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Brain Imaging Correlates of Verbal Working Memory in Children Following Traumatic Brain Injury

Elisabeth A. Wilde, PhD^{a,b,c,d}, Mary R. Newsome, PhD^{a,d}, Erin D. Bigler, PhD^{e,f}, Jon Pertab, PhD^g, Tricia L. Merkle, BS^{a,g}, Gerri Hanten, PhD^a, Randall S. Scheibel, PhD^{a,d}, Xiaoqi Li, MS^a, Zili Chu, PhD^{c,h}, Ragini Yallampalli^{a,d}, Jill V. Hunter, MD^{c,h}, and Harvey S. Levin, PhD^{a,b,d,i,j}

^a Physical Medicine and Rehabilitation Alliance of Baylor College of Medicine and the University of Texas-Houston Medical School, Houston, TX

^b Department of Neurology, Baylor College of Medicine, Houston, TX

^c Department of Radiology, Baylor College of Medicine, Houston, TX

^d Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX

^e Department of Psychology, and Neuroscience Center, Brigham Young University, Provo, Utah

^f Department of Psychiatry and the Utah Brain Institute, University of Utah, Salt Lake City, Utah

^g Department of Psychology, Brigham Young University, Provo, Utah

^h Department of Pediatric Radiology, Texas Children's Hospital, Houston, TX

ⁱ Department of Pediatrics, Baylor College of Medicine, Houston, TX

^j Department of Neurosurgery, Baylor College of Medicine, Houston, TX

Abstract

Neural correlates of working memory (WM) based on the Sternberg Item Recognition Task (SIRT) were assessed in 40 children with moderate-to-severe traumatic brain injury (TBI) compared to 41 demographically-comparable children with orthopedic injury (OI). Multiple magnetic resonance imaging (MRI) methods assessed structural and functional brain correlates of WM, including volumetric and cortical thickness measures on all children; functional MRI (fMRI) and diffusion tensor imaging (DTI) were performed on a subset of children. Confirming previous findings, children with TBI had decreased cortical thickness and volume as compared to the OI group. Although the findings did not confirm the predicted relation of decreased frontal lobe cortical thickness and volume to SIRT performance, left parietal volume was negatively related to reaction time (RT). In contrast, cortical thickness was positively related to SIRT accuracy and RT in the OI group, particularly in aspects of the frontal and parietal lobes, but these relationships were less robust in the TBI group. We attribute these findings to disrupted fronto-parietal functioning in attention and WM. fMRI results from a subsample demonstrated fronto-temporal activation in the OI group, and parietal activation in the TBI group, and DTI findings reflected multiple differences in white matter tracts that engage fronto-parietal networks. Diminished white

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Corresponding author: Elisabeth A. Wilde, PhD, Baylor College of Medicine, 1709 Dryden Rd., Ste 1200, ewilde@bcm.edu, voice: 713-798-7331; fax: 713-798-6898.

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matter integrity of the frontal lobes and cingulum bundle as measured by DTI was associated with longer RT on the SIRT. Across modalities, the cingulate emerged as a common structure related to performance after TBI. These results are discussed in terms of how different imaging modalities tap different types of pathologic correlates of brain injury and their relationship with WM.

1. Introduction

Deficits in working memory (WM) are common following traumatic brain injury (TBI) in children (Levin et al., 2002; Levin et al., 2004) and adolescents (McDowell et al., 1997; Vallat-Azouvi et al., 2007; Willmott et al., 2009), and are presumed to be related to underlying pathology or dysfunction in the networks supporting WM including the frontal and parietal lobes and the cingulate. Previous studies have demonstrated significant TBI-induced parenchymal differences including smaller frontal and cingulate white and gray matter volumes (Levine et al., 2008; Wilde et al., 2005; Yount et al., 2002), reduced cortical thickness in the frontal lobes (McCauley et al., 2010), pronounced cortical abnormalities on surface-based morphometry in the frontal lobes (Turken et al., 2009), and histological evidence of reduced cortical thickness associated with neuronal loss in the cortical mantle following TBI in frontal and cingulate regions (Maxwell et al., 2010). Additionally, previous findings have shown TBI-related alteration in white matter microstructure in the frontal, parietal and cingulate regions using advanced techniques such as diffusion tensor imaging (DTI) (Kurowski et al., 2009; Levin et al., 2008b; McCauley et al., 2011; Oni et al., 2010; Wilde et al., 2010; Wozniak et al., 2007).

The Sternberg Item Recognition Task (SIRT; Sternberg, 1966) is commonly used to measure WM, the ability to hold and manipulate a limited amount of information in consciousness, for use in guiding behavior after the information is removed from the environment (Baddeley, 1986). In this task, the subject is asked to remember a memory set consisting of items presented on a screen (typically 2–6 letters or digits shown sequentially or simultaneously depending on the study) which he or she attempts to encode in WM. After a short delay (maintenance), a single item (probe) is presented and the subject responds by indicating whether or not the item was present in the previous memory set by pressing one of two buttons (or by using levers as in the original studies). To add demands on cognitive control, the SIRT in this study also had an interference condition wherein a negative probe letter (i.e., not part of the memory set presented at the beginning of the trial) was presented which had been part of a memory set on recent trials. This interference condition was present on 20% of the trials.

