain function even 1 year after mTBI despite resolution of PCS, although given the small sample size such inferences must be considered preliminary.

Using a similar N-back task as well as measures of selective attention (Counting Stroop task) and motor functioning (right hand finger movements), Smits et al. (Smits et al. 2009) examined the relationship of brain activation to subjective report of PCS as assessed by the Rivermead Post Concussion Symptoms Questionnaire in 21 mTBI patients (~one month post-injury) and 12 healthy controls. The N-back task included rest, 0-, 1-, and 2-back conditions, using aurally presented numbers as stimuli. The Counting Stroop included rest, neutral, and interference conditions, with animal names or number words as stimuli. In the neutral and interference conditions participants pressed a button corresponding with the number of words presented (1–4); for “oddball” items in the interference trial, when the number word was capitalized, participants pressed the button corresponding with the

number word itself, not the number of presentations of the word. Patients were grouped based on a median split of PCS symptoms, resulting in three groups: no PCS (healthy controls), moderate PCS, and severe PCS. Patients with severe PCS showed poorer performance on both the 1- and 2-back tasks than both other groups, and showed poorer Counting Stroop interference performance than the control group. While regression analyses showed no association between brain activation and PCS for the motor task, N-back activation for the 0-back>rest, 2-back>0-back, and 2-back>1-back contrasts (though not 1-back>0-back) showed a positive correlation with PCS (greater activation corresponding with increased PCS severity; it is not clear if negative correlations were examined) in a number of brain regions which were largely within typical WM circuitry. However, a positive relationship between PCS and activation in brain regions outside of typical WM circuitry was also apparent at higher WM load. A positive correlation between PCS and brain activation was also seen for Counting Stroop activation for the interference>neutral contrast. These findings were interpreted by the authors to support previous work (McAllister et al. 1999; McAllister et al. 2001b) demonstrating increased task-related activation during WM processing in mTBI, as well as to demonstrate process- and/or brain region-specific abnormalities related to PCS, including potential compensatory recruitment of brain regions outside of typical task-related neural circuitry in order to support cognitive functioning after mTBI. While alterations in task-related activation have consistently been reported, what is not clear from work to date is whether the increased activation reported in mTBI participants is compensatory (i.e., helps improve performance) or is an epiphenomenon of increased effort required in this group to maintain performance relative to controls.

In contrast to the focus on typical WM circuitry activation, Stulemeijer et al. (Stulemeijer et al. 2010) examined the effect of mTBI on declarative memory circuitry deactivation elicited by the N-back task in 43 patients (within 6 weeks of injury) and 20 healthy controls, with a focus on relationship to injury severity as measured by length of post-traumatic amnesia (PTA). As these authors note, in addition to robust activation of neocortical regions, execution of the N-back task typically produces deactivation of medial temporal lobe regions critical for declarative memory. In this study the N-back task used visually presented digits, and included only 0-back and 2-back conditions. As the authors note, accurate assessment of PTA duration can be very difficult in mTBI, since most mTBI patients have very brief (if any) PTA, and first formal assessment of PTA may not take place for some time after injury. Participants were therefore grouped into four clinically relevant and easy to operationalize PTA classifications based on all available information (patient and eyewitness reports, medical records, clinical assessment, etc.): controls, mTBI patients with no PTA, PTA of 1–30 min, and PTA>30 min. Of note, mTBI patients showed impairment relative to controls on a number of declarative memory measures, though not on most tests of attentional functioning or on the N-back task. No between-group differences were found in task-related activation or deactivation, and there was no relationship between task-related frontal activation and PTA. However, there was a significant negative correlation between PTA duration and left hippocampal activation (0-back>2-back contrast), with a trend for the same association in the right hippocampus (i.e., less WM task-related deactivation in patients with longer PTA). PTA severity was also related to cognitive complaints and verbal declarative memory delayed recall performance (patients with greater PTA had greater complaints and worse memory scores). These findings suggest that in addition to the altered task-related activation described by prior studies, mTBI may also interfere with task-related deactivation, such that patients show less effective deactivation of declarative memory circuitry when performing a WM task (see further discussion of fMRI during episodic memory processing below).

Mayer et al. (Mayer et al. 2009) approached the question of attentional dysfunction after mTBI via examination of fMRI activation during an auditory orienting task in 16 mTBI

patients (within 3 weeks of injury) and 15 matched controls. Participants were required to indicate via button press which ear a tone was presented to, following an orientation tone which correctly predicted target tone location on 50 % of trials. As in other studies in this area, patients reported significantly more cognitive and somatic complaints and anxiety and mood symptoms than controls. Behavioral findings suggested that mTBI patients (relative to controls) showed an impaired ability to disengage attention following invalid cues at a shorter stimulus onset asynchrony (SOA) and a failure to inhibit attentional allocation to a correctly cued spatial location at longer SOA, findings which were accompanied by hypoactivation of a number of regions within attentional circuitry. In addition, regression analysis showed that a much broader network of brain regions accounted for significant variance for the control group than for mTBI patients. The authors note that these objective neural findings may have potential for use as a biomarker for the spatial attention deficits often reported after mTBI (see Mayer et al. 2012 for further investigation of attentional functioning after mTBI using fMRI).

