7-6-2012

A fMRI study of auditory orienting and inhibition of return in pediatric mild traumatic brain injury

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A fMRI Study of Auditory Orienting and Inhibition of Return in Pediatric Mild Traumatic Brain Injury

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DISSERTATION

Submitted in Partial Fulfillment of the
Requirements for the Degree of

Doctor of Philosophy
Psychology

The University of New Mexico

Albuquerque, New Mexico

May, 2012

Dedication

This dissertation is dedicated to my wonderful parents Shirong Yang and Pingxiang Wang, my loving and supportive husband Hongbo He, and my cherished daughter Cassiah K. He. Special thanks to my mother-in-law Zulian Li, my host-family mother Carol Hammans, and my friend David Padilla for their support and encouragement.

Acknowledgments

I wish to express my deep gratitude to my advisor and dissertation chair, Dr. Ronald Yeo for his continuous guidance, support, and encouragement. His broad knowledge and wisdom have truly inspired and enlightened me. I am also deeply grateful to my co-advisor, Dr. Andrew Mayer, who introduced me to the field of multimodal imaging and traumatic brain injury and taught me to think creatively and critically. I would also like to thank my committee members Dr. Vince Clark and Dr. John Phillips who have generously provided their time and expertise to improve my work.

So many other people were greatly supportive and encouraging throughout the entire process. I especially wish to thank Josef Ling for his scripts, Amanda Pena for her help with so many aspects of the project, Stefan Klimaj for his help with double checking results, and Dr. Richard Campbell and David Doezema, M.D. for their comments on the manuscript. Special thanks also go to Diana South, George Mallory, Cathy Smith, Terri Teshiba, Flannery Merideth, and Jim Youngblood for their assistance with data collection and data entry, and to Jesse Rael, M.D. for review of anatomical images.

This dissertation was supported by the Graduate Deans Dissertation Fellowship sponsored by the Office of Graduate Studies and The Benjamin Franklin Haught Scholarship sponsored by the Department of Psychology, University of New Mexico. This research was also supported by grants from The Mind Research Network [DOE Grant No. DE-FG02-99ER62764] through Dr. Andrew Mayer.

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Abstract

Studies in adult mild traumatic brain injury (mTBI) have shown that two key measures of attention, spatial reorienting and inhibition of return (IOR), are impaired during the first few weeks of injury. However, it is currently unknown whether similar deficits exist following pediatric mTBI. The current study used fMRI to investigate the effects of semi-acute mTBI (<3 weeks post-injury) on auditory orienting in 14 pediatric mTBI patients (age 13.50 ± 1.83; education: 6.86 ± 1.88) and 14 healthy controls (age 13.29 ± 2.09; education: 7.21 ± 2.08) matched for age and years of education. Results indicated that patients with mTBI showed subtle (i.e., moderate effect sizes) but non-significant deficits on formal neuropsychological testing and during inhibition of return. In contrast, functional imaging results indicated that patients with mTBI demonstrated significantly decreased activation within the bilateral posterior cingulate gyrus, thalamus, basal ganglia, midbrain nuclei, and cerebellum. The spatial topography of hypoactivation was very similar to our previous study in

adults, suggesting that subcortical structures may be particularly affected by the initial biomechanical forces in mTBI. Current results also suggest that fMRI may be a more sensitive tool for identifying semi-acute effects of mTBI than the procedures currently used in clinical practice such as neuropsychological testing and structural scans. fMRI findings could potentially serve as a biomarker for measuring the subtle injury caused by mTBI and documenting the course of recovery.

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Chapter 1

Introduction

Traumatic brain injury (TBI) is one of the most common causes of acquired disability in the pediatric population, the outcome of which can interfere with subsequent academic achievements, occupational performance, and interpersonal relationships (Keenan and Bratton, 2006). In the United States alone, the rate of TBI-related emergency department visits was over 500 per 100,000 for children less than 17 years of age (Faul et al., 2010), and 75% of these injuries can be classified as mild in nature (CDC, 2003). While the majority of mTBI patients fully recover within the first several months of injury (Babikian and Asarnow, 2009; Satz et al., 1997), a small subset of patients may experience persistent neurocognitive or psychosocial dysfunction for years (Anderson et al., 2001; Babikian et al., 2011; Catale et al., 2009; Fay et al., 2010; McKinlay et al., 2002, 2009, 2010; Sterr et al., 2006) or even decades (Hessen et al., 2007; Klonoff et al., 1993) (see Daneshvar et al. (2011) for a review). Thus, it is critical to identify neuroimaging and behavioral markers sensitive to mTBI to better understand recovery and to prevent potentially long term adverse outcomes from repeated mTBI.

Attentional dysfunction is one of the most commonly reported cognitive sequelae

of pediatric TBI (Allen et al., 2010; Babikian and Asarnow, 2009; Ginstfeldt and Emanuelson, 2010). Behavioral or neuropsychological studies examining the acute and chronic effects of TBI on attention functions have generally compared the deficits among mild, moderate, and severe TBI groups and, not surprisingly, found that severe TBI groups have greater problems on various measures of attention (Catroppa and Anderson, 1999, 2003, 2005; Catroppa et al., 1999; Kaufmann et al., 1993). However, the use of mTBI as a control group for more severely injured groups prevents an examination of deficits that are specific to this patient population. Other studies that directly compared attention functioning of mTBI patients with non-injured controls have generally reported null outcomes during both acute (Jaffe et al., 1992) and chronic (Anderson et al., 2005; Babikian et al., 2011; Catroppa et al., 2011; Fay et al., 1994) injury phases (for reviews, see Babikian and Asarnow (2009); Satz et al. (1997)). However, subtle deficits (Catroppa et al., 2007) and adverse outcomes (Catale et al., 2009) have been occasionally reported in specific attention domains. Moreover, the large heterogeneity in time post-injury in previous studies coupled with variability in performance across a cohort in different development phases may have hindered the ability to detect the effects of mTBI on cognition.

Therefore, a primary goal of research should be to characterize the neural abnormalities following mTBI during the semi-acute phase of injury and determine how they relate to cognitive abnormalities. These are especially important issues for the pediatric population, as late childhood and adolescence constitutes a critical time for brain development (Giedd et al., 1999; Sowell et al., 2002), and the developing brain has been shown to be more vulnerable to diffuse white matter injury (Adelson and Kochanek, 1998; Levin, 2003). However, clinical imaging techniques such as Magnetic Resonance Imaging (MRI; T1 and T2 weighted images) and Computed Tomography (CT) are generally insensitive to mTBI, providing little information about the brain regions that may have sustained initial damage (Hughes et al., 2004). In contrast, functional MRI (fMRI) offers great promise for elucidating the potential

neural substrates for cognitive disruption, given its capability for measuring dynamic changes in neural functioning (Belanger et al., 2007; McAllister et al., 2006). A better biomarker would potentially be helpful with diagnosis information and guide clinical management of mTBI (e.g., medical interventions and return to play/school decisions).

Existing studies using fMRI to examine TBI have focused largely on adults, with many focusing on working memory paradigms (McAllister et al., 1999, 2001; Chen et al., 2004, 2007; Newsome et al., 2007b; Chen et al., 2008; Smits et al., 2009; Cazalis et al., 2011; Turner et al., 2011). A few have examined attentional functioning (Soeda et al., 2005; Scheibel et al., 2007; Turner and Levine, 2008; Kim et al., 2009; Mayer et al., 2009; Smits et al., 2009; Witt et al., 2010), with the majority of studies being limited to more severely injured populations. Only three studies examining attentional functioning have focused on the mTBI population (Mayer et al., 2009; Smits et al., 2009; Witt et al., 2010). Mayer et al. (2009) examined spatial orienting using an Auditory Orienting Task and reported a hypoactivation in both the disengagement network including supplementary motor area, frontal eye fields and inferior parietal lobes and the regions associated with attentional allocation inhibition in mTBI. Smits et al. (2009) examined selective attention using Counting Stoop Tasks and reported that a hyperactivation within the anterior cingulate gyrus, inferior frontal gyrus, insula and posterior parietal cortex with increased incidence of post-concussive symptoms in mTBI. In a recent study, Witt et al. (2010) examined executive function using an Auditory Oddball Task and reported a hypoactivation in right dorsalateral prefrontal cortex in mTBI.