Functional magnetic resonance imaging (fMRI) studies examining normal subjects using the SIRT have found fronto-thalamo-parietal network and anterior cingulate cortex (ACC) involvement in WM (Braver et al., 1997; Bunge et al., 2001; Gazzaley et al., 2004; Narayanan et al., 2005; Sanchez-Carrion et al., 2008b). fMRI studies of verbal WM in adults with moderate-to-severe TBI have reported a variety of patterns, including increased activation in frontal, temporal, and parietal regions (Christodoulou et al., 2001), attenuated increases in activation with increased memory load (Perlstein et al., 2004), and decreased frontal activation (Sanchez-Carrion et al., 2008b). Adolescents with moderate-to-severe TBI demonstrated a disruption in allocation of neural resources necessary for WM performance, with increasing frontal, parietal, and temporal activation during the encoding and retrieval subcomponent processes and decreasing activation during maintenance (Newsome et al., 2008). A spatial working memory task in adolescents with moderate-to-severe TBI resulted in decreased activation in anterior cingulate cortex coupled with increased activation in sensorimotor cortex (Cazalis et al., 2011). However, studies using participants with TBI are

sparse and, to date, there have been no reports in pediatric TBI which utilize multiple imaging modalities.

To address this gap, we examined neural correlates of SIRT performance in children with TBI and a comparison group of children with orthopedic injury (OI) using multiple structural and functional neuroimaging techniques. We measured parenchymal volume and cortical thickness by volumetric analysis, and in a subgroup of these participants, we acquired DTI to evaluate white matter integrity, and fMRI to study the effects of TBI on cortical representation of WM. We specifically focused upon brain regions presumed to be related to working memory performance, including the frontal lobes, including the middle frontal gyrus (MFG), the parietal lobes, and the cingulate. Regarding performance on the SIRT, we hypothesized that although there may not necessarily be differences on the easiest (load 1) condition, the OI group would demonstrate greater accuracy and decreased reaction time (RT) on the two higher memory load conditions, and particularly on the interference condition. Next, we hypothesized that decreased regional volumes and cortical thickness in the frontal and parietal lobes and cingulate of the TBI group would be related to their accuracy and RT on the task. For fMRI, we hypothesized that the functional activation patterns associated with WM would differ in the TBI group as compared with the OI patients. Based on our previous fMRI study using the SIRT (Newsome et al, 2008), we hypothesized that the TBI group would exhibit more working memory-related activation of the frontal-parietal region during encoding and retrieval, whereas the OI group would show greater activation during the maintenance (delay) phase of working memory. Finally, we hypothesized that there would be differences in DTI metrics between the TBI and OI groups, with the TBI group demonstrating less integrity of the microstructure of the white matter as indicated by lower fractional anisotropy (FA) and higher apparent diffusion coefficient (ADC) in comparison to the OI group. In addition, because slowed RT during task performance is a frequent finding after moderate-to-severe TBI that has been attributed to diffuse white matter pathology and reduced connectivity, we predicted that slower RT would be related to decreased microstructural integrity of white matter as measured by DTI, especially in the frontal, cingulate and parietal regions. Given that each method of imaging taps a unique element of either structural or functional brain integrity, we assumed that each method would also contribute unique information about the effects of TBI on WM-related neural networks and their structural substrate in children.

2. Materials and Methods

2.1 Subjects

2.1.1 Cohort 1—Forty children who sustained TBI between the ages of 7 and 17 years were studied. Post-resuscitation Glasgow Coma Scale (GCS) scores recorded in the emergency center ranged from 3–15 with a mean of 7.7 ± 4.2 . Severe TBI was defined by the lowest post-resuscitation GCS score of 3–8, which is indicative of coma, whereas moderate TBI was defined by GCS score of 9–12, which reflects impaired consciousness but not coma (Teasdale and Jennett, 1974). Participants with “complicated mild” TBI (GCS score of 13–15, but with an intracranial abnormality evident on computed tomography (CT)) were also included using the rationale that these patients have been shown to exhibit cognitive deficits at 12 months post-injury despite mild impairment of consciousness (Levin et al., 2008a). Based on this classification, the TBI group was comprised of 25 children with severe TBI, 8 children with moderate TBI, and 7 children with complicated mild TBI. Eligibility criteria for participants with TBI included having a score less than 4 on an Abbreviated Injury Scale (AIS) (Committee on Injury Scaling, 1990) for injuries to body regions other than the head and absence of post-resuscitation hypoxia or hypotension exceeding 30 minutes. All participants with TBI were recruited as consecutive admissions to the trauma centers of

participating hospitals. Fourteen of the 40 participants with TBI underwent a neurosurgical procedure.