In a similar fashion, Witt et al. (Witt et al. 2010) also sought to determine whether mTBI patients showed abnormalities in frontal lobe activation during a less complex WM and attention task than the WM paradigms described above. In 31 patients (mean 2 months post-injury) and 31 controls, they utilized a three-stimulus (standard, target, and novel stimuli) auditory oddball paradigm. There were no between-group differences in task performance. Primary region of interest analyses showed decreased right dorsolateral prefrontal cortex (DLPFC) activation during detection of target stimuli for mTBI patients, confirming the main study hypothesis. In exploratory whole-brain between-group analyses mTBI patients demonstrated increased activation in bilateral inferior frontal, precentral, and postcentral gyri, suggestive of potentially compensatory activation during target detection, as well as decreased right superior parietal activation. During novel stimulus detection, mTBI patients showed increased right superior and inferior parietal activation, as well as decreased activation (greater deactivation) in a wide variety of brain regions which overlap with those comprising the default mode network (DMN). These findings were interpreted to demonstrate that prefrontal dysfunction after mTBI influences more elemental attentional/executive functions which may in part underlie the altered activation patterns seen for more complex cognitive processes, such as WM. However, it should be noted that activation patterns were not correlated with measures of clinical status (e.g., mTBI symptomatology) or cognitive/behavioral data (e.g., task performance), making such interpretations preliminary. Findings were also thought suggestive of DMN dysfunction in mTBI (discussed further below).

The work reviewed thus far sheds light on mechanisms of altered cognition and cognitive complaints shortly after injury. In one of the few fMRI studies of mTBI that examined patients at a greater temporal distance from their injury, Gosselin et al. (Gosselin et al. 2011) used an fMRI WM task and event-related potentials (ERP) to assess 13 mTBI patients with persistent PCS (mean ~6 months post-injury) and 23 controls. The fMRI and ERP task used visually presented abstract images. For each trial, four out of five possible images were shown sequentially, followed by a brief delay and then a probe image. Participants responded by button press to indicate if the probe image was in the target set or not. The control condition included repeated presentation of an image followed by a cued button press. There were no between-group differences in task performance. Relative to controls, less fMRI activation was apparent in the mTBI group in bilateral DLPFC, putamen, caudate nucleus, and right thalamus. mTBI patients also failed to show expected task-related deactivations of hippocampus and parahippocampal gyrus. PCS as measured by the Postconcussion Scale (Lovell et al. 2006) correlated with right DLPFC activation, with patients with more severe symptoms showing lower activation. In contrast, in the left angular gyrus patients with more severe PCS showed higher activation. mTBI patients also

showed weak ERP N350 amplitude for both WM and control tasks, without the expected larger amplitude for the WM task. Across all participants, N350 amplitude change correlated with right DLPFC signal change. The authors interpreted their results as providing objective neurally based evidence for persistent symptoms after mTBI, indicating that such complaints cannot be attributed entirely to psychological or motivational factors.

Episodic memory functioning after mTBI

Problems in episodic memory encoding and retrieval are also commonly reported after mTBI. To examine neural correlates of these changes McAllister et al. (McAllister et al. 2001a; McAllister et al. 2006) studied 23 mTBI patients (~one month post-injury) and 15 controls using an event-related fMRI task (Saykin et al. 1999) in which participants listened to novel versus familiar words (familiar words were memorized to criterion prior to scanning). No response was required in this task, so performance was not assessed. Consistent with prior studies in healthy individuals, results demonstrated increased right DLPFC activation when hearing familiar words (recognition), and increased medial temporal lobe activation when hearing novel words (encoding). For both conditions, intensity and spatial extent of activation was reduced in mTBI patients relative to controls. These findings were interpreted as indicative of abnormalities in “passive” stimulus processing after mTBI. It was also noted that the abnormalities in novelty detection and recognition observed in this episodic memory task may also be reflected in the alterations in WM processing and brain activation described above, as these functions are also integral to many WM tasks (see also discussion of Stulemeijer et al.’s (Stulemeijer et al. 2010) work above regarding the interaction of working and episodic memory circuitry).

fMRI studies of mTBI in military populations

With the high incidence of TBI among American soldiers deployed to Afghanistan and Iraq, a recent area of fMRI research in mTBI has focused on military populations, both with regard to their unique mechanism of injury (i.e., blast exposure) and the effect of common comorbid pathologies (e.g., MDD, PTSD) on brain activation after mTBI. Understanding the relationship of these factors is critical, given the potential overlap of somatic and cognitive symptoms of mTBI and these psychiatric disorders. Scheibel et al. (Scheibel et al. 2012) examined brain activation after blast-induced mTBI in 15 soldiers (all male, 11 of whom reported exposure to multiple blasts, six of whom reported multiple blast-related TBIs) who served in Iraq or Afghanistan relative to 15 soldiers (one female) who did not experience blast exposure or TBI during deployment. Of note, this mTBI sample was studied on average 2.6 years post-injury. A stimulus–response compatibility task was used during fMRI scanning, in which 75 % of trials required participants to respond with a button press matching the direction of an arrow, while in 25 % of trials they were to respond in the opposite direction. mTBI participants showed higher depressive, PTSD, and somatic symptoms (based on self-report scales) than non-TBI participants. There were no between-group differences in fMRI task accuracy, though mTBI participants showed slower response times when task conditions were combined. The mTBI group showed greater activation than the non-TBI group in a distributed network including anterior and posterior cingulate gyrus, medial frontal cortex, parietal lobe, and other regions during stimulus–response incompatibility. This greater activation was accentuated when analyses controlled for task reaction speed and depressive and PTSD symptoms. Activation in posterior regions was negatively correlated with PTSD symptoms across all participants. These results were interpreted as consistent with prior studies showing increased task-related activation after mTBI, as well as to show potential effects of both mTBI and mood/traumatic symptoms on brain functioning. These results are particularly interesting given the long injury to assessment interval. For this study mTBI patients were largely recruited from a TBI clinic