The few fMRI studies examining cognitive functions following TBI in children and adolescents have primarily focused on more severely injured patients (Cazalis et al., 2011; Karunanayaka et al., 2007; Kramer et al., 2009, 2008; Newsome et al., 2007a, 2008; Tlustos et al., 2011; Wilde et al., 2011), with only two studies focusing

on a well-defined mTBI population (Krivitzky et al., 2011; Talavage et al., 2010). Krivitzky et al. (2011) reported no difference in brain activations between children with mTBI and healthy controls (HCs) on a working memory task, but they found a hyperactivation in mTBI patients in the posterior cerebellum with the addition of a demand for inhibitory control process. In contrast, Talavage et al. (2010) reported hypoactivation in concussed adolescent football players within left middle and superior temporal gyri, left middle occipital gyrus, and bilateral cerebellum during an N-back working memory task.

Among studies with adequate sample sizes ($n > 8$) of more severely injured patients, Newsome and colleagues have reported that the nature of group differences in patterns of activation depended on memory load and behavioral performance in the N-back task (Newsome et al., 2007a). At low memory load hypoactivation was seen in frontal and extrafrontal areas, and behavioral performance of the TBI group was worse than HC. In contrast, hyperactivation was observed in these areas in the TBI group at high memory loads, where both groups had comparable performance. A follow-up study by the same group showed that TBI hyperactivation or hypoactivation also depended on the components of working memory, with hyperactivation during the encoding and retrieval components and hypoactivation during the maintenance of working memory (Newsome et al., 2008). Another study examining working memory showed hyperactivation in the anterior cingulate gyrus and hypoactivation in the left sensorimotor cortex (Cazalis et al., 2011). Similarly, a mixed pattern was observed in language function with a hyperactivation found within the Brocas Area and dorsolateral prefrontal cortex and a hypoactivation found within the superior/middle temporal gyrus and angular gyrus (Karunanayaka et al., 2007). In contrast, a more consistent hyperactivation was observed within right frontal and parietal regions during an inhibitory control task (Tlustos et al., 2011).

One major factor contributing to the inconsistent results may be clinical hetero-

geneity in time post-injury. The two fMRI studies on pediatric mTBI were conducted either within the semi-acute phase (Talavage et al., 2010) or with a heterogeneous time interval spanning from 8 to 82 days (Krivitzky et al., 2011), comprising a range in which the majority of patients are expected to recover. Most studies on moderate to severe TBI were conducted at the chronic injury phase, from 7 months to 4 years. As different subgroups of TBI have different recovery trajectories, and significant individual variation in the time course of recovery also exists within each subgroup (Lovell et al., 2007; Kirkwood et al., 2008; Yeates et al., 2009), this clinical heterogeneity makes uncovering the specific pathology quite difficult and may contribute to the inconsistent results in the literature. Thus, fMRI studies based on relatively larger samples of pediatric mTBI patients, all within the semi-acute phase of injury, are needed to characterize the subtle alterations in brain activation following mTBI during this critical phase of injury.

The orienting of attention to different locations in space is critical for everyday functioning and has been shown to be mediated by distributed networks in the prefrontal and parietal cortices, regions which may be impaired as a result of diffuse axonal injury and focal lesions (Cicerone et al., 2006). Covert orienting requires attention to be dynamically shifted in the spatial environment, disengaging from the currently attended location to new spatial coordinates based on information from the environment (Corbetta and Shulman, 2011; Mayer et al., 2007). Behavioral and functional imaging studies in adults have demonstrated that spatial orienting is typically impaired in mTBI during the semi-acute stages of injury (Drew et al., 2007; Halterman et al., 2006; Mayer et al., 2009) and that difficulties with disengagement (i.e. shifting attention from one focused target to another) might account for the majority of attentional deficits observed in this population (Halterman et al., 2006). However, it is unknown whether these deficits also exist in the pediatric mTBI population and which neuronal structures are responsible for the cognitive difficulties. In the current study, we used event-related fMRI to examine the neural circuitry

underlying spatial orienting in pediatric mTBI patients during the semi-acute phase of injury (< 3 weeks). To our knowledge, this is the first study using fMRI to examine the semi-acute effects of mTBI on bottom-up (i.e., exogenous/stimulus-driven) attentional orienting in the pediatric population.

In this study, spatial orienting was measured with a spatial Auditory Orienting Task (AOT) in which participants were asked to identify a target preceded by either a valid or invalid cue (i.e., cues presented on the same or opposite side as the subsequently presented target). When the stimulus onset asynchrony (SOA) between the cue and target is less than 250 milliseconds, invalid trials are typically associated with longer response times as invalid trials have the addition requirement of disengaging and reorienting attention to the targets new location. Accordingly, an increased activation within the disengagement network, including supplementary motor area, frontal eye fields and inferior parietal lobes have been observed with invalid trials (Arrington et al., 2000; Mayer et al., 2004; Thiel et al., 2004; Mayer et al., 2007). At longer SOAs during bottom-up orienting, there is a reversal in reaction time between valid and invalid trials so that valid trials are associated with longer response times. This reversal in reaction time has been traditionally called inhibition of return (IOR) and is believed to be an inhibitory mechanism to promote novelty exploration in the spatial environment by preventing either attention or repetitive eye movements to previous cued location. This reversal in response times is frequently reflected by an equalization or reversal in functional activation within the frontal and parietal areas compared to the greater activation observed for invalidly cued trails at short SOAs (Lepsien and Pollmann, 2002; Mayer et al., 2007).

As the maturation of the orienting system may be completed before the age of 10 years (Brodeur and Enns, 1997; Goldberg et al., 2001; Rueda et al., 2004; Waszak et al., 2010), we hypothesized that the current pediatric mTBI sample would exhibit similar deficits in spatial orienting as reported in the adult mTBI sample (Mayer

et al., 2009). Specifically, we predicted that mTBI patients would exhibit deficits in disengagement and reorienting auditory attention following invalid cues and accordingly exhibit hypoactivation in the disengagement network at shorter SOAs. At longer SOAs, we predicted that mTBI patients would fail to inhibit attentional allocation to a previously cued spatial location (IOR).

Chapter 2

Methods

2.1 Participants

A total of 16 pediatric patients with mTBI (fourteen males, two females; 13.50 ± 2.13 years old; 6.94 ± 2.18 years of education) and 16 age- and education-matched HCs (twelve males, four females; 13.19 ± 1.97 years old; 7.06 ± 1.98 years of education) were recruited for the current study (age range 10-17). All patients with mTBI experienced a closed head injury and were recruited from the Emergency Departments at local hospitals. Patients were evaluated with both neuropsychological tests (mean days post-injury = 15.56 ± 4.52) and brain imaging (mean days post-injury = 16.06 ± 4.82) within 21 days of injury (semi-acute phase of injury; see Supplemental Information Table D.1). The inclusion criteria (American Congress of Rehabilitation Medicine) for the mTBI patients were a Glasgow Coma Score of 13-15 at the initial assessment, an alteration in mental status at the time of injury, a loss of consciousness (if present) of less than 30 minutes, and post-traumatic amnesia (if present) that was limited to 24 hours. The alteration in mental status was evaluated by the principle investigator. Other inclusion criteria were evaluated by the

emergency department. Exclusion criteria for both mTBI and HC sample included a positive history of neurological disease, psychiatric disturbance, prior closed head injuries with more than 5 min of loss of consciousness, learning disorder, attention deficit hyperactivity disorder (ADHD), substance abuse, or alcohol abuse. Informed consent was obtained from participants according to institutional guidelines at the University of New Mexico.

2.2 Clinical assessment

All participants completed an age appropriate neuropsychological battery. All neuropsychological tests were administered and scored according to normative procedures. Raw test scores were converted to T-scores (mean = 50, SD = 10) using published age-specific norms. To reduce redundancy amongst similar neuropsychological measures, composite indices were calculated by averaging T scores of relevant tests for the following five cognitive domains: attention [Trail Making Test A, Stroop Interference Test (color-word and interference scores)], memory [Wide Range Assessment of Memory and Learning (WRAML) Story Memory immediate recall, short-delay recall and recognition], processing speed [Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) digit symbol coding and symbol search], working memory (WISC-IV digit span and letter-number sequencing), and executive function [Wisconsin Card Sort Test standard version (WCST 128) (errors and perseverative errors), Trail Making Test B, and Controlled Oral Word Association FAS test]. In addition, the Wide Range Achievement Test, Fourth Edition (WRAT-IV) Word Reading Test was used to provide an estimate of overall premorbid intellectual functioning. Behavioral and emotional issues were measured by Self-Report of Personality (SRP) and Parent-Rating Scales (PRS) of the Behavior Assessment System for Children, Second Edition (Reynolds and Kamphaus, 2004). The cognitive test-

ing and imaging sessions occurred within one week of each other for all participants (mean day difference = 0.43 ± 0.92).