The comparison group comprised 41 children aged 7–17 years who had sustained OI and were recruited from the emergency room or local community health care facilities. In this study, OI was defined by any traumatic bone fracture or other extracranial injury requiring at least an overnight hospitalization provided that the AIS score was 1–3, indicating relatively mild injury. The OI comparison group controls for risk factors (Bijur and Haslum, 1995; Stancin et al., 2001; Stancin et al., 1998) that predispose to injury, including preexisting behavioral problems, subtle learning disabilities, and family variables. The absence of significant previous head trauma in the OI group was confirmed through detailed developmental questionnaire administered to the parent or legal guardian, and the absence of concurrent head injury was confirmed via medical records and/or physician report of physical examination findings and clinical imaging results.

All participants were English-speaking, had at least a reported 37-week gestational period before birth, and had no previous hospitalization for head injury. In addition to ensuring comparable distributions of age and gender in the TBI and OI groups, recruitment of the OI group was guided to ensure that a socioeconomic index (SCI) based on occupational status of the parent, annual family income, and years of maternal education did not differ from the children with TBI. The SCI was calculated according to the guidelines outlined in Yeates et al. (1997); with higher scores reflecting higher socioeconomic status (Yeates et al., 1997). This information was collected via a questionnaire completed by the parent.

All children included in both groups were English-speaking, and had no pre-existing head injury, neurologic disorder associated with cerebral dysfunction and/or cognitive deficit (e.g., cerebral palsy, mental retardation, epilepsy), diagnosed learning disability, psychiatric disorder, or history of child abuse. As part of the study design, neuroimaging and cognitive assessment for cohort 1 were planned for three months post-injury. Demographic and injury-related characteristics for each group, including age at injury, race/ethnicity, gender, handedness, socioeconomic index, time post-injury, injury severity as measured by GCS, ISS score, and mechanism of injury appear in Table 1.

2.1.2 Cohort 2—fMRI and DTI data were available for six participants with TBI (mean age at scanning=15.1 years, SD=1.7, range=13.2–17.7 years; 5 males, 1 female) and 11 OI subjects (mean age=14.0 years, SD=3.0, range=9.8–17.4 years; 7 males, 4 females) from cohort 1. Participants with TBI in cohort 2 were studied between 1.4 years and 2.1 years (mean 1.6 years) post-injury, and OI controls were studied between 0.4 and 2.8 years (mean 1.3 years) post-injury. In this cohort, 5 children had severe and 1 had moderate TBI. Data for three of the TBI patients had been included in a previous report (Newsome et al., 2008).

2.2 MRI Acquisition

Structural imaging was obtained in all participants and therefore, volumetric and cortical thinning measurements were available on most participants. However, DTI and fMRI were performed on only a subset (Cohort 2) of the total sample (Cohort 1). Regular quality assurance testing was performed on all scanners utilized in this study including American College of Radiology (ACR) phantom and Weisskoff testing (Weisskoff, 1996) for echo planar imaging sequences.

2.2.1 MRI acquisition for Structural Imaging (Cohort 1)—All subjects underwent magnetic resonance imaging (MRI) without sedation on Philips 1.5 T Intera scanners (Philips, Best, Netherlands) at hospitals in Houston, Dallas and Miami, using comparable scanner models and software platforms. T1-weighted (15 ms repetition time (TR), 4.6 ms

echo time (TE), 1.0 mm slices, 0 mm gap), 3D sagittal acquisition series were used for volumetric analysis. A 256 mm field of view (FOV) was used for these series with a reconstructed voxel size of $1 \times 1 \times 1$ mm.

2.2.2 MRI Acquisition for Additional fMRI and DTI Imaging (Cohort 2)—All subjects in cohort 2 underwent additional scanning on Philips 3 T Intera scanners (Philips, Cleveland, OH). For DTI acquisition, transverse multi-slice spin echo, single shot, echo planar imaging (EPI) sequences were used (6161 ms TR; 51 ms echo time, 2.0 mm slices, 0 mm gap, 2 sensitivity encoding (SENSE) reduction). A 224 mm FOV was used with a measured voxel size of $2.0 \times 2.0 \times 2.0$ mm and a reconstructed voxel size of $1.75 \times 1.75 \times 2.0$ mm. Diffusion was measured along 30 directions (number of b-value=2, low b-value=0, and high b-value=1000 s/mm²). To improve signal to noise ratio, high-b images were acquired twice and were averaged. Each acquisition took approximately 5 min 45 seconds, and 55 slices were acquired. For fMRI, blood oxygen level dependent (BOLD) parameters for the EPI sequence included 1700 ms TR; 30 ms TE; 3.75 mm slices; 0.5 mm gap; 2 SENSE reduction; 143 dynamic scans. A 240 mm FOV was used with a voxel size of $3.75 \times 3.75 \times 4.25$ mm.

2.3 Volumetric and Cortical Thickness Analysis

Cortical reconstruction, cortical parcellation, and subcortical segmentation of the structural MRI scans were performed using the Freesurfer neuroimage analysis suite, as described previously (Bigler et al., 2010a; Merkley et al., 2008). Cortical surface reconstruction results were inspected for accuracy, and editing was performed to optimize the results where necessary. The cortical models were then registered to a spherical atlas which used individual cortical folding patterns to match cortical geometry across subjects, and the cerebral cortex was parcellated into regions based on gyral and sulcal structure (Desikan et al., 2006). Cortical thickness at each point on the cortical mantle was measured as the distance between the reconstructed pial surface and the gray/white matter boundary. Cortical volume of the regions of interest (i.e., right and left frontal and parietal lobes, middle frontal gyrus and cingulate, as identified in Figure 1) were computed as the product of the surface area and thickness. Both white and gray matter were included in the calculation of these regions of interest. For volumetric analysis, the volume for each region of interest was corrected for total intracranial volume (TICV). Prior to cortical thickness analysis, the data for each participant were resampled to a template customized to our pediatric population, and surface smoothing was performed with a 10mm full-width half-maximum (FWHM) Gaussian kernel.