(i.e., patients seeking services), while controls were mostly recruited via a research database (i.e., a more community-based sample). As the authors note, future work in this area will be important to address limitations of this study, including group matching for combat exposure and sample selection bias.

In one of the few studies in mTBI examining treatment effects, Roy et al. (Roy et al. 2010) are in the process of studying Iraq or Afghanistan veterans with blast-induced mTBI, PTSD, both, or neither (controls), to determine whether fMRI activation patterns during an Affective Stroop task can distinguish these groups, and whether virtual reality exposure therapy (versus imaginal exposure) for PTSD alters brain activation patterns post-treatment. While enrollment is ongoing, this paper presents data on the first eight participants to complete pre- and post-treatment scans (three PTSD only, five mTBI/PTSD participants, time since injury unclear), collapsed across treatment condition. Clinical Global Impression scores showed improvement after treatment, while fMRI activation patterns showed changes in multiple brain regions of interest, including decreases in activation in amygdala, subcallosal gyrus, and lateral prefrontal cortex, as well as increased activation in anterior cingulate cortex. Amygdalar and inferior frontal gyrus activation in response to negative stimuli was decreased from pre- to post-treatment, while activation in these regions to neutral stimuli was unchanged to increased. While very preliminary, these findings offer suggestive evidence that fMRI can be used to monitor behavioral treatment response in individuals with mTBI and PTSD (see further discussion of behavioral and pharmacological intervention studies below).

In addition to PTSD, depressive symptoms as well as new onset MDD can be sequelae of TBI, with potentially significant negative effects on functioning and quality of life. Matthews et al. (Matthews, Strigo et al. 2011) examined a group of male Afghanistan or Iraq veterans who had experienced blast-related mTBI and had current MDD to those who did not develop MDD ($N=11$ in each group) using fMRI and diffusion tensor imaging (DTI) to assess white matter integrity. Of note, all but one participant in each group reported having experienced multiple mTBIs (mean of 2.8–3.3 years since most severe mTBI), and all but three participants also met criteria for current combat-related PTSD. Participants with MDD were significantly more likely to have experienced LOC than the non-MDD group, and PTSD symptom severity was also significantly worse in the MDD group. Participants completed an emotional face matching task (angry, fearful, happy stimuli), with a control condition of shape matching; there were no between-group differences in task performance. Consistent with study hypotheses, the MDD group showed significantly greater activity in bilateral amygdalae during face matching than the non-MDD group, and also showed greater activation in cerebellum, thalamus, and middle temporal gyrus, and lower activation in DLPFC, middle frontal gyrus, and other cortical and subcortical regions when matching fearful stimuli. The MDD group showed lower fractional anisotropy (FA), a DTI measure of white matter integrity, in corona radiata, corpus callosum, and superior longitudinal fasciculus (SLF). Greater depressive symptoms correlated negatively with SLF FA within the MDD group, while fMRI activation did not correlate with depression, and neither fMRI nor DTI metrics correlated with PTSD symptoms. These findings were interpreted as suggestive of a role for LOC in the development of MDD after mTBI, and as indicating that microstructural changes (e.g., alterations in white matter) may also play a role in development of MDD symptoms. Overall, findings were also consistent with prior fMRI and DTI studies in patients with MDD independent of mTBI, showing dysregulation of brain networks subserving the fear response and regulating executive control.

To further determine the role of LOC in mTBI sequelae, this group (Matthews, Simmons and Strigo 2011) examined differences in brain activation during a stop signal task between male soldiers who served in Iraq or Afghanistan and experienced alteration of consciousness

(AOC; $N=12$) versus loss of consciousness (LOC; $N=15$) after blast-related mTBI (mean of 3.2–3.6 years since most severe mTBI). The fMRI task was individualized to ensure comparable difficulty across participants, and activation was examined for correct hard minus correct easy inhibit trials in terms of ability to predict AOC/LOC status, after controlling for the presence of MDD. There were no between-group differences in task performance. Left ventromedial prefrontal cortex (VMPFC) showed a significant interaction effect, with decreased activation in LOC participants during easy trials. Brain activation in this region during easy inhibitory trials showed a positive correlation with somatic symptoms in LOC patients. Analysis of the effect of depressive symptoms showed that participants with MDD showed less inhibition-related activation in anterior cingulate, cerebellar, and superior frontal gyrus regions. These findings were interpreted as suggesting a role for VMPFC in self-awareness, such that LOC patients were thought to be less self-aware, therefore reporting fewer somatic symptoms (correlating with lower VMPFC activation).