2.3 Task procedure

All participants completed an auditory orienting task (AOT) while undergoing fMRI (see Fig. A.1). Participants rested supine in the scanner with their head secured by a forehead strap. Additional foam padding was added to limit head motion within the head coil. Presentation software (Neurobehavioral Systems) was used for stimulus presentation, recording of response times (RTs) and accuracy data, and synchronization of stimulus events with the MRI scanner. A non-ferrous key-press device was positioned directly under the subjects right hand to record responses.

Auditory stimuli were presented with an Avotec Silent Scan 3100 Series System. The first tone (2000 Hz) served as a spatial cue that correctly (i.e., valid trials) or incorrectly (i.e., invalid trials) predicted the location of a second target tone (1000 Hz). To reduce the occurrence of clicks during auditory stimulus presentation, both tones were sampled with a 10 ms linear onset-offset ramp. The ratio of valid to invalid cues was 50%, which was chosen based on parameters commonly used in the cognitive literature to evoke bottom-up (i.e., exogenous) orienting (Mayer et al., 2007, 2009). To maximize bottom-up orienting effects, participants were informed before the start of the experiment that the cues did not contain any useful information about the target location.

The SOA between the cue and the target was 200, 400, or 700 ms, and SOA and cue validity was pseudo-randomly varied throughout the experiment. There were a total of 72 valid (24 trials per SOA) and 72 invalid trials presented across three separate imaging runs. The laterality of the target (a target either presented on the left or the right side of the headphone) was controlled by presenting equal

number of left and right trials for each condition. The inter-trial interval was pseudo-randomly varied between 4, 6 or 8 s. These intervals were selected to both facilitate the sampling of the hemodynamic response (Burock et al., 1998) and to minimize the likelihood of non-linear summing of hemodynamic responses (Glover, 1999).

Participants were instructed to respond to the target location by pressing a button with their right middle finger for targets appearing in the right headphone and right index finger for targets appearing in the left headphone. Response time was measured from the onset of the target stimulus to the completion of a key press. Response times shorter than 100 ms or longer than 2000 ms were considered anticipatory or missed responses, and were discarded from future analyses. To minimize neuronal activation associated with eye movements, participants were instructed to maintain fixation throughout the task on a white central fixation cross on a black background (visual angle = 1.02°), which was rear-projected using a Sharp XG-C50X LCD projector onto an opaque white Plexiglas projection screen. Participants were required to both practice the tasks and to demonstrate 100% proficiency before entering the scanner environment.

2.4 Functional magnetic resonance imaging

All images were collected on a 3 Tesla Siemens Trio scanner. High resolution T1-weighted anatomic images were acquired with a 5-echo multi-echo MPRAGE sequence [echo time (TE) = 1.64, 3.5, 5.36, 7.22, 9.08 ms, repetition time (TR) = 2.53 s, TI = 1.2 s, 7° flip angle, number of excitations (NEX) = 1, slice thickness = 1 mm, field of view (FOV) = 256 × 256 mm, voxel resolution = 1 × 1 × 1 mm^3]. T2-weighted images were collected with a fast spin echo sequence [TE = 77.0 ms, TR = 1.55 s, flip angle 152°, NEX = 1, slice thickness = 1.5 mm, FOV = 220 × 220 mm, matrix = 192 × 192, voxel size = 1.15 × 1.15 × 1.5 mm^3]. Susceptibility

weighted images were collected with a gradient echo sequence [TR = 28 ms; TE = 20 ms; flip angle 15°; bandwidth = 120 Hz/Px; FOV = 180 × 240 mm; matrix = 177 × 256; slice thickness = 1.5 mm; number of slices per slab = 88]. Functional images were collected using a single-shot, gradient-echo echo planar pulse sequence [TR = 2000 ms; TE = 29 ms; flip angle = 75°; FOV = 240 mm; matrix size = 64 × 64] with a total of 148 images per run for 3 runs. The first image of each run was eliminated due to T1 equilibrium effects, leaving a total of 441 images for the final analyses. The whole-brain volume was covered by thirty-three contiguous sagittal 3.5-mm thick slices with a gap factor of 1.05 mm (voxel size: 3.75 × 3.75 × 4.55 mm).

2.5 Imaging processing and statistical analysis

Functional imaging data was processed and analyzed using Analysis of Functional NeuroImages (AFNI) software package (Cox, 1996). Time series data were spatially registered to the second echo-planar image of the first run in two- and three-dimensional space to reduce the effects of motion, temporally interpolated to correct for slice time acquisition differences and de-spiked. These images were then converted to a standard stereotaxic coordinate space (Talairach and Tournoux, 1988), re-sampled to 3 mm^3, and blurred using a 6 mm Gaussian full-width half-maximum filter.

Deconvolution was performed on a voxel-wise basis, resulting in a hemodynamic response function (HRF) that spanned the first 16 seconds post-stimulus onset for each condition (valid and invalid trials at each SOA). To minimize the effect of head motion, six rigid-body motion parameters were entered as noise regressors. The HRF was then normalized by the baseline and re-sampled to 1 mm^3. The third and the fourth images (4.0 to 8.0 seconds post-stimulus onset) corresponding to the peak of

the HRF were averaged to obtain an estimate of percent signal change.

A voxel-wise, 2 × 2 × 3 (Group × Validity × SOA) mixed-design ANOVA was then performed on the percent signal change data. For all voxel-wise analyses, multiple comparisons were corrected ($p < 0.05$) based on Gaussian Random Field Theory as implemented in the FSL package ($z > 2.3$).

Chapter 3

Results

The data of one HC was compromised secondary to an issue with hearing acuity in the left ear. One mTBI patient was an outlier on behavioral performance (accuracy below chance levels) and was therefore excluded from the study. Additionally, one HC and one mTBI were outliers (greater than three inter-quartile ranges) relative to their cohort on several fMRI motion parameters. Both participants were eliminated from subsequent analyses, leaving data from a total of 14 HC and 14 mTBI for final analyses. There were no significant differences between groups on any of the major demographic variables including age, self-education, parent education, and number of siblings: all p's > 0.10) or for hand preference determined through a self-report measure ($p > 0.10$). There was a marginally significant group difference in gender [$\chi(1) = 3.36$, $n = 28$ $p = 0.07$]) with mTBI group having a higher proportion of males than HC group.

3.1 Clinical assessment

The results of neuropsychological testing are presented in Table B.1. Independent samples t-tests indicated that there were no significant ($p > 0.10$) group differences in estimates of premorbid levels of intelligence (WRAT-IV). The composite indices of attention, memory, working memory, processing speed, and executive functioning were correlated to varying degrees (r's ranged from 0.12 to 0.47). A MANOVA was performed to examine group differences in the cognitive scores. The multivariate effect of group was not significant ($p > 0.10$), although univariate effects indicated trends in the domains of memory [$F(1,26) = 3.36$, $p = 0.08$; HC > TBI; $d = -0.69$] and processing speed [$F(1,26) = 3.48$, $p = 0.07$; HC > TBI; $d = -0.70$]. Moreover, effect sizes in the domains of processing speed, memory, and attention were moderate, suggesting that current results may have become significant with an increased sample size.

Two MANOVAs were performed to examine group differences in the composite scores on Self-Report Personality and Parent-Rating Scales, separately. The multivariate effects of group were not significant for both MANOVAs (all p's > 0.10), although there was a trend for mTBI (46.64 ± 9.92) reporting more internalizing problems [$F(1,26) = 4.00$, $p = 0.06$; $d = 0.76$] relative to HC (41.00 ± 3.62).

3.2 Behavioral Data

Behavioral accuracy for both mTBI and HC were very high and approached ceiling (mTBI: $95.9\% \pm 5.3\%$; HC: $94.0\% \pm 7.4\%$), suggesting that participants had little difficulty distinguishing cues from targets. As a result of low variability across participants, accuracy data was not subjected to further analyses.

Individual participants median reaction time (RT) for correct trials was used for

all behavioral analysis. A 2 × 2 × 3 mixed-measures ANOVA with group (mTBI, HC) as between-subjects factor and cue validity (valid, invalid) and SOA (200, 400 or 700 ms) as within-subjects factors were conducted. There was a significant main effect of SOA [F (1,26) = 13.46, p = 0.001] with significantly faster RT at the 700 (566.8 ± 39.3 ms) relative to the 400 (598.2 ± 44.7 ms) ms SOA [t (27) = -2.9, p < 0.01], as well as for the 400 relative to 200 (704.0 ± 42.3 ms) ms SOA [t (27) = -9.3, p < 0.001] (see Fig. A.2(a) and A.2(b)). No other main effects or interaction effects were significant (p > 0.10).