2.4 fMRI Analysis (Cohort 2)

fMRI data were processed and analyzed using Statistical Parametric Mapping software (SPM8, Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (Mathworks Inc. Sherborn MA, USA). After slice-timing correction, the fMRI time series was realigned and unwrapped to correct for head motion and susceptibility-by-movement interactions. No series had head motion greater than 2.0 mm translational or 2.0 degrees rotational. The high-resolution anatomical scan was co-registered to the fMRI images, which were normalized to the stereotactic coordinates of the Montreal Neurologic Institute and spatially smoothed with a 6 mm isotropic FWHM Gaussian filter. Significant coordinates were then transformed to Talairach space using the mni2tal script (<http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach>). The Talairach Daemon (<http://ric.uthscsa.edu/projects/talairachdaemon.html>) was used to determine the anatomical locations of the transformed coordinates.

Results from random effects group analyses are reported for activation during the retrieval subcomponent process (limited to positive probe trials) for the highest load level (load 4). The intertrial interval, during which a single crosshair was presented, was used as the control condition. The voxel-level (height) cluster-defining threshold was $p < .05$, uncorrected, and cluster-level statistical significance was defined as $p < .05$, using a false discovery rate correction for multiple comparisons over the whole brain. In addition, as a preliminary investigation into relating activation to brain volume, multiple regression was performed regressing total ACC volume onto whole brain activation. The ACC was chosen as it is a single well-defined structure with relevance to WM. To increase power and the range of variability, we combined both groups for the regression.

2.5 DTI Analysis (Cohort 2)

The Philips PRIDE-registration tool was used to remove shear and eddy current distortion and head motion prior to calculating FA maps with Philips fiber tracking 4.1v3 Beta 2 software. Regions of interest (ROIs) were created using established methodology and protocols detailed in previous publications (Bigler et al., 2010b; Levin et al., 2008b; Oni et al., 2010; Wilde et al., 2006; Willmott et al., 2009). For this investigation, FA and ADC were computed for the following structures: 1) the inferior frontal occipital fasciculus (IFOF), 2) the inferior longitudinal fasciculus (ILF), 3) frontal white matter, 4) uncinate fasciculus (UF), 5) anterior limb of the internal capsule (AIC), 6) posterior limb of the internal capsule (PIC) and 7) cingulum bundle (CB). These ROIs are highlighted in Figure 2. Bonferroni correction for multiple comparisons was performed, and the threshold for statistical significance was set at $p < 0.006$.

2.6 Sternberg Memory Task Without Imaging

All subjects were administered a computerized version of the SIRT in a quiet room. An illustrative example of the SIRT is depicted in Figure 3. Each child viewed a memory set of 1, 4, or 6 uppercase letters (Load 1, Load 4, and Load 6) for 1700 ms on a 13" laptop computer screen and after a 4000 ms delay identified whether a probe letter had been in the memory set. On interference trials (limited to sets with 4 letters), the probe letter which was not part of the memory set presented at the beginning of the current trial was present in the memory set on the immediately preceding trial, thus introducing interference. The children were not informed of the interference condition. Twenty-four randomized trials of each memory load were presented using E-prime software. Variables collected were the number of errors and RT for each condition, separated into target present ("yes") trials and target absent ("no") trials. All analyses of relations between performance on the SIRT and imaging variables were performed using only Load 4. This was guided by our previous experience indicating that load 4 was more sensitive in distinguishing group differences than load 1 (which may be too simple) or load 6 (which may be too challenging for some participants with TBI). The task performed outside of the scanner had two Load 4 conditions, with one condition presenting a probe letter that did not appear in the memory set of the current trial, but had appeared in the immediately preceding trial (interference condition; (Bunge et al., 2001) and the other condition (without interference condition) presenting a probe which was one of the letters in the memory set for the current trial. Because an accurate response in the interference condition requires the rejection of an item that is still in WM but incorrect, this condition provides a measure of the ability to suppress information that is irrelevant to the current trial. Thus, subjects without TBI might be expected to have a longer response time and more errors in Load 4-Interference relative to Load 4. For the analyses of interference, Load 4 without interference was subtracted from Load 4 with interference, which resulted in a measurement of the effect of interference on RT and errors. On all RT analyses, only values from correct responses are used.

2.7 Sternberg Memory Task With Imaging

In the fMRI sessions, only loads 1 and 4 with no interference condition were administered. To reduce data, and to arguably make the conditions analyzed consistent with those in cohort 1, data for the fMRI analyses are reported for retrieval events. Because we were interested in brain regions associated with retrieving an item presented in the memory set, rather than rejecting an item that had not been presented, activation patterns are reported for when the target had been presented in the memory set.

