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Functional Magnetic Resonance Imaging of Working Memory and Response Inhibition in Children with Mild Traumatic Brain Injury

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Abstract

The current pilot study examined functional magnetic resonance imaging (fMRI) activation in children with mild traumatic brain injury (mTBI) during tasks of working memory and inhibitory control, both of which are vulnerable to impairment following mTBI. Thirteen children with symptomatic mTBI and a group of controls completed a version of the Tasks of Executive Control (TEC) during fMRI scanning. Both groups showed greater prefrontal activation in response to increased working memory load. Activation patterns did not differ between groups on the working memory aspects of the task, but children with mTBI showed greater activation in the posterior cerebellum with the addition of a demand for inhibitory control. Children with mTBI showed greater impairment on symptom report and "real world" measures of executive functioning, but not on traditional "paper and pencil" tasks. Likewise, cognitive testing did not correlate significantly with imaging results, whereas increased report of post-concussive symptoms were correlated with increased cerebellar activation. Overall, results provide some evidence for the utility of symptom report as an indicator of recovery and the hypothesis that children with mTBI may experience disrupted neural circuitry during recovery. Limitations of the study included a small sample size, wide age range, and lack of in-scanner accuracy data. (*JINS*, 2011, *17*, 1143–1152)

Keywords: Concussion, Brain, Inhibition, Traumatic brain injury, Cerebellum, Prefrontal cortex, Post concussive symptoms

INTRODUCTION

Traumatic brain injury (TBI) is an important public health issue in the United States. Pediatric TBI has an estimated annual incidence of 180 cases per 100,000, accounting for over 400,000 hospital visits each year (Kraus, Sivak, & Kucera, 1995; Langlois, Rutland-Brown, & Thomas, 2004). Mild TBI (mTBI) accounts for 80 to 90% of all treated cases (Cassidy et al., 2004). However, current published rates of mTBI may be an underestimate given that many mild injuries go untreated or are otherwise unaccounted for (Cassidy et al., 2004; McCrea, Hammeke, Olsen, Leo, & Guskiewicz, 2004; Williamson & Goodman, 2006). mTBI has been defined by the Centers for Disease Control (CDC) as an injury that occurs when an impact or forceful motion of the head results in a brief alteration of mental status, loss of consciousness less than 30 min (or not at all), and post-traumatic amnesia less than 24 hr. A range of neurobehavioral changes are seen in the first days and weeks after mTBI and include somatic, cognitive, and emotional/behavioral difficulties. Commonly reported somatic and emotional symptoms include headache, dizziness, fatigue, sensitivity to light and noise, difficulty concentrating, trouble remembering, and increased anxiety (Mittenberg, Wittner, & Miller, 1997; Yeates et al., 1999). Cognitive changes typically include problems in attention, speed of processing, working memory, and response inhibition (Babikian & Asarnow, 2009; Levin et al., 2002; Satz et al.,1997).

Resolution of these neurobehavioral changes following pediatric TBI can be variable across children and may range from a few hours to days or months. In well-controlled pediatric studies, cognitive and achievement deficits have

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been shown to resolve in the majority of cases within 2–3 months post-injury (Carroll et al., 2004; Satz et al., 1997; Yeates & Taylor, 2005), although there is a subset of children who are "slow to recover" in which resolution of subjective somatic and emotional symptoms may be more variable (Gagnon, Galli, Friedman, Grilli, & Iverson, 2009; Kirkwood et al., 2008; Yeates et al., 2009). Yeates et al. (2009) found that there were two subsets of children with persistent post-concussive symptoms: those that had a moderate level of symptoms throughout the first year of recovery (12% of their mTBI sample), and those who had a high number of symptoms in the acute recovery period and a moderate level of symptoms up to 12 months following their injury (9% of their mTBI sample). Regardless of time course, the presence of symptoms has the potential to have both short- (hours to days) and long-term (weeks to months) consequences for developing children—at a minimum including school absenteeism and limitations in play and other activities (Mittenberg et al., 1997). Thus, a better understanding of the neural mechanisms underlying mTBI in children is critical in further understanding predictors of time to and extent of recovery.

The nature and exact location of the underlying brain insult is not fully understood in mTBI. Despite the presence of significant, and for some, enduring symptoms, standard structural neuroimaging often reveals no overt insult to the brain (Ruff et al., 1994), leading researchers to speculate that symptoms may be accounted for by metabolic changes affecting functioning or microscopic injury to white matter tracts (Capruso & Levin, 1992; Evans, 2006; Giza & Hovda, 2001; Levin et al., 1987). Leading researchers have suggested that mTBI does not typically cause cell death (as may be seen in more severe injuries) but rather a temporal neural dysfunction as a result of the complex biochemical disturbance triggered by the injury (Signoretti, Vagnozzi, Tavazzi, & Lazzarino, 2010).