To examine a priori predictions of increased costs (200 ms SOA) and reduced IOR (700 ms SOA) across different groups, independent samples t-tests were conducted on the validity effect scores (invalid valid RT). Results indicated that there was no difference between groups at both SOAs (all p's > 0.10), which may have been a result of limited power, as the effect size related to the group difference in IOR was medium (d = 0.62). Specifically, follow-up one-sample t-tests indicated that the magnitude of IOR was significantly different from zero for HC [t(13) = -2.9, p = 0.01] but not for mTBI patients (p > 0.10) (see Fig. A.2(c)).

3.3 Correlations between the behavioral data and clinical assessment

To examine whether the predictive power of the simple behavioral measure (AOT) to daily cognitive functions differs between two groups, correlations between validity effect scores and cognitive composite scores were computed separately for mTBI and HC. The validity effect score at 700 ms SOA predicted the attention composite score for HC (r = -0.63, n = 14, p = 0.02; uncorrected; with a larger IOR being associated with better attention function), but not for mTBI patients (p > 0.10).

3.4 Structural Imaging Data

All mTBI patients were found to be "non-complicated", that is, free of trauma-related pathology on conventional imaging. Specifically, ten of fourteen mTBI patients had a CT scan at the time of their emergency department visit, which were all deemed to be negative by a board-certified neuroradiologist. In addition, T1-weighted, T2-weighted and susceptibility weighted images (SWI) were also acquired for all participants (mTBI patients and HC) and reviewed by a neuroradiologist who was blind to patient diagnosis. All images were deemed to be free of trauma-related pathology.

3.5 Functional Imaging Data

Two MANOVAs were first conducted to investigate any potential group differences in head motion (both rotational and translational displacements in image space), which could confound our interpretation of fMRI data. However, results indicated that the multivariate effect of group was not significant ($p > 0.10$) for either of the MANOVAs and the effect sizes were small for all six parameters (range from -0.23 to 0.49).

Similar to the behavioral data, a $2 \times 2 \times 3$ mixed-measures ANOVA (Group $\times$ Validity $\times$ SOA) was conducted on the percent signal change data of each trial type. A significant main effect of group was observed within several clusters (see Fig. A.3; Table B.2) including the bilateral posterior cingulate gyrus (BA 23), bilateral medial dorsal, ventral anterior, and ventral lateral nucleus of thalamus, basal ganglia (including bilateral caudate and left putamen/globus pallidus), bilateral substantia nigra, bilateral subthalamic nucleus, left red nucleus, right pons, and bilateral cerebellar (lingual and culmen). For all regions, mTBI patients exhibited decreased

activation (i.e., hypoactivation) relative to HC.

Several regions exhibited a significant Validity by SOA interaction (see Fig. A.4; Table B.3). These areas included bilateral pre-supplementary/supplementary motor area and cingulate gyrus (BAs 6/8/24/32), left precentral and middle frontal gyrus (BA 6) corresponding to the area near the frontal eye fields, left pre- and postcentral gyrus and inferior parietal lobe (BAs 2/3/4/5/7/40), and bilateral precuneus, cuneus, and superior parietal lobe (BAs 5/7/18/19/31). Simple effects testing indicated increased activation for invalidly than validly cued trials at 200 ms SOA followed by a reversal in this pattern at 400 ms SOA. There were no differences in activation in these regions at the 700 ms SOA.

In addition, several clusters also demonstrated a main effect of SOA that were not implicated in the SOA x Validity interaction, which could generally be characterized by three different patterns of activation: shorter SOA dominance, crossing SOA dominance, and longer SOA dominance (see Supplemental Information Table D.2). The first major pattern was associated with either decreased activation or deactivation at the 700 ms SOA in conjunction with increased activity at the earlier SOAs. Specifically, increased activation for the 200 and 400 ms SOA relative to the 700 ms SOA was observed in the bilateral anterior cingulate/cingulate gyrus (BAs 24/32) and left medial temporal lobe extending into posterior insula (BAs 13/19).. A similar pattern but with deactivation for the 700 ms SOA was seen in the right ventrolateral prefrontal cortex extending into anterior insula (BAs 10/13/46/47), right basal ganglia, right medial temporal lobe extending into fusiform gyrus (BAs 20/27/30/35/36/37) and right culmen of the cerebellum. Second, the right dorsal medial frontal/anterior cingulate gyrus (BAs 8/9/10), left fusiform gyrus and cerebellum vermis (BAs 18/19/37) exhibited the greatest activation at 400 ms SOA (crossing SOA dominance), with activation also greater at the 200 relative to 700 ms SOA (400 > 200 > 700 ms SOA). Similarly, the right fusiform gyrus and cerebellum

vermis (BAs 19/37) also exhibited the greatest activation at the 400 ms SOA, although there were no differences between the 200 and 700 ms SOA data. Finally, the right primary and secondary auditory cortex (BA 22/41/42/43), anterior insula (BA 13), pre- and postcentral gyrus (BA 6), and inferior parietal lobe (BA 40) exhibited increased activation at the longer SOAs (400 and 700 ms SOA) relative to the 200 ms SOA.

3.6 Predicting behavioral and neuropsychological performance from brain activation

To examine which clusters from the main effect of group were capable of predicting the subtle deficits in behavioral and neuropsychological performance, hierarchical backwards multiple regressions were conducted for HCs and mTBI patients separately. Specifically, the PSC measures served as independent variables and the validity effect score at 700 ms SOA (inhibition of return), attention, processing speed, or memory composite scores served as a dependent variable. In HCs, the right thalamus/basal gangalia (t_{28}=3.10, p=0.009) predicted the attention performance (overall model $F_{1,12} = 9.60$, p = 0.009) and the bilateral posterior cingulate gyrus (t_{28}=2.28, p=0.04) predicted the memory performance (overall model $F_{1,12} = 5.19$, p = 0.04). There is a trend that left thalamus/basal ganglia (t_{28}=-1.86, p=0.09) predicted the processing speed (overall model $F_{1,12} = 3.47$, p = 0.09). In contrast, none of these relationships were significant for mTBI patients (p > 0.10), which suggested a potential disconnection between the neural regions mediating cognitive functions and the neuropsychological performance following mTBI. Interestingly, the left thalamus/basal ganglia (t_{28}=2.69, p=0.02) but not the bilateral posterior cingulate gyrus predicted the memory performance (overall model $F_{1,12} = 7.26$, p = 0.02) for the patients with mTBI suggesting an altered functional engagement in mTBI patients.

3.7 Classifying mTBI and HC from brain activation

The ability of cluster PSC to objectively classify individual mTBI and individual HC was examined using binary logistical regression. The PSC measures of the four regions implicated in the main effect of group were entered as independent variables and the group was entered as a binary dependent variable. Results indicated that the PSC measures of these clusters were able to successfully classify 12/14 HC and 12/14 mTBI patients (overall 85.7% accuracy). In addition, a hierarchical cluster analysis was conducted on 14 mTBI patients based on the PSC measures using centroid clustering method to examine whether patients can be further clustered into subgroups based on brain activation. Results indicated that 13 participants are within one cluster (92.9%) suggesting that the current mTBI sample is homogenous and did not contain different subtypes of mTBI (see supplementary Fig. C.1 for data distribution).

Chapter 4

Discussion

The orienting of attention to different locations in space is critical for everyday functioning (e.g., crossing the street) and deficits in spatial orienting have been reported in adult mTBI population during the first few weeks of injury (Drew et al., 2007; Halterman et al., 2006; Mayer et al., 2009). Current behavioral results indicated that pediatric mTBI patients showed subtle but non-significant deficits on formal neuropsychological testing and during inhibition of return (i.e., a moderate effect sizes). These effects may not have reached conventional levels of statistical significance secondary to low power. In contrast, functional results indicated that patients with mTBI demonstrated significantly decreased activation in hemodynamic activation during the orienting task, with a spatial topography that was very similar to our previous study in an adult mTBI population (Mayer et al., 2009).