2.8 Statistical Analysis

Independent sample t-tests were used to examine group differences on demographic variables such as socioeconomic status as measured by the SCI, age of injury, and time post-injury. Fisher's exact test was used to examine group differences in gender and lateral dominance. A general linear model (GLM) was used to determine group differences on regional volumes, where TICV was included in the model. Critical assumptions of the GLM analyses were examined and no violations were noted. A between-subject general linear model was fit at each vertex for cortical thickness differences between groups and the relation of cortical thickness to SIRT RT and errors. Statistical parametric maps of the cortical mantle were created to show group differences as well as the relation of cortical thickness to SIRT RT. GLM was also used to examine group differences on SIRT performance, with age included in the model. Group differences for DTI were examined using Wilcoxon tests after ensuring that the distributions were approximately normal. The relation of SIRT reaction time and errors (with and without interference conditions) to cortical volumes was assessed with Pearson correlation coefficients, and the relation between SIRT variables and DTI was examined using Spearman correlation coefficients. The threshold for determining statistical significance was set at $p < 0.05$.

3. Results

3.1 Demographic and Injury Characteristics

No significant differences were noted in gender composition, handedness, SCI score, or post-injury interval between the two groups. Race/ethnicity did differ between the groups, with a higher percentage of African Americans in the OI group and a higher percentage of Hispanic participants in the TBI group. The OI group was younger than the TBI group ($t(79) = -2.52$, $p = 0.014$); therefore, age at testing/scanning was controlled in subsequent statistical models. As expected, participants in the TBI group were more frequently injured as a result of high-speed mechanisms of injury, such as motor vehicle crashes ($\chi^2(1) = 11.62$, $p = 0.0007$), where the participants in the OI groups were most commonly injured as a result of sports or play. Results of each statistical test are presented in Table 1.

As with cohort 1, handedness and gender distribution, post-injury interval and SCI score did not differ between groups (all p 's $> .20$) in cohort 2. Unlike cohort 1, there were no significant differences in age at testing/scanning in cohort 2.

3.2 SIRT Performance

Load 1. GLM analysis, controlling for age, revealed no significant group differences for SIRT accuracy or RT on load 1.

Load 4 (without interference). Accuracy for load 4 significantly differed between the groups ($F(1,77) = 5.88$, $p = 0.018$, Cohen's $f = 0.28$), where children with TBI made more errors than those with OI. RT for load 4 was not significantly different between the groups.

Load 4 (with interference). After covarying for age, GLM revealed a significant group difference on the effect of interference (that is, the difference between Load 4 without interference and Load 4 with interference) on SIRT performance for accuracy ($F(1,77)=4.59$, $p=0.035$, Cohen's $f = 0.24$) and on RT ($F(1,77)=5.39$, $p=0.023$, Cohen's $f = 0.26$), such that the OI group showed a greater negative effect of interference on both RT and accuracy than the TBI group.

Load 6. GLM analysis, controlling for age, revealed no significant group differences for SIRT accuracy or RT on load 6.

3.3 Volumetric and Cortical Thickness Findings

Significant right and left frontal and right MFG volume reductions were observed in the TBI children compared to the OI subjects when Bonferroni correction for multiple comparisons was applied. There was a trend for left cingulate, left MFG and right and left parietal volume being reduced in the TBI subjects that was not significant when correction was applied. Least squared means, standard errors and F-statistics, p-values and effect sizes (Cohen's f) are included in Table 2.

Cortical thickness differences were observed predominantly over both frontal lobes (pars triangularis, pars orbitalis, lateral orbital frontal, medial orbital frontal, rostral middle frontal, frontal pole, superior frontal) and right temporal lobe (superior, middle and inferior temporal gyri and fusiform gyrus) where participants with TBI demonstrated cortical thinning as compared to OI children ($0.01 > p > 0.00001$, see Figure 4).

3.4 Relation between Regional Volumes and Working Memory (Cohort 1)

No significant correlations were found between SIRT accuracy or reaction time variables (interference and without interference conditions) and volume of the frontal lobes, MFG, cingulate or parietal lobes in the OI group. However, in the TBI group, there were negative correlations between the right ($r = -0.35$, $p = 0.028$) and left ($r = -0.34$, $p = 0.033$) cingulate volumes and SIRT RT for the non-interference condition and between left parietal lobe volume and SIRT non-interference RT ($r = -0.37$, $p = 0.020$). For the TBI group, smaller volume was associated with longer RT. Accuracy (for both interference and without interference conditions) was not related to volume of the frontal or parietal lobes, MFG, or cingulate in the TBI group.

3.5 Relation between Cortical Thickness and Working Memory (Cohort 1)

Cortical thickness in the OI participants was positively correlated ($0.01 > p > 0.00001$) with SIRT errors in bilateral caudal middle frontal gyrus, left superior frontal, superior parietal, and cuneal regions and right rostral middle frontal, precentral gyrus, posterior cingulate, and precuneus regions. Greater cortical thickness in the OI participants was also associated with longer RT in the left superior frontal gyrus and right precuneus and paracentral lobule (Figure 5). For the TBI group, SIRT errors were positively associated with cortical thickness in small areas of the left parietal and inferior temporal regions and the right frontal, paracentral, rostral middle frontal and superior parietal regions. Greater cortical thickness in the TBI participants was associated with longer RT in similar regions as the OI participants, however the regional extent was greatly reduced (see Figure 5). There was no suggestion of a group difference with errors.