The above studies are the first to examine mTBI in military populations using fMRI, and offer important preliminary findings. Additional considerations will need to be addressed in future work in this area. As is often the case in mTBI more generally, careful attention must continue to be paid to acquiring the most accurate data possible regarding diagnosis and injury-related factors such as loss of consciousness and its duration, length of peritraumatic amnesia, and any available objective data regarding confirmatory evidence of traumatic injury. This can be especially difficult for blast injury, where it can be unclear whether an actual blow to the head was sustained (versus examination of the potential effects of exposure to a blast wave itself).

Functional connectivity abnormalities after mTBI

Analysis of “default mode” or “resting state” brain networks has recently become an active area of fMRI research (see Stevens et al. 2012), allowing the investigation of the relationships between brain regions without requiring performance of a specific cognitive task. In brief, early (Biswal et al. 1995) and subsequent studies have demonstrated that analysis of low frequency fluctuations from BOLD fMRI scan acquisition while participants are at rest can reveal patterns of intrinsic connectivity among brain regions (see (Deco et al. 2011; Raichle and Snyder 2007) for review). Many reports have focused on the “default mode” (Raichle et al. 2001), in which a characteristic network of regions including the retrosplenial or posterior cingulate cortex (PCC) and ventral anterior cingulate cortex (ACC) show enhanced and connected activity at rest and deactivation during any type of task performance.

To date, two published studies have begun to examine the effect of mTBI on resting state/default mode functional connectivity (see also Stevens et al. 2012). Tang et al. (Tang et al. 2011) examined thalamic resting state networks in 24 mTBI patients (~three weeks post-injury) and 17 healthy control participants. Relative to controls, the mTBI group showed more widely distributed resting cortico-thalamic functional connectivity, with significant connectivity in an expanded extent of neural circuitry than that demonstrated in the control group (significantly greater connectivity in mTBI than controls in cingulate, temporal, and frontal regions). mTBI patients also showed decreased symmetry of thalamic resting state networks relative to the control group. Correlational analyses corrected for multiple comparisons showed that older mTBI patients and those with greater depressive symptoms showed significantly lower asymmetry. No relationships between fMRI activation and cognitive or injury-related variables survived correction for multiple comparisons. Findings were interpreted as suggesting upregulation of thalamocortical connectivity due to subtle thalamic injury in mTBI.

Mayer et al. (Mayer et al. 2011) used functional connectivity analyses to attempt to predict persistent cognitive symptoms in mTBI via examination of the DMN and its relationship with activity in a frontoparietal task-related network (TRN), as well as assessment of white matter integrity with DTI. They first examined 26 mTBI patients within 3 weeks of injury (mean ~12 days), in comparison to 25 control participants. Fifteen of the mTBI patients and 15 controls then had usable follow-up data 3–5 months later (mean 110–115 days). At the initial assessment, mTBI patients showed greater emotional, cognitive, and somatic complaints than controls, though objective cognitive functioning did not significantly differ between groups. This between-group difference in emotional and somatic complaints persisted over time, though mTBI patients showed decreased cognitive complaints at the second study visit (complaints were still greater for mTBI than controls at follow-up). At initial assessment mTBI patients showed decreased functional connectivity within the DMN relative to controls. DMN and TRN activation have been shown to be strongly anticorrelated (i.e., negatively correlated) in healthy individuals. In this cohort, mTBI patients showed varying differences from controls in terms of anticorrelations between the DMN and TRN, demonstrating regions of both greater and weaker connectivity. Functional connectivity measures were predictive of group status (mTBI or control) and cognitive complaints within 3 weeks of injury, but did not show changes at the later assessment. DTI metrics showed increased FA in the mTBI group in the external capsule and anterior corona radiata (white matter tracts important in connectivity of nodes of the DMN and TRN) relative to controls at the first visit, with a significant change (partial normalization) of external capsule values at the second visit, but no change in anterior corona radiata. Regression analyses showed relationships between structural and functional connectivity metrics for controls, but not mTBI patients. These findings were interpreted to show reduced connectivity within the DMN after mTBI, consistent with prior studies in more severely injured TBI patients, as well as disruption in DMN-TRN connectivity.

Intervention after mTBI: cognitive rehabilitation and pharmacological challenges

In addition the work of Roy et al. (Roy et al. 2010) described above, a few other studies have examined alterations in fMRI brain activation patterns after interventions targeting mTBI symptoms. In a case series of five patients, Laatsch et al. (Laatsch et al. 2004) examined changes in fMRI activation on visually guided saccade and reading comprehension tasks after cognitive rehabilitation therapy (CRT). In all patients notable improvements were evident from pre- to post-treatment on objective neuropsychological testing. Patients showed varying changes in brain activation, with both increases and decreases in task-related neural circuitry, which were interpreted potentially to reflect the effects of treatment as well as the normal process of spontaneous recovery in those patients who were within a relatively short time period from injury.