Although cognitive deficits in the domains of attention, memory, and processing speed on traditional neuropsychological measures were not statistically significant, moderate effect sizes were noted, with HC showing better functioning than our pediatric mTBI patients. Furthermore, a moderate effect size related to a group difference in inhibition of return was observed during the auditory orienting task, with

mTBI patients failing to exhibit the expected reversal in reaction times for invalid and valid cues. Finally, a larger behavioral IOR was found to be associated with better attention function (as indexed by the attention composite score) in controls, but not in patients, suggesting a potential disruption in the relationship between the basic orienting function and the everyday cognitive functions measured with the neuropsychological tests following mTBI.

Current results are consistent with previous studies that have reported subtle deficits in attention (Catroppa et al., 2007), memory (Babikian et al., 2011), and processing speed (Babikian et al., 2011) following pediatric mTBI. However, other studies and literature reviews suggest that the effects of mTBI on neurocognitive functions in children are negligible during both acute and chronic injury phase (Babikian and Asarnow, 2009; Satz et al., 1997). Given the greater variability in performance for pediatric samples and the differences in cognitive functioning across relatively small age ranges, the quantitative assessment of neurobehavioral sequelae following pediatric mTBI is very challenging. Our inclusion of a well-defined mTBI cohort studied during a relatively homogeneous interval post-injury may have contributed to the higher effect size observed in the current study. In addition, controls were carefully matched on age and education and not statistically different on primary indicators of socioeconomic status (i.e., parental education), which likely controlled for the pre-injury risk factors. Thus, our careful selection of the control group may have also decreased variability.

Across both control and patient groups, our functional results showed the characteristic activation of the fronto-parietal attention network during attentional reorienting (Corbetta and Shulman, 2011). Specifically, increased activation within the frontal oculomotor sites and posterior parietal lobe was observed associated with invalidly compared to validly cued trials at 200 ms SOA. In contrast, the functional activation for all these sites was reversed at 400 ms SOA and was approximately

equivalent at 700 ms SOA for both validly and invalidly cued trials. These results are generally consistent with previous studies on bottom-up auditory orienting in adults (Mayer et al., 2007, 2009) and provide additional evidence that the covert exogenous orienting network has matured during late childhood and adolescence (Brodeur and Enns, 1997; Rueda et al., 2004; Waszak et al., 2010).

Our primary clinical observation was that patients with mTBI demonstrated hypoactivation within the bilateral posterior cingulate gyrus, thalamus, basal ganglia, midbrain nuclei, and cerebellum relative to the control group. This pattern of results is similar to our previous study examining auditory orienting on adult patients with mTBI using the same task (Mayer et al., 2009) and provides preliminary evidence of replication. Moreover, these findings suggest that similar neural networks are impaired during the involuntary reorienting of auditory attention following mTBI regardless of age. Similar regions have been shown to be recruited by healthy populations during various spatial attention tasks, and also produce spatial attention deficits across other neurological disorders. For example, the thalamus has been shown to be involved in spatial orienting in both children and adults (Posner and Rothbart, 2007; Salmi et al., 2007), and neuroimaging studies in healthy controls have reported cerebellar activation in various forms of spatial attention tasks in youth (Clements-Stephens et al., 2009) and adults (Belin et al., 2002; Mayer et al., 2007; Salmi et al., 2007; Zatorre et al., 2002). Autistic children with cerebellar hypoplasia exhibit impaired attentional shifts (Harris et al., 1999) as do adult patients with cerebellar or basal ganglia pathology (Ravizza and Ivry, 2001). Finally, children with spina bifida meningomyelocele (SBM) with congenital dysmorphology of the midbrain showed a higher cost of attentional disengagement and a lack of inhibition of return compared to either healthy controls or children with SBM with no midbrain dysmorphology (Dennis et al., 2005).

We had initially predicted that hemodynamic functioning within the fronto-

parietal attentional network would be particularly affected by mTBI. One potential explanation for the observation of altered hemodynamic response within subcortical, thalamic and cerebellar regions, rather than higher-order cortical areas, may be the nature of shear stress forces following biomechanical injury. Specifically, Zhang et al. (2004) used a finite element head model to demonstrate that the midbrain and the thalamus experienced the highest shear stress following mTBI, and that the shear stress response of these regions predicted injury severity. Furthermore, a recent animal study has shown that a single controlled cortical impact (CCI) injury, consistent with a mild injury to the left parietal cortex, resulted in metabolic and microstructural changes in the bilateral hippocampus and thalamus as early as 2 hours post-injury (Xu et al., 2011). Diffusion kurtosis imaging was able to detect microstructural alterations in these subcortical areas even during the post-acute injury stage (Zhuo et al., 2012). Therefore, it is possible that the initial biomechanical forces may particularly affect the metabolism and microstructure of the midbrain and thalamus, which in turn alters hemodynamic brain function.

Previous fMRI studies on pediatric mTBI have reported either no difference (Krivitzky et al., 2011), or hypoactivation (Talavage et al., 2010) during a visual n-back working memory task, or hyperactivation during an inhibitory control task (Krivitzky et al., 2011). As noted earlier, a potential explanation for the differences in brain activation pattern across different fMRI studies includes heterogeneity in time post-injury. Current results are consistent with previous findings of hypoactivation during the semi-acute phase of injury (Talavage et al., 2010). In contrast, no difference was observed when data were collected with a heterogeneous time interval spanning from the semi-acute to post-acute phase (Krivitzky et al., 2011), comprising a range in which the majority of patients are expected to recover. These results underscore the important role of homogeneity in time post-injury in examining the neural mechanisms of cognitive disruption and suggest that the semi-acute phase of injury may be a critical period to characterize the subtle alterations in brain activa-

tion following mTBI. An additional explanation for current findings of hypoactivation versus previous findings of hyperactivation (Krivitzky et al., 2011) is that bottom-up orienting task is likely to be more consistent with a lower cognitive load, which has been shown to result in hypoactivation in adult mTBI patients (McAllister et al., 1999, 2001).

Head injury typically involves mechanical forces and produces transient neurologic dysfunction with the potential for secondary injury symptoms. Consistent with previous work indicating that brain trauma may result in less activation in damaged brain regions that typically subserve cognition (Adelson et al., 1997), the current observation of hypoactivation may reflect a weaker maintenance of activation in regions mediating spatial orienting following mTBI. As the blood-oxygen-level-dependent (BOLD) signal is an indirect measure of neuronal functioning whose basic signal properties depend on cerebral blood flow, blood volume, and the ratio of deoxyhemoglobin to oxyhemoglobin (Logothetis, 2008), the occurrence of neuronal dysfunction can be attributed to many factors. The neurometabolic cascade initiated by mild head injuries includes abrupt neuronal depolarization, release of excitatory neurotransmitters, disruption of ionic balance, changes in glucose metabolism, altered cerebral blood flow, and impaired axonal function (Barkhoudarian et al., 2011). The microvascular response to biomechanical forces included loss in microvascular density and decreased capillary density and diameter (Park et al., 2009). The neuroinflammatory cascade triggered by the injury is characterized by a cascade of events, including breakdown of the blood-brain barrier, edema formation and swelling, infiltration of peripheral blood cells and activation of resident immunocompetent cells, and the intrathecal release of numerous immune mediators such as interleukins and chemotactic factors (Lenzlinger et al., 2001). The neurometabolism dysfunction, microvascular impairment, and neuroinflammation may in turn result in the occurrence of secondary injury symptoms such as ischemia, hypotension, cerebral hypoxia, cerebral edema, changes in blood flow to the brain, and raised intracranial pressure

(Scalea, 2005).

Rodent models suggest that molecular responses associated with growth, maturation, and metabolism may play a particularly important role in the injury response and the recovery process following developmental TBI (Babikian et al., 2010). Finally, damage to white matter tracts could also contribute to hypoactivation within the reorienting network, as alterations in fractional anisotropy have also been observed after a few days of injury in adolescents with mTBI (Wilde et al., 2008). Decreased white matter integrity of the frontal lobes, the cingulum bundles, or corpus callosum was associated with a broad range of cognitive dysfunctions following more severe TBI in children, including processing speed (Wilde et al., 2006), executive function (Wozniak et al., 2007; Kurowski et al., 2009; Wilde et al., 2010), and working memory (Ewing-Cobbs et al., 2008; Wilde et al., 2010, 2011). Thus, there are a variety of different physiological factors that could result in the observed hypoactive hemodynamic responses.