This study examines the neural circuitry underlying two specific areas of cognitive functioning commonly affected in pediatric mTBI: working memory and response inhibition (Levin et al., 2002). These cognitive functions have been shown to be associated with the prefrontal cortex and frontal-striatal circuitries (Aron & Poldrack, 2005; Casey et al., 1995; Wager & Smith 2003), regions of the brain known to be vulnerable to the effects of TBI. These cognitive functions have been argued to serve as critical foundations for most aspects of cognitive and daily function (Miyake & Shah, 1999). Specifically, working memory involves manipulation of information during problem-solving, facilitation of information encoding and retrieval, planning, organization, and self-monitoring. Inhibitory control, defined as the ability to inhibit prepotent responses or to withhold a response that is inappropriate is essential to most aspects of self-regulation (Barkley, 1997).

Functional MRI (fMRI) is an imaging technique well suited to studying the neurobiological underpinnings of cognitive functioning and has successfully measured the blood oxygen level dependant (BOLD) response as a proxy for brain activity during tasks of working memory and inhibitory control in children (Casey et al., 1995, 1997). There is converging evidence that prefrontal and parietal cortices support the maintenance of information in working memory, and that the pattern and magnitude of brain activation depends partly on the nature and amount of information maintained in working memory (Thomason et al., 2008; Wager & Smith, 2003). Additionally, developmental differences in patterns of increasing activation in regions such as the frontal and parietal lobe, as well as cerebellum, have been reported, corresponding to maturational increases in working memory (O'Hare, Lu, Houston, Bookheimer, & Sowell, 2008). Similarly, inhibitory control has been reported to be subserved by a distributed network including prefrontal cortex, parietal lobe, as well as subcortical and other regions that also show maturational changes (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002; Tamm, Menon, Ringel, & Reiss, 2004). Thus, fMRI has the potential to elucidate networks important for working memory and response inhibition in children with mTBI.

fMRI has also been used to measure changes in brain functioning secondary to TBI in adults and children, although there are few fMRI studies in children with mild TBI. In an fMRI study by McAllister et al. (1999, 2001), adults with mTBI demonstrated different activation patterns in the prefrontal and parietal cortices when performing working memory tasks, even when objective performance on these tasks was comparable between the groups. Specifically, the adults with mTBI showed less activation increase than controls in a 1 back *versus* 0 back comparison (mild working memory demand) but more extensive activation increases in the 2 back *versus* 1 back comparison. These findings have been interpreted as inefficient brain functioning secondary to mTBI in adults, given the need for greater allocation of resources to accomplish the same working memory task. Newsome et al. (2007) found that children with TBI who performed as accurately as controls on an n-back task, showed greater activation on frontal and non-frontal brain regions. In contrast, children who had impaired n-back performance showed less extensive frontal and extrafrontal brain activation relative to controls (Newsome et al., 2007). A pilot fMRI study of children with moderate to severe TBI also noted greater activation of attention networks (including frontal and parietal regions) in a mTBI group *versus* controls on a CPT sustained attention task (Kramer et al., 2008).

To assess both working memory and inhibitory control, this study adapted a newly designed neuropsychological measure for in-scanner use. The Tasks of Executive Control (TEC) is a computerized assessment of two critical components of executive functioning, working memory and inhibitory control. It uses the n-back paradigm to assess working memory, the n-back having been used in both children and adults for the assessment of working memory and commonly used in fMRI studies. A recent meta-analysis of 24 studies of healthy adults found strong effects for several frontal lobe areas to be active during n-back tasks, including lateral and medial pre-motor areas, dorsolateral and ventrolateral prefrontal cortex, dorsal anterior cingulate, frontal poles, along with the posterior parietal cortex (Owen, McMillan, Laird, & Bullmore, 2005).

Other areas of activation may be observed during n-back tasks, such as the cerebellar and basal ganglia (Gazzaley, Rissman, & D'Esposito, 2004; Wager & Smith, 2003).

To assess inhibitory control, the TEC uses a go/no-go paradigm, which has also been used extensively in neuroimaging studies. In this paradigm, the individual must make a quick response when they see "go" stimuli and inhibit responding when they see "no-go" stimuli. Functional imaging studies in adults have found that neural circuitry for inhibitory control involves both frontal lobe regions (including inferior and orbital frontal regions) and regions outside the frontal lobes (Garavan, Ross, & Stein, 1999; Kelly et al., 2004; Konishi et al., 1999; Roth, Randolph, Koven, & Isquith, 2006; Roth et al., 2007).