McAllister et al. (McAllister, Flashman et al. 2011; McAllister, McDonald et al. 2011) have recently reported results from pharmacological challenge studies examining the effects of dopaminergic and alpha-2 adrenergic agents on cognitive functioning and brain activation after mTBI. Based on evidence that altered dopaminergic regulation may play a role in WM deficits after mTBI (for review see (Arnsten 2011; Gamo and Arnsten 2011; McAllister, Flashman et al. 2004)), particularly in prefrontal regions (Arnsten et al. 1998), these authors (McAllister, Flashman et al. 2011) examined the effects of dopamine D₂ receptor agonist bromocriptine (1.25 mg) versus placebo in 26 mTBI patients about 1 month post-injury relative to 31 healthy controls. The N-back task used was the same as that described above (McAllister et al. 2001b), except that letters were presented visually instead of aurally. On bromocriptine relative to placebo controls showed stable to improved task performance, whereas mTBI patients showed poorer performance. Between-group differences were also

seen on bromocriptine (though not on placebo), with poorer performance in the mTBI group. Controls showed greater activation than mTBI patients in typical WM circuitry in both drug conditions; this effect was more prominent on bromocriptine than placebo. In contrast, when on bromocriptine mTBI patients showed greater activation than controls outside of typical WM circuitry. Across both groups, greater right middle frontal gyrus activation when on bromocriptine was correlated with better 3-back task performance. Findings were interpreted as supportive of study hypotheses that dopaminergic functioning is altered after mTBI, which may in part underlie observed WM deficits.

This group (McAllister, McDonald et al. 2004; McAllister et al. 2006) also examined the relationship of brain activation patterns to the catechol-O-methyl transferase (*COMT*) *val158met* allele in a subset of the participants studied in (McAllister, Flashman et al. 2011). This polymorphism has been shown to influence frontal executive performance, with the *val* allele associated with more efficient dopamine metabolism and poorer task performance, presumably due to decreased DA availability (Egan et al. 2001; Lipsky et al. 2002). In a group of 27 mTBI patients and 13 controls, McAllister et al. (Fig. 3) demonstrated significantly greater WM-related activation (3-back>0-back contrast) on fMRI in individuals homozygous for the *met* allele compared to those with a *val* allele.

It was therefore hypothesized that *val*-positive participants would show greater increases in frontal cortical activation after bromocriptine administration. Ten mTBI patients and nine controls were divided by polymorphism status (12*val*-positive, 7*val*-negative), and their placebo and bromocriptine scans were compared. On placebo, *val*-negative participants showed greater anterior frontal activation during the 3-back>0-back contrast, while *val*-positive participants showed more posterior frontal and parietal activation. In contrast, on bromocriptine *val*-positive participants showed a significant increase in bifrontal regions, particularly left DLPFC and inferior prefrontal cortex. These findings suggest an interaction between *COMT* genotype and drug response, whereby individuals with presumably more efficient dopamine metabolism showed focal frontal increases in brain activation during WM processing following administration of a dopamine agonist. This contrasted to brain activation patterns when on placebo, where these participants showed essentially no increased frontal activation relative to *val*-negative individuals.

To further investigate catecholaminergic system alterations after mTBI, McAllister et al. (McAllister, McDonald et al. 2011) examined the effects of the alpha-2A adrenergic agonist guanfacine using the same challenge paradigm. In contrast to the above findings with bromocriptine, mTBI patients who received guanfacine (2 mg) showed improved WM performance (relative to placebo), particularly for the 2-back condition. This was accompanied by increased task-related activation in WM circuitry, particularly in the right middle frontal gyrus. This contrasted with activation in the mTBI group on placebo, where greater activation was seen outside of typical WM circuitry. The control group showed nonsignificantly poorer performance on guanfacine than placebo, accompanied by increased activation outside of typical WM circuitry, similar to that seen in the mTBI group on placebo. These findings were supportive of differential catecholaminergic system response to pharmacological challenge after mTBI. While patients showed improved task performance accompanied by increased task-related activation, particularly in frontal regions, control subjects showed increased activation outside of typical WM circuitry, accompanied by somewhat poorer task performance. For both pharmacological challenge studies (McAllister, Flashman et al. 2011; McAllister, McDonald et al. 2011) the pattern of greater activation outside of neural circuitry typically used for WM processing in different groups and drug conditions raises the question of whether this might represent ineffective compensatory activation versus a failure to deactivate brain regions which typically are not associated with WM.

Conclusions and future directions

Overall, there have been relatively few fMRI studies examining mTBI, which is surprising given the predominance of mTBI among individuals who have experienced brain injury. More studies with large and well-characterized samples are clearly needed. As highlighted by the recent work in the area of blast injury, one area of continued interest will be the examination of whether investigation of different mechanisms of injury will provide insight into the pathophysiology of mTBI and its sequelae (i.e., are there unique features of different injury types, or do commonalities outweigh differences?). Relatedly, it will continue to be important to consider psychosocial factors in the study of individuals after mTBI, including the effects of psychiatric symptoms (e.g., PTSD, MDD) as well as other potential confounding variables which may be population-specific (e.g., secondary gain issues, desire to return to play in athletes, etc.; see also Rosenbaum and Lipton 2012 regarding consideration of patient heterogeneity in mTBI research).