3.6 Relation between fMRI and Working Memory (Cohort 2)

3.6.1 In-Scanner Working Memory Performance—There were no group differences in overall accuracy or RT. However, there was a significant effect on RT depending on

whether the probe was a letter that had been presented as part of the memory set at the beginning ($F(1,14) = 13.2$, $p = 0.003$), such that the RT was longer for stimuli where the probe was presented (734 ms for absent, and 814 ms for present). 3.6.2 fMRI Activation Results

3.6.2.1 Within Groups: Activation in the OI group was limited to one anterior right-sided cluster that included inferior frontal gyrus (BA47), insula (BA13), temporal pole, and superior temporal gyrus (BA38). The TBI group demonstrated significant activation in three clusters that included bilateral medial frontal (BA6) and anterior cingulate (BA32) gyri, paracentral lobule, and left precuneus (Cluster 1); left lingual gyrus (BA18,19), middle temporal gyrus (BA22, 37), and bilateral cerebellum (Cluster 2); left posterior cingulate (BA31), precuneus (BA7, 31), and cuneus (BA7) (Cluster 3).

3.6.2.2 Between Groups: Patterns of different fMRI activation are shown in Figures 6a and 6b. The OI group demonstrated greater activation than the TBI group in one anterior right-sided cluster, which included the inferior frontal gyrus (BA45, 47), middle frontal gyrus (BA11, 47), and superior temporal gyrus (BA38). In contrast, the TBI group (cluster level $p = .07$, false discovery rate-(FDR) corrected for multiple comparisons) demonstrated greater activation in one posterior cluster, which included the left posterior cingulate (BA31), inferior parietal lobule (BA40), superior parietal lobule (BA7), and precuneus (BA7, 31).

3.6.2.3 Regression: A positive regression of total ACC volume onto activation across groups revealed a single significant cluster in right insula (BA13), inferior frontal gyrus (BA46), ACC (BA32), precentral gyrus (BA 6, 9), superior frontal gyrus (BA8), and superior temporal gyrus (BA 22). Negative regression was nonsignificant.

3.7 Between-Group Differences in DTI and Relation of DTI to Working Memory (Cohort 2)

Wilcoxon tests (one-tailed) indicated significantly higher ADC in the TBI group than OI participants for left IFOF ($p = 0.007$), left uncinate fasciculus ($p = 0.004$), left frontal white matter ($p = 0.005$), and left anterior limb of the internal capsule ($p = 0.010$), with a trend for the right frontal white matter ($p = 0.06$). Correlations with performance variables of the in-scanner SIRT variables yielded significance in two regions, the left frontal lobe and the left cingulum bundle.

3.7.1 Left frontal lobe—In the OI group, ADC in the left frontal lobe was negatively related to accuracy during load 4 when the target was absent in the memory set ($r = -0.837$, $p = .0025$). There were no relationships with RT. The left frontal lobe was also related to performance in the TBI group, who showed a positive relation between ADC and RT (target present; $r = 1.00$, $p < .0001$). Left frontal white matter and WM performance appear to be closely related. Specifically, better ability to correctly reject false alarms in the OI group was related to better white matter integrity, while slower response times in the TBI group were related to diminished white matter integrity.

3.7.2 Left cingulum bundle—There was no relation between DTI indices for the left cingulum bundle and performance in the OI group. However, in the TBI group, this area was associated with RT regardless of whether or not the target was absent or present in the memory set ($r = 0.94$, $p = .005$; for both), such that greater ADC was associated with longer RT.

4. Discussion

Consistent with our previous findings (Wilde et al., 2005), the TBI group exhibited smaller brain region volumes than the OI group which had a similar distribution of age and gender. Likewise, cortical thinning was evident in children with TBI within regions known to be vulnerable to TBI, in particular frontal and temporal polar regions (see Figure 4). These findings indicate that brain regions identified in the frontal executive network were damaged in the children with TBI.

Analysis of SIRT performance measured outside of the scanner disclosed that the groups did not differ significantly under Load 1, on which both groups performed well (errors for around 5% of trials), or at Load 6, which each group found difficult (errors in more than 17% of the trials). However, Load 4 was sensitive to between-group differences in performance. As would be expected, the TBI group exhibited more errors in performing the SIRT on load 4. However, contrary to expectation, the OI group demonstrated longer RT in comparison to the TBI group. This may have reflected an accuracy-RT tradeoff, whereby the OI group approached the task with intent to maximize accuracy, even if this increased RT.