The TEC has been previously shown to be sensitive to mTBI in children and adolescents (Isquith, Roth & Gioia, 2010). A group of 101 children with recent mTBI were reported to have greater difficulty with increases in working memory load and showed slower and more variable response speed than a typically developing group. Significant improvements in were seen in subsets of children with mTBI followed for several months post-injury, while the typically developing group showed only minor changes in performance over time. These findings support the utility of the TEC in identifying and tracking cognitive difficulties in children with mTBI.

In the present investigation, we adapted the TEC for use in the fMRI environment with children having sustained an mTBI. The primary aim of the study was to assess for potential differences in activation patterns on fMRI between children with symptomatic mTBI relative to controls. It was hypothesized that children with mTBI would show greater activation of relevant networks to increasing demand for working memory and inhibitory control. We hypothesized that traditional paper and pencil measures of neuropsychological functioning would not significantly differ between the groups, with the exception of the "real-world" measurements of functioning demonstrating greater impairments in the mTBI group. We based this hypothesis on our clinical experiences and prior work by McAllister et al. (1999, 2001). We also hypothesized that that worse performance on out of scanner measures of working memory/metacognitive skills would correlate with more atypical activation patterns on the fMRI tasks assessing similar domains.

METHODS

Participants

Thirteen children with symptomatic mTBI were closely age, gender, and IQ matched to 13 typically developing children (see Table 1 for subject characteristics). mTBI was defined by the Centers for Disease Control (CDC) definition (described in introduction). All subjects had no significant medical history (as determined by a pre-screening questionnaire) including history of a prior concussion. None of the patients had positive imaging findings on routine clinical CT or MRI when they were seen for initial evaluations in the emergency department or by their primary care physicians. Children were excluded if they had an estimated IQ score below 80 on the WASI (Wechsler, 1999) or a prior history of significant neurological injury/illness. In other fMRI studies, our group has found that an IQ cutoff of 80 is generally appropriate to ensure that the subjects will be able to follow the instructions and participate in the scanning procedure. Children with mTBI were recruited through the Safe Concussion Outcome Recovery and Education (SCORE) clinic at Children's National Medical Center (CNMC) in Washington, DC. Approximately 50–60 patients were approached, although several were eliminated due to contraindications for scanning and several declined due to the distance factors. Our final study population was generally representative of our clinic in terms of age and mechanism of injury, but not in terms of gender for the control group (i.e., control group: 54% male *versus* clinic population: typically approximately 67% male). All included subjects reported at least a minimal level of ongoing post-concussive symptoms,

Table 1. Subject characteristics

	Control ($n = 13$)	mTBI ($n = 13$)
Age (years)	$m = 12.2$ $SD \pm 3.5$	$m = 13.3$ $SD \pm 3.1$
Handedness		
Right	92% ($n = 12$)	92% ($n = 12$)
Race		
Caucasian	92% ($n = 12$)	85% ($n = 11$)
African American	8% ($n = 1$)	15% ($n = 2$)
Gender		
Male	54% ($n = 7$)	62% ($n = 8$)
+ Loss of consciousness (<30 min)	N/A	30% ($n = 4$)
Time interval from injury to testing (days)	N/A	29 (22) Range = 8–82, 70% tested within 30 days
Method of injury		
Sports related	N/A	85% ($n = 11$)
Motor vehicle accident		8% ($n = 1$)
Falls		8% ($n = 1$)

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using a cutoff of a score >10 on the parent report Post Concussion Symptoms Inventory (PCSI; range = 13–80). Control children were recruited through flyers posted in the community and advertisements in the CNMC newsletter. The study was approved by CNMC Institutional Review Board and consent/assent was obtained for all subjects enrolled in the study based on the guidelines in the Declaration of Helsinki.

MATERIALS: TASKS

fMRI Task

The task used in the present study was an adapted version of the TEC, a computerized test that combines a visual n-back working memory paradigm with a visual go/no-go inhibitory control paradigm (Isquith, Roth, & Gioia, 2010). The task is composed of separate zero-, one-, and two-back conditions; three of the conditions have only a working memory demand (0B, 1B, 2B), while three have demands for both working memory and inhibitory control (0BI, 1BI, 2BI). The 0B conditions serve as a vigilance control, with the 1B and 2B involving increasing working memory load. See Table 2 for stimuli included in each condition.

Each condition involved the sequential presentation of stimuli, which included color images of objects with very low verbal demand (e.g., tree, dog) in the center of the visual field. The participant is asked to place the color objects into one of two toy boxes based on the rules of the particular condition. Depending on the condition, participants are asked to respond to the following types of stimuli: (1) Frequent non-target stimuli (referred to as standards) with a right hand button press (into the right toy box); (2) Infrequent target stimuli (referred to as targets) with a left hand button press (into the left toy box). The subject was able to identify objects as targets based on the instructions (e.g., in the 1B condition, a target was any picture seen twice in a row- such as apple_ **apple;** in the 2B condition, a target was any picture seen for a second time after being sandwiched between another picture- such as shoe_chair_**shoe**); (3) Inhibit cues (only for the three inhibit conditions) in which there was a cartoon box surrounding a particular object. For inhibit cues, the correct response was no button push.