Another highly probable source of individual difference in mTBI injury and recovery profiles is genetic variation. Although smaller studies can productively examine the role of polymorphisms of candidate genes such as *APOE*, *BDNF*, and *COMT*, large multicenter studies will be needed to collect sufficient data to permit genome-wide association studies (GWAS) that require hundreds to thousands of participants to investigate up to seven million imputed single nucleotide polymorphism (SNP) markers on a microarray. Further, we are now entering the era of large scale whole exome and whole genome sequencing that can identify novel and rare variants, including discovery of new SNPs related to trauma or treatment response. Pharmacogenomics combined with fMRI is likely to take on an increasingly important role in the development of personalized medicine approaches to mTBI over the next decade.

It will also be critical to begin to examine the interaction between mTBI and aging, including cognitive disorders of aging. While age ranges varied somewhat, all of the studies described above include patients (and controls) with mean age in the 20s–30s. These data therefore cannot adequately address the issue of age-related variation in functional brain changes after mTBI. The issue of developmental differences is also equally applicable to fMRI of mTBI in children (e.g., (Krivitzky et al. 2011)).

Timing of functional imaging assessments in relation to one or more mTBIs will have major implications for injury characterization and measurement of recovery/therapy mechanisms. To date, most fMRI studies of mTBI have focused on the subacute post-injury period (1 to 2 months post-injury). The very limited number of longer-term follow-up studies or longitudinal investigations of activation changes over time shows the need for further work in this area. Although challenging to conduct, acute fMRI studies in the minutes to hours after injury would be valuable as well. The sports concussion field discussed by Slobounov et al. (2012) is one context where such studies may be feasible, as evidenced by studies which have imaged participants within days to a week of injury (Breedlove et al. 2012; Jantzen et al. 2004; Lovell et al. 2007; Pardini et al. 2010).

The majority of studies to date have utilized cognitive tasks where mTBI patients show comparable performance to healthy controls. While this is helpful for understanding brain activation patterns that sustain “intact” cognitive processing, it will be useful for future work to examine the relationship between brain activation and task performance explicitly, either by examining relationship of activation to performance within and across patient and control groups or by imaging TBI patients during performance of cognitive tasks where functioning is in fact impaired relative to controls. The few studies which have looked at performance-brain activation relationships to date have typically shown increased activation in task-

related neural circuitry to correlate with better performance. However, measures of symptomatology (e.g., PCS, PTA, PTSD, MDD) have shown both positive and negative correlations with brain activation, which may be region-specific. The same has been true for the small number of resting state studies in this area (i.e., both increases and decreases in functional connectivity have been reported). Continued research to determine factors which drive alterations in brain activation in mTBI will be of benefit to advance understanding of the relationship of these changes to symptom status and treatment response. Along these lines, continued investigation of both task-related activation and deactivation of specific brain networks, as well as examination of activation within and outside of expected neural circuitry for a given task are likely to lead to additional insights regarding alterations in brain function after mTBI.

Much has been written using earlier pathological and structural imaging data with regard to differential regional vulnerabilities to more severe TBI. fMRI is ideally suited for noninvasive analysis of the impact of mTBI on both regional vulnerabilities to injury and on key functional circuits (e.g., memory, attention, emotion regulation) both shortly after injury as well as during recovery. The fMRI studies reviewed here show a notable convergence of evidence demonstrating abnormalities in frontal lobe function after mTBI, with several studies reporting specific alterations in mTBI patients in the middle frontal gyrus. This suggests that continued investigation of dysfunction of the frontal lobes and related neural circuitry modulating cognition and behavior will be fruitful.

In conclusion, fMRI is a key tool for understanding the sequelae of mTBI. New knowledge is most likely to emerge from larger cross-sectional and longitudinal fMRI studies including various points in the lifespan. Individual variation in injury and response will remain critical topics, and studies that specifically address injury mechanics and genetic and environmental influences on outcomes will be highly valuable. As the preeminent method that can capture temporal dynamics, fMRI will remain important as a repeatable bio-marker for research on neurorehabilitative interventions, including behavioral and/or pharmacological approaches. However, going forward it will be insufficient to simply show “activation differences” between injured and non-injured groups. Rather, the functional significance of such differences must be demonstrated, and must be consistent with plausible neurobiological models of the target signs and symptoms. This is of particular importance for resting state studies, where disruption of widespread networks is to be expected given the diffuse nature of the typical TBI. The critical issue is to establish the functional significance of these disruptions and ascertain the implications of these findings for treatment. In this context, benefit is likely to derive from multimodality imaging studies combining structural, functional, and molecular techniques. For example, changes on fMRI in mTBI could be analyzed in relation to gray and white matter integrity on structural MRI, to changes in cerebral blood flow using MR perfusion, and to PET molecular imaging probes targeting tau, amyloid or neuroinflammation. fMRI, coupled with enhanced research designs and other imaging modalities and biomarkers, will provide a deeper understanding of mTBI pathophysiology and thereby facilitate development of therapeutic and possibly preventative strategies.