There are several limitations of the present study. First, our modest sample size may have obscured important effects of mTBI on behavioral and neuropsychological variables, as moderate to large effect sizes were observed for group differences for both types of measures. Second, we did not match strictly on gender and observed a trend level difference in gender composition across groups. Thus, the differential rate of development between pre-pubescent and pubescent males and females may contribute to the functional abnormality observed in the mTBI patients. However, the sex-specific differences in brain activation typically favor a greater activation in the task related regions in males compared to females in various attention tasks (Clements-Stephens et al., 2009; Tomasi et al., 2008). Thus, more males in the mTBI group may make the finding of hypoactivation in the mTBI group more compelling. Third, we used healthy non-injured participants as the control group instead of participants with other injuries not involving the head (e.g. orthopedic injuries),

which may prevent differentiating whether the altered neural activation is unique to mTBI or non-specific following any type of trauma (Babikian et al., 2011). In addition, the current study did not exclude the participants who might have ADHD but was not formally diagnosed and did not record the participants sports experience which could serve as potential confounding variables. Finally, it is worth noting is that the current findings represent neural activation at only a single point in time during the acute recovery phase (< 3 weeks). They do not provide information about the chronic changes in brain activation levels, nor do they shed light on the process of neural recovery over time. Longitudinal studies with larger sample sizes are needed to elucidate how alteration of brain activation during spatial attention at different recovery phases evolves over the time. This information may potentially provide a sensitive marker to the course of recovery that may help in measuring effects of intervention or guide in management of mTBI.

In conclusion, current results provide evidence that pediatric patients with mTBI may experience hemodynamic alterations in neural circuitry supporting spatial orienting during the semi-acute injury phase. These objective neuroimaging findings could potentially serve as a biomarker for the subtle injury caused by mTBI, and hence, provide important information on both diagnosis and the course of recovery. Such data could help guide clinicians in the management of mTBI, for example, in monitoring patients responses to interventions, or in revealing when hemodynamic abnormalities have subsided and the risk of a significant second injury response may be reduced. It is critical to specifically examine pediatric patients as the semi-acute injury response and recovery trajectories following mTBI are likely to be different for the immature and mature brain (Suskauer and Huisman, 2009). For example, both animal (Bayly et al., 2006; Huh et al., 2008)) and human (Hessen et al., 2007) studies have shown that the developing brain is more susceptible than the developed brain to mild diffuse brain injury (for reviews, see Adelson and Kochanek (1998); Levin (2003)). Finally, current results also demonstrate that fMRI is more sensitive to

the effects of mTBI than behavioral, neuropsychological, and traditional MRI measures, and they underscore the promise of fMRI for elucidating the potential neural substrates of subtle cognitive deficits associated with this condition.

Appendices

Appendix A

Figures

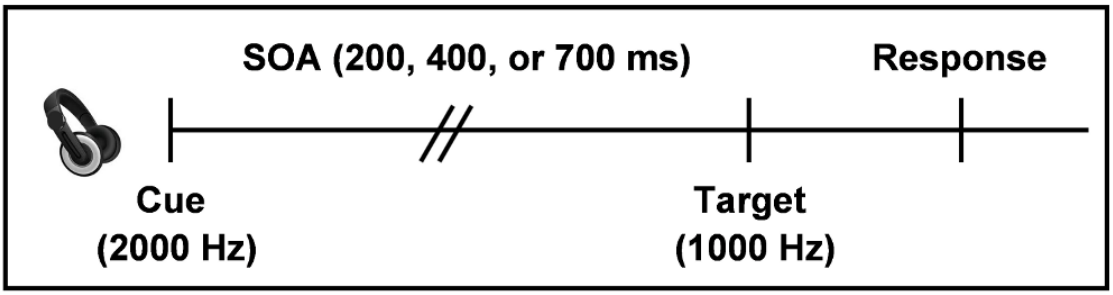

Figure A.1: This figure presents a diagrammatic representation of the auditory orienting task. The Headphones were used to present the cue (a 2000 Hz pure tone) and the target (a 1000 Hz pure tone). The stimulus onset asynchrony (SOA) between cues and targets was 200, 400, or 700 milliseconds. Cues correctly predicted the target location on half of the trials (50% validity ratio). Participants responded to the target location by pressing a button with their right index (left target) or middle (right target) finger.

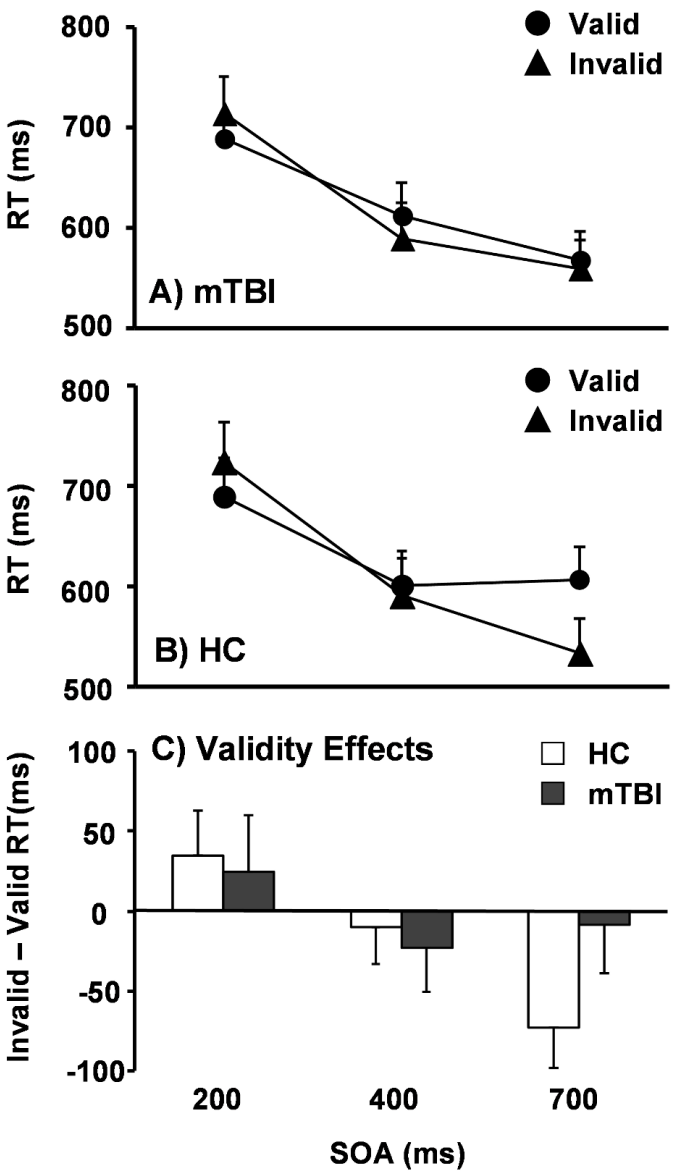

Figure A.2: Graphs A and B shows the reaction time (RT) in milliseconds (ms) for patients with mild traumatic brain injury (mTBI: Panel A) and healthy controls (HC: Panel B). In both panels, RTs for valid (sold circle) and invalid (solid triangle) trials were plotted as a function of the stimulus onset asynchronies (SOAs). Graph C depicts the validity effect score (RT: invalid valid trials) for HC (white bars) and mTBI patients (grey bars) at each SOA. Error bars correspond to the standard error of mean.