4.1 Brain Region Volumes and WM Performance

Volumes of both frontal lobes and the MFG were significantly reduced in the TBI group compared to the OI group. While the volumes of MFG, cingulate, and total parietal and frontal lobes were not related to accuracy or RT variables on the SIRT in the OI group, the left and right cingulate volumes were related to SIRT RT in the TBI group such that smaller volume was associated with longer RT. This relation is consistent with findings that have suggested that the anterior cingulate plays a central role in higher level cognitive functions including WM (Miller and Cohen, 2001). Although regional volumes were not related to RT in the OI group, tissue volume in regions highly vulnerable to injury during TBI such as the cingulate may be associated with WM performance after TBI. Practice in WM tasks that have been associated with increased brain volume in healthy adults (Klingberg, 2006) may prove useful to cognitive rehabilitation after TBI.

4.2 Cortical Thickness and WM Performance

As expected, moderate-to-severe TBI was associated with cortical thinning, especially in the frontal region (Figure 4). This is consistent with previous reports of cortical thinning following TBI detected via neuroimaging (Merkley et al., 2008) as well as histopathological analysis (Maxwell et al., 2010). However, in this study, decreased cortical thickness appeared to be most prominent in frontal regions, which are highly vulnerable to TBI-related insult. Additionally, the frontal and parietal lobes are regions which are undergoing significant maturational change during the age range of the participants in this study. Protracted cortical maturation of prefrontal and parietal gray matter is characterized by an inverted-U shaped relation of gray matter volume to age wherein the inversion begins in early adolescence at about age 11 years in girls followed a year later in boys (Giedd, 2008; Gogtay et al., 2004). Cortical thickness in the frontal and parietal regions was positively and significantly related to out of scanner performance on the SIRT task in terms of RT in the OI group. This type of association is most likely related to brain maturation where the most efficient neural system maximizes connectivity with the least amount of gray matter. Given the importance of parietal systems in attention and WM, the observation in the OI group that the fastest RTs occurred in subjects with less parietal gray matter supports the maturation-based interpretation that pruning of excess synapses during late childhood and adolescence enhances cognitive efficiency.

Despite frontal thinning in the TBI group, cortical thickness of these areas was not related to RT. With TBI, this maturational effect within the parietal lobe was ostensibly weakened by the effects of the injury, lessening the relationship between frontal and parietal cortical thickness and RT. Disrupted underlying white matter integrity could lead to slowed processing time disrupting parietal function in WM. As shown in Figure 4, there was minimal thinning of parietal cortex associated with TBI; therefore, it is reasonable to assume that the reduced correlations in parietal cortex between gray matter thickness and WM in the TBI group was not due to an overall reduction in gray matter. We suggest that the effects of TBI disrupted cortical maturation and its relation to working memory as seen in children without brain injury.

4.3 fMRI and WM Performance

Although based on a smaller sample size and in children, the current study found activation in lateral prefrontal cortex in the OI group during retrieval, which is consistent with established findings on WM activation (Braver et al., 1997; D'Esposito et al., 2000). In group comparisons, the OI group demonstrated greater activation in this region than the TBI group, whereas the TBI group demonstrated greater activation in posterior regions associated with WM, i.e., parietal lobules, suggestive of disrupted frontal connections and greater reliance on posterior regions associated with working memory and neighboring regions. In mild TBI samples, parietal and temporal lobes showed increases in activation during verbal working memory tasks (Chen et al., 2004; Pardini et al., 2010; Smits et al., 2009). In subjects with moderate-to-severe TBI, both increased and decreased patterns of activation have been reported during performance of verbal working memory tasks. For example, Christodoulou et al. (2001) reported augmented frontal, temporal, and parietal activation using the Paced Auditory Serial Addition Task (PASAT) as the memory task. Perlstein et al. (2004) reported lesser magnitude increases with load in an n-back task in frontal and parietal regions in TBI patients relative to healthy controls. Sanchez-Carrion et al. (2008b) reported reduced frontal activation in TBI patients during an n-back task. With reduced frontal activation and increased posterior activation in the TBI group, our results are most like those of Sanchez-Carrion et al. (2008b) (reduced frontal activation) and of Christodoulou et al. (2001) (increased temporal and parietal activation), whose increased frontal activation may have in part been due to the cognitive control demands of the PASAT. Indeed, in a task designed to isolate executive control from maintenance, Turner and Levine (2008) reported augmented activation in adult moderate to severe TBI patients, which they attributed to traumatic axonal injury (TAI) independent of focal lesions and with performance equated between groups. Our findings of both ACC and sensorimotor cortex (paracentral lobule) activation within this chronic TBI group are also, in general, consistent with the spatial WM findings of increased sensorimotor cortex and decreased ACC over time in adolescents following TBI (Cazalis et al., 2011).

Findings are also consistent with Newsome et al. (2008) in that the control sample activated working memory regions and the TBI group showed greater activation in the retrieval subcomponent process than the control group. However, in the present study, the control group showed greater activation than the TBI group in fronto-temporal regions, which was not seen in the previous study. The inclusion of a greater ratio of severe to moderate TBIs in the present study may have been associated with the reduced frontal activation in this TBI sample.