Three task runs were presented. The order of conditions was always the same for the first run (0B, 0BI,1B, 1BI, 2B, 2BI) to facilitate comprehension of task demands, then counterbalanced for the subsequent two runs, with the restriction that for each working memory load (0-, 1-, 2- back) the condition without inhibitory demand always preceded the condition with inhibitory demand. Total in scanner time for the TEC was approximately 20 min.

Neuropsychological Testing

Subjects underwent a brief battery of pen/paper neuropsychological tests and parent questionnaires, which were completed on a different day within the week before scanning. Working memory was assessed with Digit Span (Wechsler, 2004) and Auditory Consonant Trigrams (ACT; Brown, 1958, Peterson & Peterson, 1959); cognitive fluency/speed with Verbal Fluency (Delis, Kaplan, & Kramer, 2001; Korkman, Kirk, & Kemp, 1997) and academic fluency (Woodcock, McGrew, & Mather, 2001); and motor speed with the Digit Symbol Modalities Test (Smith, 1982) and Grooved Pegboard (Matthews & Klove, 1964); Parent/self report of post-concussion symptoms was assessed using the Post Concussion Symptom Inventory (PCSI; Gioia, Schneider, Vaughan, & Isquith, 2009) and "real world" executive functions with the Behavior Rating Inventory of Executive Function Parent report (BRIEF; Gioia, Isquith, Guy, & Kenworthy, 2000). Outcome measures were based on normative standardized scores, with the exception of the PCSI which was measured in raw scores.

Functional MRI Procedures

Preparation for imaging included an out-of-scanner practice version of the TEC and a mock scanner to ensure that the child felt comfortable and to emphasize staying still. Visual stimuli were presented using E-prime software version 1.1 (Psychology Software tools, Inc., Pittsburgh, PA). Subjects' task performance was recorded during the scan via left and right-hand button presses.

Functional data were acquired using a 3.0 Tesla (T) Siemens Magnetom Trio equipped with a standard circularly polarized (CP) head coil. Blood oxygen level-dependent (BOLD) changes were measured using a whole brain echo-planar imaging (EPI) sequence with parameters: repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, field of view (FoV) = 256 mm, and voxel size = $4.0 \times 4.0 \times 3.7$ mm. Whole brain volumes consisted of 34 axial slices of 3.7-mm thickness and with 0.2 mm between slices. Axial images were collected parallel to the anterior commissure-posterior commissure plane, which served as an origin of reference.

Table 2. Breakdown of stimuli in each of the conditions

Condition	No. of standards or "non-targets" (red button)	No. of targets (blue button)	No. of inhibitory trials (no button press)	Total trials
0 Back (0B)	48	12	0	60
0 Back inhibit (0BI)	39	12	9	60
1 Back (1B)	48	12	0	60
1 Back inhibit (1BI)	39	12	9	60
2 Back (2B)	48	12	0	60
2 Back inhibit (2BI)	39	12	9	60

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fMRI Analysis

Image data preprocessing and group analyses were performed using Statistical Parametric Mapping software (SPM5, Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (Version 7.4, Mathworks, Inc., Sherborn, MA). Images were reconstructed and realigned, normalized to Montreal Neurological Institute (MNI) standard anatomical space, and spatially smoothed using an 8 mm full width at half maximum Gaussian kernel and temporally filtered (high-pass filter: 128 s). Individual t-maps were generated by comparing the experimental conditions with different loads against each other with movement parameters as covariates of noninterest. One of the controls had to be removed from the scanner due to experiencing peripheral nerve stimulation. None of the other subjects moved more than a voxel (3 mm in any direction) during the scan, thus all were included in the analysis. A group map was generated from individual subject activation maps using a random-effects model to obtain a whole brain activation map and determine the network of brain regions activated during the task.

For region of interest analyses (ROI), ROIs were built based on coordinates from the Wager & Smith meta-analysis (2003) that were most appropriate for the particular scanner task used in this study (see Table 3). These ROIs included areas in the cerebellum, posterior parietal, frontal, and prefrontal regions.