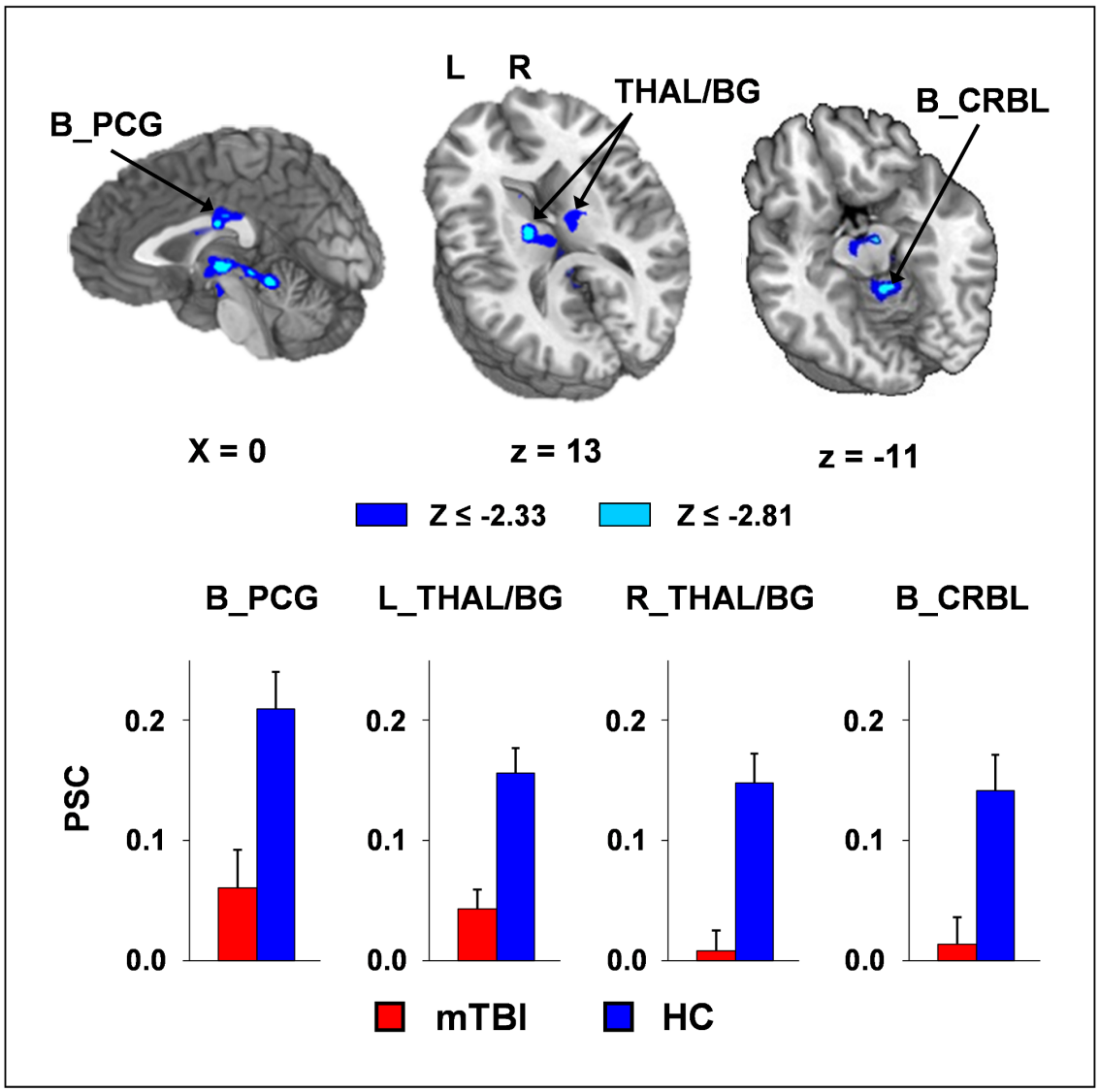

Figure A.3: This figure presents regions showing the significant group difference across all task conditions and the percent signal change (PSC) values for mild traumatic brain injury (mTBI: red bars) and healthy controls (HC: blue bars). The magnitudes of z-scores are represented by either blur or cyan coloring. Locations of the sagittal (X) and axial (Z) slices are given according to the Talairach atlas (L = left and R = right). Decreased activation for mTBI patients compared to HC was observed within bilateral posterior cingulate gyrus (B_PCG), left and right thalamus and basal ganglia (L_THAL/BG & R_THAL/BG), and bilateral cerebellum (B_CRBL). Error bars correspond to the standard error of mean.

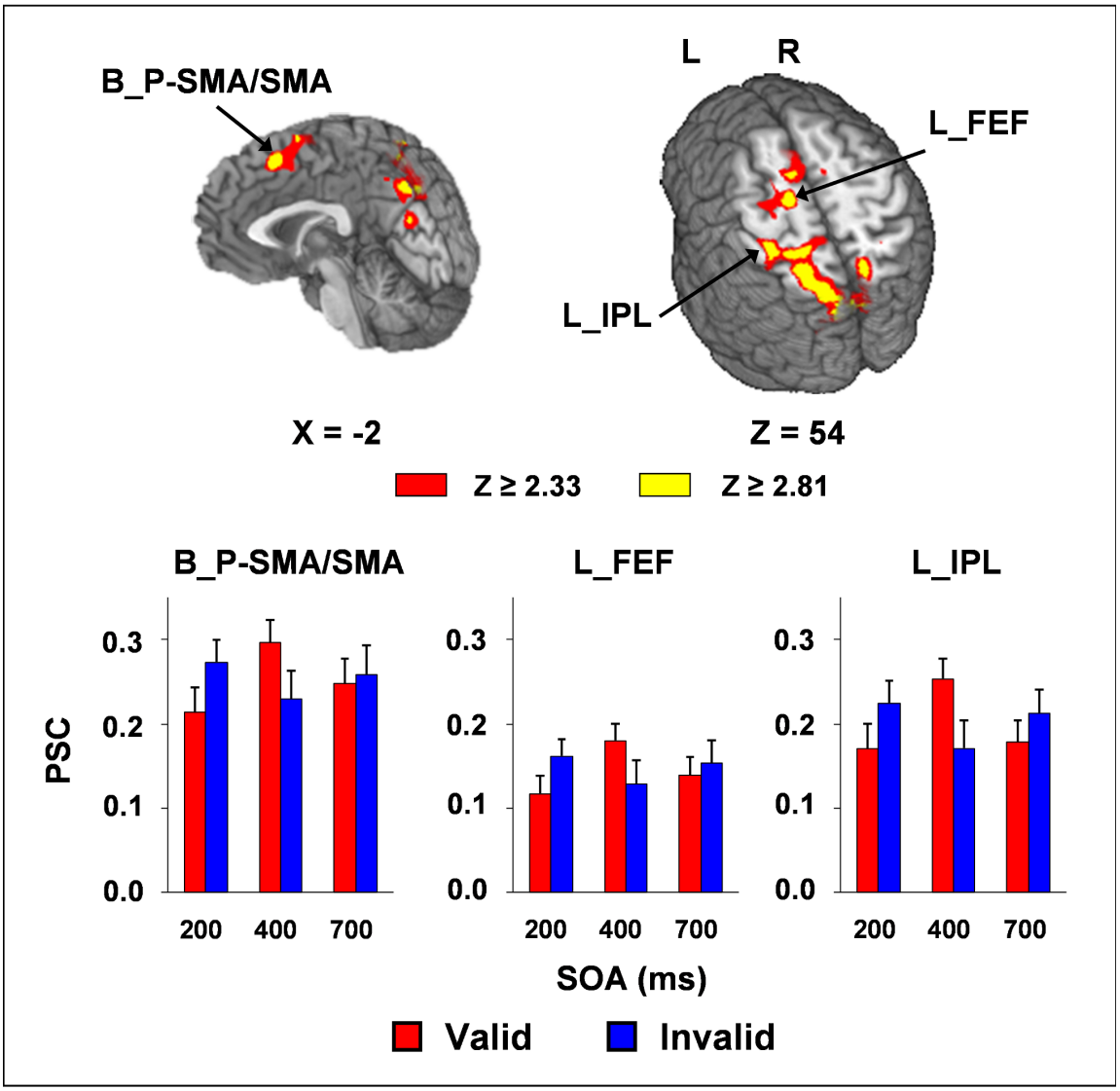

Figure A.4: This figure presents the regions exhibited a significant Validity x SOA interaction when mild traumatic brain injury (mTBI) and healthy controls (HC) were collapsed. The magnitudes of z-scores are represented by either red or yellow coloring. Locations of the sagittal (X) and axial (Z) slices are given according to the Talairach atlas (L = left and R = right). Percent signal change (PSC) values for the regions implicated in the interaction are presented for valid (red bars) and invalid (blue bars) trails at 200, 400, and 700 ms SOA. The areas included bilateral pre-supplementary/supplementary motor area (B_P-SMA/SMA), near left frontal eye fields (L_FEF), and left inferior parietal lobe (L_IPL). Error bars correspond to the standard error of mean.