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Summary points

- Despite extensive research regarding the potential morbidity related to mild TBI, relatively few published studies (< 20) have examined cognitive sequelae using fMRI since the first studies just over a decade ago.
- This limited literature in adult mTBI has focused on a relatively circumscribed set of topics, including frontal lobe/executive functions, episodic memory, resting state/ functional connectivity, blast injury in military populations and comorbid psychiatric conditions, and response to behavioral/pharmacological intervention. A recent development has been the study of sports-related concussion and subconcussive injury, and a very small literature has examined pediatric mTBI in other contexts.
- The evidence consistently demonstrates differences between mTBI patients and healthy controls, with findings of increased or decreased brain activation in task- and region-specific patterns. However, studies vary in the degree to which such differences are demonstrated to have specific functional or diagnostic correlates, making it difficult to assess the significance of some findings.
- fMRI in combination with related methods can be expected to play an increasing role in research related to studies of pathophysiological mechanisms of the sequelae of mTBI as well as in diagnosis and treatment monitoring.

Fig. 1.
Verbal N-back task design showing 0-back, 1-back, 2-back, and 3-back conditions

Fig. 2.
Typical bifrontal and biparietal working-memory task-related activation for 3-back>0-back condition in a group of 35 healthy adult control participants

Fig. 3.
Regions of increased activation in working memory circuitry (3-back>0-back) as a function of COMT genotype (*met/met*>any *val*) in 40 individuals (27 with mTBI, 13 healthy controls)

fMRI studies in mTBI

Table 1

Study	Participants (% Male) ^a	Age Mean(SD)	Time since mTBI Mean(SD), range	fMRI tasks used	fMRI task performance	Major fMRI findings
McAllister et al. 1999	mTBI N=12(50) HC N=11(36)	29.4(10.2) 30.6(11.2)	22.1 days(10.5), 6–35 days	Auditory-verbal N-back (0-back, 1-back, 2-back conditions)	No group difference	mTBI greater increase in activation than HC with higher WM load
McAllister et al. 2001b	mTBI N=18(44) HC N=12(50)	31.8(12.5) 27.8(8.0)	26.9 days(NR), NR	Auditory-verbal N-back (0-back, 1-back, 2-back, 3-back conditions)	No group difference	HC gradual increase in activation with WM load; mTBI greater increase at moderate WM load, less increase at highest WM load
Laatsch et al. 2004	mTBI N=5(40)	32.8(14.8)	9.4 months(11.8), 2–29 months	Visually guided saccade (tracking, fixation conditions); Reading comprehension (reading conditions); fixation conditions	NR	Patients showed increases and decreases in activation from pre- to post-treatment, thought to reflect treatment effects and normal spontaneous recovery
McAllister et al. 2006 (McAllister et al. 2002)	mTBI N=11(45) HC N=6(33)	33.3(11.6) ^b 27.8(8.8)	~One year (Details NR) (subset of McAllister et al., 2001b)	Auditory-verbal N-back (0-back, 1-back, 2-back, 3-back conditions)	No group difference	mTBI showed greater increase in right frontal activation than HC over time; Across groups increased task performance correlated with increased left frontal activation over time
McAllister et al. 2006 (McAllister et al. 2001a)	mTBI N=23(NR) HC N=15(NR)	NR NR	~One month (Details NR)	Word listening task (novel and familiar conditions)	NA	Frontal/medial temporal activation reduced in mTBI relative to HC when listening to novel/familiar words, respectively
McAllister et al. 2006 (McAllister, Flashman et al. 2004)	mTBI N=10 ^c HC N=9	Overall group mean = Mid-30s (SD NR)	~One month (Details NR) (subset of McAllister, Flashman et al. 2011)	Visual-verbal N-back (0-back, 1-back, 2-back, 3-back conditions)	NR	On placebo participants with the COMT <i>val</i> allele showed lower anterior frontal activation than those without the allele; after administration of bromocriptine those with the <i>val</i> allele showed focal frontal activation increases
Mayer et al. 2009	mTBI N=16(50) HC N=15(NR)	27.2(7.6) 27.3(7.4)	11.9 days(5.9), 3–20 days	Auditory orienting (valid and invalid cue conditions)	mTBI greater reaction time for invalid than valid trials	Attentional abnormalities in mTBI accompanied by hypoactivation within attentional circuitry; A broader network of brain regions accounted for variance in HC than mTBI
Smits et al. 2009	mTBI N=21(57) HC N=12(67)	25.9(7.2) 27.8(10.0)	30.6 days(NR), 18–40 days	Motor (right hand finger tapping, rest conditions) Auditory-numerical N-back (rest, 0-back, 1-back, 2-back conditions) Counting Stroop (rest, neutral, interference conditions)	Patients with severe PCS had lower N-back and Stroop interference performance	Positive correlation between PCS and brain activation during N-back and Counting Stroop tasks. At higher WM load a positive correlation was noted between PCS and activation outside typical WM circuitry
Roy et al. 2010	PTSD N=3 ^d PTSD/mTBI N= 5	Overall group mean = 34 (NR)	NR	Affective Stroop (picture, number sequences,	NR	After treatment for PTSD patients showed decreased activation in amygdala, subcallosal gyrus, and lateral prefrontal