Masks were created in the Wake Forest Pick Atlas according to anatomical regions (Maldjian, Laurienti, Kraft, & Burdette, 2003). The masks were applied in SPM5 to both groups in the two conditions that were shown to demonstrate positive findings in the whole brain analysis (1BI > 1B and 2B > 0B). This method involves subtracting out the activation in the baseline condition with lower level cognitive demand (e.g., 0B) from the active condition (e.g., 2B) to try to capture the true activation related to the skill we were trying to assess. The 2B > 0B was chosen to represent the basic working memory effect and the 1BI > 1B was chosen to represent the addition of the response inhibition effect. We did not choose the 2BI > 2B, as the difficulty level appeared to be too high for some subjects in the 2BI. A parameter estimate for magnitude of activation was calculated for each subject for each condition for each ROI according to the statistical significance of the activation. The parameter estimates were then exported to SPSS (SPSS, Inc., 2009, Chicago, IL, www.spss.com). T-tests were then run on the parameter estimates of each ROI selected with a significance level set to $p < .01$, with correction made for multiple comparisons based on the procedure of false discovery rates (Benjamini & Hochberg, 1995). Four of the ROIs were eliminated from the analysis due to little or no measurable activation. Thresholds were set at a p corrected value of <.05, with a minimum spatial extent of 20 voxels.

TEC Performance Data

Due to an E-prime programming error in the fMRI version of the TEC, we could not obtain appropriate behavioral performance on the task. Given this issue, we attempted to find other evidence that might support that the subjects were truly "doing the task." First, all subjects underwent practice outside the scanner and were not allowed to proceed with the scan until they demonstrated adequate understanding of the task (defined as correctly completing the 20 practice items for each condition). Second, a select group of subjects from both groups also underwent a letter n-back task and demonstrated high levels of accuracy across conditions (>90% accuracy in both groups), suggesting they understood the concept of the n-back task. Third, we examined imaging findings in the group of individuals with greater accuracy in the 400 ms time frame (defined as >50% accurate responses within that time frame) *versus* lower accuracy in the time frame. We acknowledge that the "lower accuracy" group may have just been using a speed-accuracy trade off, i.e., working slower and equally if not more accurate overall. However, this was at least one more way of looking at group differences to see if

Table 3. Regions of interest (ROI) for the 2B > 0B and 1BI > 1B

ROI #*	Center coordinates	Location estimates	*p* values
		2B > 0B Analysis	
1	−12, −70, 46	Posterior parietal	.307
3	−37, −51, 41	Parietal	.069
5	−45, 7, 32	Frontal	No activation
8	31, −59, 43	Parietal	.073
10	36, 36, 28	Prefrontal	No activation
11	45, 1, 29	Frontal	0.218
		1BI > 1B Analysis	
3	−37, −51, 41	Parietal	.162
4	−42, −55, −20	Cerebellum/ventral temp and occip	Not enough activation
7	29, −56, −26	Cerebellum/visual	.005**
9	34, 31, −4	Orbito-prefrontal/putamen	.43
10	36, 36, 28	Prefrontal	No activation

*From Wagner & Smith (2003).
**Significant after correction made for multiple comparisons.

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there was any evidence of differential activation in the slower *versus* faster responders. In this analysis, there were no differences found in brain activation between groups (data not shown), which may lend further evidence supporting the argument that the majority of participants were able to perform the task with reasonable accuracy. In addition to indirect evidence from our study, a similar research study in adults linked accuracy on an fMRI n-back task to greater activation in left frontal brain regions (McAllister et al., 1999). This prior finding provides some indirect support for the idea that performance accuracy may not have differed between our groups, as this particular brain region did not show any group differences in activation in our study. Thus, although we acknowledge the lack of in-scanner behavioral data as a limitation and plan to correct it in future studies, we believe that it is most likely that the subjects understood the TEC task as intended, despite having the inability to truly evaluate their behavioral responses.

Neuropsychological Test Data Analysis

Group differences on neuropsychological tasks were analyzed using *t*-tests. Select neuropsychological tests were also correlated with the fMRI contrasts, as follows; measures of working memory (i.e., ACT, Digit Span) were correlated with the n-back task (2B>0B); measures of symptom severity (i.e., PCSI) and real world executive functioning (i.e., BRIEF) were correlated with imaging data for each group separately. For each set of analyses, significance was set at $p < .05$, with correction made for multiple comparisons based on false discovery rates.