Appendix B

Tables

Table B.1: Differences in demographic characteristics and neuropsychological test scores between mild traumatic brain injury (mTBI) and healthy control (HC) participants.

	mTBI		**HC**			
	Mean	SD (+/-)	Mean	SD (+/-)	p value	Cohen's d
Demographic						
Age	13.50	1.83	13.29	2.09	p>0.10	0.11
EDU(self)	6.86	1.88	7.21	2.08	p>0.10	0.18
EDU(parent)	13.29	2.59	14.83	3.47	p>0.10	0.50
Siblings	2.54	1.90	3.14	1.70	p>0.10	0.33
	M	F	M	F	p value	Phi
Gender∗	14	0	11	3	p = 0.07	0.35
	R	L	R	L	p value	Phi
Handedness	13	1	14	0	p>0.10	0.19
Neuropsych	Mean	SD (+/-)	Mean	SD (+/-)	p value	Cohen's d
Attention	54.09	4.66	56.51	3.86	p>0.10	0.57
Memory∗	52.17	9.27	57.86	7.00	p = 0.08	0.69
WM	50.07	7.63	50.57	7.78	p>0.10	0.06
PS∗	49.04	7.88	53.89	5.72	p = 0.07	0.70
EF	52.34	4.47	51.63	5.58	p>0.10	0.14
WRAT	52.52	12.07	51.52	8.47	p>0.10	0.10
BASC-2 SRP						
School	52.29	11.02	48.86	11.23	p>0.10	0.31
Internalizing∗	46.64	9.92	41.00	3.62	p = 0.06	0.76
Inattention	53.36	14.87	45.57	9.32	p>0.10	0.63
Emotional	45.86	9.51	41.79	6.29	p>0.10	0.50
Adjustment	54.14	9.09	56.00	9.29	p>0.10	0.20
BASC-2 PRS						
Externalizing	50.15	8.47	52.38	8.01	p>0.10	0.27
Internalizing	47.77	7.92	52.15	8.04	p>0.10	0.55
Behavioral	48.00	8.60	52.23	7.93	p>0.10	0.51
Adaptive	54.54	10.82	49.92	6.12	p>0.10	0.53

Note: edu = education; M = male; F = female; R = right; L = left; WM = working memory; PS = processing speed; EF = executive function; WRAT = The Wide Range Achievement Test; BASC-2 = Behavior Assessment System for Children Second Edition; SRP = Self-Report of Personality; PRS = Parent-Rating Scales. Demographic data are raw scores, whereas Neuropsychological measures and BASC-2 measures are t-scores.

∗ Denotes a non-significant trend

Table B.2: Regions demonstrating hypoactivation for mild traumatic brain injury patients relative to healthy controls.

Region	**Side**	**BAs**	**X**	**Y**	**Z**	**Volume (ml)**
Parietal						
Posterior cingulate gyrus	M	23	0	-19	27	1.173
Subcortical						
Thalamus and basal ganglia	R		8	-11	2	3.432
	L		-10	-11	2	4.612
Cerebellum						
Lingual and culmen	M		0	-38	-8	1.429

Note: Side refers to the hemisphere showing activation where M = Midline; L = left, and R = right hemisphere. The Brodmann area (BA), the center of mass in Talairach coordinates (X, Y, Z) and volume are specified for each area of activation.

Table B.3: Regions implicated in the SOA by validity interaction

Region	**Side**	**BAs**	**X**	**Y**	**Z**	**Volume (ml)**	**SOA**		
							200ms	**400ms**	**700ms**
Frontal									
Pre-SMA/SMA/ anterior cingulate	M	6/8/24/32	-3	3	53	4.652	INV>VAL	INV<VAL	-
Middle frontal and precentral gyrus	L	6	-18	-12	58	3.206	INV>VAL	INV<VAL	-
Parietal and Occipital									
Posterior parietal cortex	L	2/3/4/5/7/40	-28	-38	58	4.514	INV>VAL	INV<VAL	-
Precuneus and cuneus	R	7/19	11	-66	45	3.374	INV>VAL	INV<VAL	-
	L	5/7/18/19/31	-14	-63	40	13.972	INV>VAL	INV<VAL	-

Note: Side refers to the hemisphere showing activation where M = Midline; L = left, and R = right hemisphere. The Brodmann area (BA), the center of mass in Talairach coordinates (X, Y, Z) and volume are specified for each area of activation.

Appendix C

Supplementary Figures

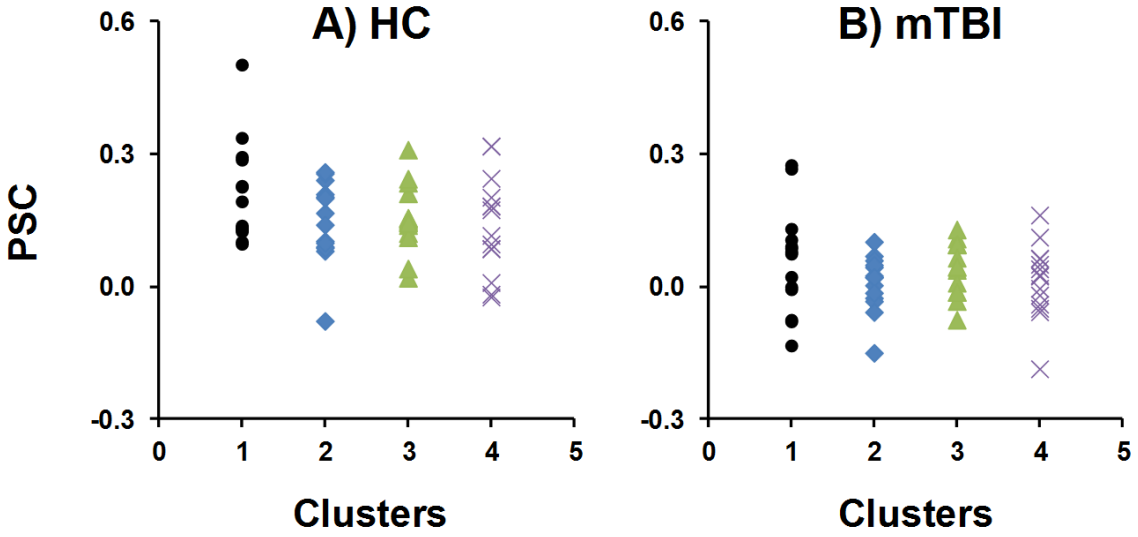

Figure C.1: The data distribution of the percent signal change (PSC) for regions implicated in the main effect of group. Panel A: healthy controls (HCs); Panel B: patients with mild traumatic brain injury (mTBI). The four clusters are: 1) bilateral posterior cingulate gyrus (black dot); 2) right thalamus/basal ganglia (blue diamond); 3) left thalamus/basal ganglia (green triangle); and 4) bilateral cerebellum (purple cross).

Appendix D

Supplementary Tables

Table D.1: Patient injury information

Age	**Gender**	**Mechanism of Injury**	**AAN Rating**	**Days post-injury MRI**	**Days post-injury NP**
12	male	SR	IIIb	20	20
14	male	Fall	III	20	19
12	male	Fall	IIIa	8	8
15	male	SR	IIIa	14	14
14	male	Fall	IIIa	19	19
14	male	MVA	IIIa	11	12
16	male	MVA	IIIb	19	20
17	male	SR	II	15	15
12	male	Fall	IIIa	17	17
12	male	Fall	IIIb	21	21
10	male	SR	IIIa	18	18
10	female	SR	II	7	7
14	male	SR	II	18	14
14	male	SR	IIIa	9	9
17	female	SR	II	20	17
13	male	SR	II	21	19

Note: MVA = motor vehicle accident; SR = sports/activity related; AAN = American Academy of Neurology; and NP = neuropsychological testing
$*$ Denotes a non-significant trend

Table D.2: Regions showing a main effect of stimulus onset asynchrony

Region	**Side**	**BAs**	**X**	**Y**	**Z**	**Volume (ml)**
Shorter SOA dominance						
Anterior insula and basal ganglia	R	10/13/46/47	34	22	-5	7.040
Cingulate gyrus	M	24/32	1	17	28	3.763
Lateral temporal-occipital cortex	L	13/19	-26	-18	-4	4.621
Lateral temporal-occipital cortex extending into medial temporal lobe	R	20/27/30 /35/36/37	22	-29	-7	8.738
Precuneus and cuneus	R	7/18/19/30 /31/37/39	27	-69	14	48.507
Crossing SOA dominance						
Superior/middle frontal gyrus	R	8/9/10	22	40	24	7.226
Precuneus and cuneus	L	7/17/18/19 /31/37/39	-27	-74	12	38.562
Fusiform gyrus and cerebellum	R	19/37	29	-67	-23	12.664
	L	18/19/37	-31	-66	-21	12.242
Longer SOA dominance						
Auditory cortex	R	6/13/22/40 /41/42/43	52	-26	13	16.836

Note: Side refers to the hemisphere showing activation where M = Midline; L = left, and R = right hemisphere. The Brodmann area (BA), the center of mass in Talairach coordinates (X, Y, Z) and volume are specified for each area of activation. Shorter SOA dominance = either decreased activation or deactivation at the 700 ms SOA; Crossing SOA dominance = greatest activation at 400 ms SOA; Longer SOA dominance = increased activation at the 400 and 700 ms SOA relative to the 200 ms SOA.

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