Study	Participants (% Male) ^a	Age Mean(SD)	Time since mTBI Mean(SD), range	fMRI tasks used	fMRI task performance	Major fMRI findings
Stulen et al. 2010	mTBI N=43(56) HC N=20(55)	31.1(NR) 33.5(NR)	24.6 days(10.5), 6–42 days	picture/number conditions Visual-numerical N-back (0-back, 2-back conditions)	No group difference	cortex, and increased anterior cingulate activation; amygdalar and inferior frontal decreases specific to negative stimuli PTA showed a significant negative correlation with hippocampal activation; Worse PTA also correlated with worse cognitive complaints and poorer memory
Witt et al. 2010	mTBI N=31(67) HC N=31(67)	33.6(14.0) 33.2(13.8)	64.9 days(47.7), 13–200 days	Auditory oddball (standard, target, novel conditions)	No group difference	mTBI showed regions of increased and decreased activation relative to HC; Frontal alterations thought related to underlying attentional abnormalities
Gosselin et al. 2011	mTBI N=13(50) HC N=23(52)	31.9(12.7) 27.8(9.7)	5.7 months(3.9), 2–11 months	Externally ordered working memory (working memory, control conditions)	No group difference	Decreased task-related activation and deactivation in mTBI relative to HC; Greater PCS correlated with higher and lower activation in varying brain regions
Matthews, Simmons and Strigo 2011	mTBI/MDD N=11(100) mTBI N=11(100)	26.8(NR) 30.3(NR)	2.8 years(1.0) ^e 3.3 years (1.1)	Emotional face matching (face, shape conditions)	No group difference	mTBI/MDD showed greater activation than mTBI in emotional circuitry during face matching, particularly for fearful stimuli
Matthews, Strigo et al. 2011	mTBI/AOC N=12(100) mTBI/LOC N=15(100)	29.0(5.1) 26.9(5.6)	3.6 years(1.3) ^e 3.2 years(1.4)	Stop signal (go, stop conditions)	No group difference	mTBI/LOC showed decreased left ventromedial prefrontal activation than mTBI/AOC for easy trials; Brain activation in this region was correlated with somatic symptoms for mTBI/LOC
Mayer et al. 2011	mTBI N=26(42) ^f HC N=25(40)	27.2(7.4) 27.1(7.3)	11.5 days (4.6), 3–20 days	Resting state	NA	mTBI showed decreased functional connectivity in default mode network relative to HC; mTBI showed altered anticorrelations between default mode and task-related networks; Findings were similar at follow-up scan
McAllister, Flashman et al. 2011	mTBI N=26(58) HC N=31(45)	28.3(11.3) 31.8(9.7)	39 days (16.1), 14–78 days	Visual-verbal N-back (0-back, 1-back, 2-back, 3-back conditions)	On bromocriptine mTBI showed poorer performance compared to placebo and compared to HC on bromocriptine	In both drug conditions HC showed greater activation than mTBI in WM circuitry; On bromocriptine mTBI showed increased activation outside of WM circuitry; Increased activation in right middle frontal gyrus on bromocriptine correlated with task performance across participants
McAllister, McDonald et al. 2011	mTBI N=13(54) HC N=14(43)	27.2(11.7) 32.0(8.5)	37.2 days (17.6), NR	Visual-verbal N-back (0-back, 1-back, 2-back, 3-back conditions)	On guanfacine mTBI showed improved task performance, while HC showed somewhat poorer performance	On guanfacine mTBI showed increased activation in WM circuitry, particularly middle frontal gyrus; mTBI on placebo and HC on guanfacine showed greater activation outside WM circuitry
Tang et al. 2011	mTBI N=24(71) HC N=17(NR)	37.3(NR) 35.2(NR)	22 days (NR), 3–53 days	Resting state	NA	mTBI showed wider distribution of cortico-thalamic connectivity and decreased symmetry of thalamic resting state networks than controls; Lower asymmetry for older patients and those with greater depressive symptoms

Study	Participants (% Male) ^a	Age Mean(SD)	Time since mTBI Mean(SD), range	fMRI tasks used	fMRI task performance	Major fMRI findings
Scheibel et al. 2012	mTBI N=15(100) HC N=15(93)	28.7(6.0) 30.9(5.6)	963.9 days (333.2), 402–1511 days	Stimulus–response compatibility (compatible, incompatible, rest conditions)	mTBI slower response times across both task conditions	mTBI greater activation in distributed network during incompatible trials; Activation in posterior regions negatively correlated with PTSD symptoms across all participants

mTBI mild traumatic brain injury, HC healthy control, WM working memory, NR not reported, NA not applicable, COMT catechol-O-methyl transferase, PCS post-concussive symptoms, PTSD post-traumatic stress disorder, PTA post-traumatic amnesia, MDD major depressive disorder, AOC alteration of consciousness, LOC loss of consciousness

^aFinal number of participants included for fMRI after any exclusions

^bAges reported are for one month post-injury time-point

^c26 % of total sample was male, age not broken down by TBI/HC status

^dThree female participants total in larger sample reported in paper

^eDuration since most severe mTBI, ranges NR

^fFifteen participants from each group returned for a second scan three to five months later