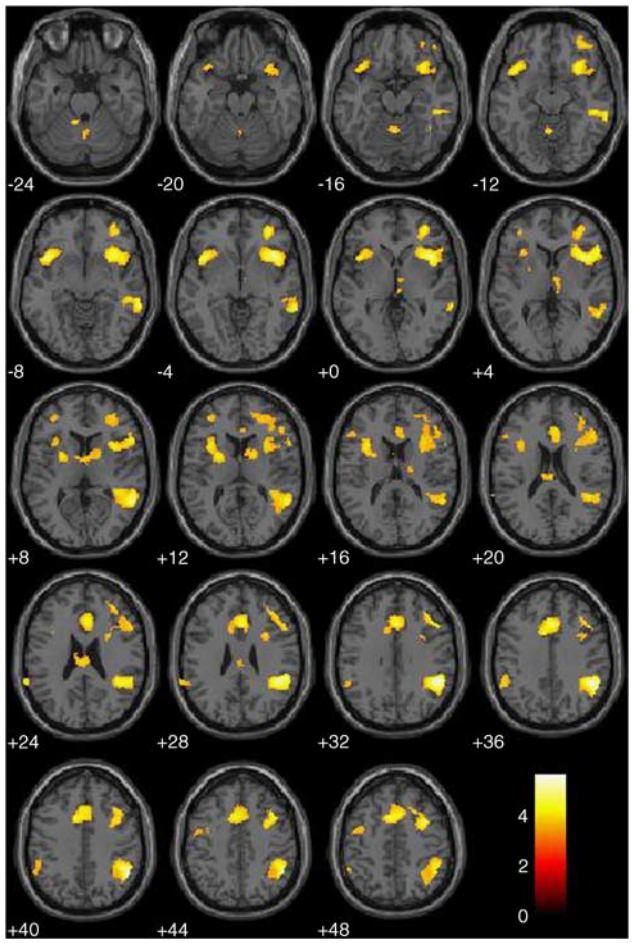

Fig. 1. Whole group maps for 2B > 0B.

RESULTS

fMRI Group Analysis: Whole Brain

A main effect of working memory load was observed in the 2B > 0B contrast for all subjects combined. As predicted, there was more activation of bilateral inferior frontal gyrus and parietal areas in response to increased working memory load (Figure 1). No group differences were noted in the n-back tasks without the inhibit component (2B > 0B and 2B > 1B). Group differences with respect to inhibitory demand were seen in the moderate load (1BI > 1B) but not high load (2BI > 2B) condition, with the mild-TBI group activating the posterior cerebellum bilaterally more than the control group (Figure 2).

fMRI Analysis: Regions of Interest

In the six ROIs examined for working memory circuitry (2B > 0B), two had no activation values. None of the remaining four areas differed significantly between the groups, although two areas in the parietal lobe showed a trend toward significance. In the five ROIs examined for inhibitory control (1BI > 1B), two had little/no activation values. One ROI in the cerebellum differed significantly between the groups showing greater activation in the mTBI group relative to controls.

Neuropsychological Tests

As hypothesized, results of neuropsychological testing did not reveal significant cognitive deficits in either the control or mTBI groups based on population normative data (Table 4). When correction was made for multiple comparisons, none of the traditional "paper and pencil" tasks showed a significant group difference and effect sizes were generally small to medium. Significant group differences on the parent report

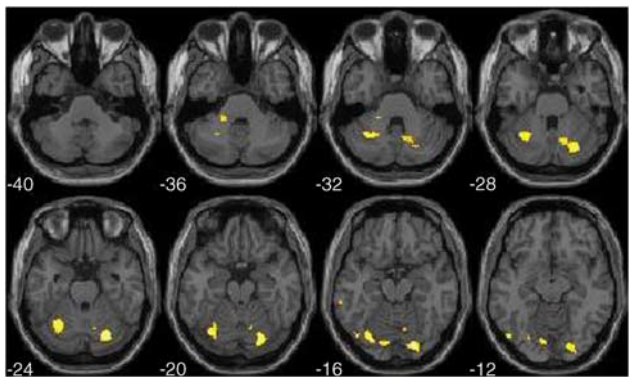

Fig. 2. Between group maps for 1BI > 1B.

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Table 4. Performance on neuropsychological paper and pencil tasks

	Control Mean (*SD*)	MTBI Mean (*SD*)	*t* statistics	Uncorrected *p* values	Cohen's *d* Effect size
Age (years)	12.2 (3.5)	13.3 (3.1)	−.823	.419	−.32
	Standard scores	Standard scores			
FSIQ (2 subtest WASI)	115 (10)	106 (13)	1.967	.063	.81
WJ-III Reading	114 (17)	103 (13)	1.580	.131	.73
WJ-III Math	98 (15)	95 (14)	.546	.591	.25
ACT total	107 (23)	108 (15)	1.643	.120	.77
Symbol Digit	115 (12)	93 (21)	1.837	.085	.90
Grooved Pegboard-dominant	102 (11)	88 (15)	2.325	.032	1.03
	Scaled scores	Scaled scores			
Verbal Fluency (ss)	14 (4)	11 (3)	2.970	.031	.97
Digit Span	11 (3)	10 (2)	1.264	.220	.52
Forward	9 (2)	9 (2)	.908	.374	.38
Backward	8 (3)	7 (2)	.922	.374	.39
	t scores	*t* scores			
BRIEF self: GEC	38 (6)	51 (20)	−1.730	.121	−.86
BRIEF self: BRI	37 (5)	49 (17)	−1.898	.093	−.95
BRIEF self: MCI	42 (6)	52 (20)	−1.550	.159	−.77
BRIEF parent: GEC	43 (6)	53 (11)	−2.676	.016	−1.10
BRIEF parent: BRI	42 (6)*	53 (12)*	−3.127	.006	−1.28
BRIEF parent: MCI	45 (6)	52 (11)	−2.068	.055	−.84
	Total symptoms	Total symptoms			
PCSI self	5 (4)**	29 (17)*	−4.800	.002	−2.39
PSCI parent	0.36 (0.92)*	38 (22)*	−.5624	.000	−1.96

*$p < .05$; corrected for multiple comparisons.
FSIQ = full scale IQ; WJ-III = Woodcock Johnson-III; ACT = Auditory Consonant Trigrams; BRIEF = Behavior Rating Inventory of Executive Function; GEC = Global Executive Composite; BRI = Behavior Regulation Index; MCI = Metacognitive Index; PCSI = Post Concussion Symptom Inventory.

BRIEF was observed, with the mTBI group reported to have greater difficulties (although not clinically elevated) in behavior regulation. As expected, the mTBI group was reported to have more post-concussive symptoms than the controls on both the parent and self report PCSI.

Correlating Functional Activations with the Neuropsychological Testing

In contrast to our hypothesis, no significant correlations were found between measures of working memory (ACT, Digit Span) and activation during the n-back task for either group (2B > 0B). In the mTBI group, the Metacognitive Index from the BRIEF was negatively correlated with activation in the posterior cerebellum on the inhibit contrast (1BI > 1B). There were no significant correlations for the BRIEF index scores and imaging results in the control group. Significant positive correlations between report of greater symptoms on the PCSI and greater activation in the cerebellum and posterior cerebrum (temporal/parietal regions) for the 2B > 0B contrast was observed for both the parent ($p < .0001$) and self ($p = .003$) report in the mTBI group (Figure 3).

DISCUSSION

The current study found that both typically developing children and children with mTBI showed greater prefrontal activation in response to increased working memory load on the TEC. This finding provides support for the TEC as a measure of working memory. With regard to group differences on fMRI, overall results provide partial support for the hypothesis that children with mTBI show increased activation relative to the typically developing children as cognitive load is increased. Although there were no group differences noted on the picture n-back task, there was a group difference when a demand for inhibitory control component was added to the task. Specifically, children with mTBI had greater activation in the posterior cerebellum on the moderate load inhibitory task (1BI > 1B) but not on the more challenging inhibitory task (2BI > 2B). As was also hypothesized and shown in prior studies, children with mTBI did not show significant deficits on traditional neuropsychological "paper and pencil tasks," but showed greater impairment on symptom report measures and "real world" measures of executive functioning.

The findings in this study support previous work with adults, which have suggested that individuals with mTBI allocate greater cognitive resources to complete the same tasks (McAllister et al., 1999, 2001). However in contrast to this work with adults, children with mTBI were not found to recruit more areas of prefrontal cortex (relative to controls) on the n-back task regardless of whether demand for inhibitory control was present or not. In the present study, children with mTBI recruited more areas in the cerebellum relative to

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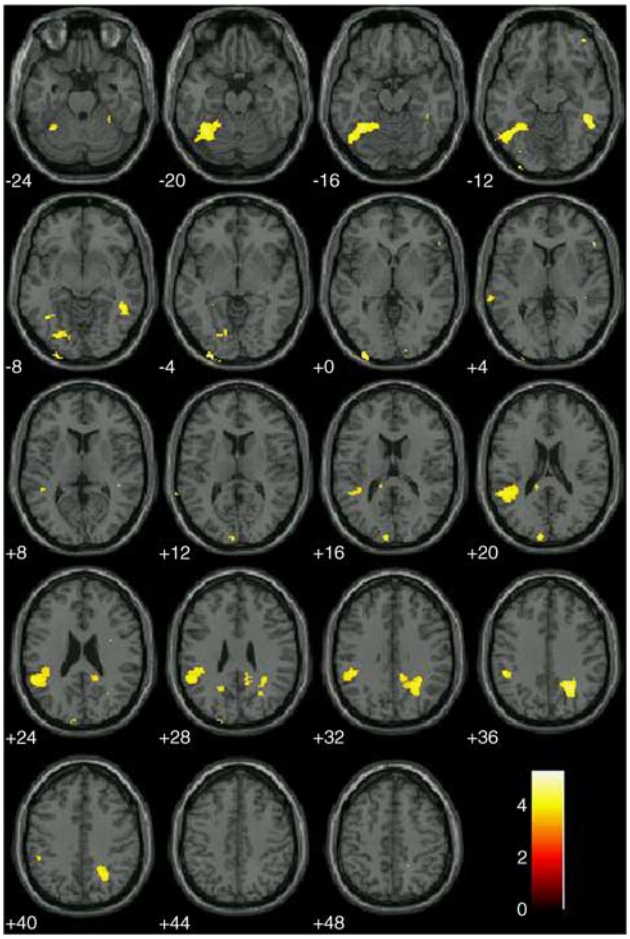

Fig. 3. Correlations between parent PCSI and activation on 2B > 0B in mTBI group.

controls. The cerebellum has been increasingly found to be important for regulating behavior, working memory, and other aspects of executive control (Desmond & Fiez, 1998; Habas et al., 2009; Tiemeier et al., 2010). It may be that nodes within working memory networks are recruited differently in children and adults, particularly when there is a concurrent demand for inhibitory control. Previous studies of working memory in normal children and adults support this hypothesis of differential activation patterns (O'Hare et al., 2008; Thomason et al., 2008), with normal children tending to recruit fewer additional areas in response to increasing working memory demand relative to adults. This is likely related to the fact that children's brains are undergoing myelination particularly in the development of frontal white matter tracts; thus they may use a less efficient network than adults, in which this maturational process in complete. This has been supported in numerous studies, including DTI studies in which children demonstrate decreased anisotropy in frontal white matter relative to adults (Klingberg, Vaidya, Gabrieli, Moseley, & Hedehus, 1999). Although not significant, there was also a trend seen in two parietal ROIs on the n-back task, again with mTBI subjects activating more than controls. Given the small numbers in this study, it may be worthwhile to continue to examine more closely areas in the posterior parietal lobe that are important for the maintenance of working memory.

Of interest was also the finding of the relationship between post-concussive symptom report and activation in the mTBI group. As expected, there was no correlation between activation and symptom report on the PCSI in the control group, as this group reports little to no post-concussive symptoms. However, in the mTBI group both the child's self report and the parent report of post-concussive symptoms was significantly correlated with activation in the cerebellum and other posterior brain regions. Interestingly, parent report of metacognitive problems in the real world was negatively correlated with activation in the cerebellum in the mTBI group. One potential hypothesis for this finding is that failure to engage compensatory mechanisms (including cerebellar activation) may be related to increased metacognitive problems for children with mTBI. In contrast, paper and pencil measures of neuropsychological functioning were not correlated with activation. Thus, it is possible that real world measurement of post-concussive symptoms may be more sensitive to the impact of mTBI than our traditional paper and pencil neuropsychological tasks. More longitudinal research with these self/caregiver report measures of symptom recovery will be crucial in answering these questions.

Although these findings provide some support for the hypothesis of inefficient/disrupted neural circuitry in children with mTBI, there are also several important limitations to consider. First, this was a pilot study with a broad age range (7–18). Data on SES were not collected and children in this study were variable in terms of when they presented to the clinic and for the imaging study, which is a crucial issue to consider when examining the rapid metabolic changes that occur in the first several hours/days following mTBI (Giza & Hovda, 2001). It is also important to note that prior literature has shown that children who sustain TBI are more likely to have had prior behavioral and cognitive risk factors, such as a higher prevalence of ADHD and complex psychosocial issues (Yeates, 2010). Thus, some of the differences noted on the BRIEF and even the PCSI could reflect premorbid group differences. Finally, this study used a new fMRI task that had an error in recording data, which made it difficult to evaluate the performance accuracy in the scanner. Although we believe that we have provided some indirect evidence of likely appropriate in-scanner accuracy (e.g., subjects met criteria for accuracy/understanding during out of scanner practice, select subjects also underwent a letter n-back task and demonstrated high levels of accuracy across conditions, no group differences in brain activation when looking at slow *versus* fast responders, previous studies linking increased accuracy to activation in brain regions other than those that differed between our groups), this issue clearly needs to be addressed in the future use of this task.

In summary, the results of this study provide preliminary support for the hypothesis that despite showing no significant injury on traditional structural imaging, children with mTBI may show disrupted neural circuitry during their recovery

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from injury. However, their pattern of disruption may be different from that of adults with mTBI, which is consistent with previous studies in which normal children demonstrated a different pattern than adults when they are presented with increasing working memory load. Of potentially the greatest clinical utility was the finding that report of ongoing concussion symptoms correlated with imaging findings, which supports the notion that symptom report may be a valuable tool in tracking neurologic recovery in children with mTBI.

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