While the DTI evidence reported here, and a lack of frontal activation in the TBI group, are consistent with TAI, an interaction of brain injury with late-maturing frontal lobes in these younger adolescents may also have contributed to the reduced activation in frontal areas. An effect of injury on development is further suggested in findings by Newsome and colleagues, who reported a positive correlation between frontal activation and age in TBI

subjects, but not in typically developing control subjects (Newsome et al., 2007). Additionally, in contrast to the present findings of reduced frontal activation in younger adolescents (mean age 15 years), an event-related study on WM after moderate-to-severe TBI in adolescents, Newsome et al. showed greater activation during retrieval in frontal, temporal, and parietal regions in older adolescents (mean age 18 years) (Newsome et al., 2008). Such a pattern may have a corollary in adult subjects with TBI as well; in a longitudinal study, Sanchez-Carrion and colleagues showed increase in frontal activation over time (Sanchez-Carrion et al., 2008a).

Given the role of the ACC in verbal WM in adults (Cohen et al., 1997) and typically developing youth (Newsome et al., 2008), we related volume of ACC to activation in the ACC. A positive relationship was found in the ACC, suggesting that the volume of the ACC may influence the degree to which it is activated. Activation in the positive regression was not limited to the ACC, however, and occurred in more lateral and anterior areas, which may be consistent with activation in BA32 frequently co-occurring with activation in lateral prefrontal cortex (PFC) (Casey et al., 2002). In addition, because increases in ACC activation may be related to increases in accuracy (Hillary, 2008), a future study may find larger volume size to be related to higher accuracy and activation in the ACC, supported in part by the relation of reduced cingulate volume and increased response times reported here. While results are strongly limited by the small sample size, they encourage further investigation of how brain volume may influence activation in multiple regions of the brain.

4.4 DTI and WM Performance

The fronto-parietal attentional network is obviously dependent on the interconnectiveness of the two lobes and two hemispheres and therefore white matter pathology that may disrupt these connections may be most important to WM. Despite the small sample size, white matter disruptions in the TBI group as measured by DTI were found in the frontal lobes and the left IFOF, which projects between the frontal lobes and parieto-occipital region. Any disruption in the effectiveness and efficiency of white matter connections of frontal and attentional systems would likely be disruptive to WM. Other tracts also demonstrated similar relations including the left UF (which projects between the frontal and temporal poles) and the left AIC (which projects into the frontal lobes). The left frontal lobe and cingulum bundle also showed relations to performance, implicating a wide network of connections that likely participate in WM. White matter in the left frontal lobe was related to accuracy in WM performance in the OI control group, where being able to correctly reject a false answer was related to better integrity of left frontal lobe (lower ADC). The TBI group showed a different type of relationship in that condition, however, with better performance associated with higher ADC in the left cingulum bundle. The left cingulum bundle was also related to the speed with which they responded in other conditions. Because group differences were not observed in these samples in the cingulum bundle, which projects between the frontal, parietal, and temporal pole regions, these findings may partially suggest one way in which pathways redirect when frontal white matter is damaged, with the cingulum playing a more prominent role compared to pre-injury, despite volume loss. Thus, the integrity of the pathway as assessed by DTI may be more influential to WM performance than a reduction in its volume. The TBI group still made use of the white matter in the left frontal lobe during an easy WM task, however, where faster speed of correctly recognizing an item from a memory set size of one was associated with lower ADC.

4.5 Summary of SIRT Performance and Multi-modality Imaging Findings

TBI was associated with reduced bilateral frontal and right MFG volumes, although these regions were not associated with performance. Rather, RT was related to bilateral cingulate and left parietal lobe volumes. Because there was no relation between volume and

performance in the OI group, volume in general may have limited contribution to performance until the system is taxed by injury, upon which the volume of non-prefrontal regions relevant to WM may compensate, as the areas that related to performance in the TBI group were not reduced in size¹. However, it is important to note that regions not associated with WM were not measured.

Across the modalities, the cingulate cortex and cingulum bundle emerged as being associated with WM performance in the TBI group, with associations between greater volume and better white matter integrity and shorter RTs. Examining only the anterior portion of the cingulate, the TBI group showed reduced ACC activation. Possibly, when frontal portions of the cingulate are altered, performance may depend on remaining portions to some extent.

While the volumetric and cortical thickness analyses were based on the entire sample, the DTI and fMRI aspects of this investigation were based on a smaller subset of subjects from the original sample, and therefore, we can be less confident in the fMRI and DTI findings. This is a major limitation of the study and these analyses should be considered exploratory. Nonetheless, a rather coherent picture of the role of the frontal lobe emerges from these results. In the OI controls, activation in the right frontal lobe was associated with recognition of items in WM, while white matter integrity in the contralateral lobe was associated with better ability to reject negative, or false, probes. However, neither of these patterns were not observed in the TBI subjects, who instead underactivated in the frontal lobe and showed a relation between activation and white matter integrity in the frontal lobe for the easiest load only. In addition, their WM performance was associated with the cingulum bundle. Findings suggest minimized structural integrity that corresponds with minimized reliance in frontal structures during WM.

4.6 Limitations and Future Directions

Our study represents the first to specifically examine changes in WM in children with TBI using multi-modal imaging methods. Strengths of the study include its prospective design with imaging performed at a generally uniform post-injury interval, the relatively large size for Cohort 1, and the use of a comparison group of children with OI.

Limitations include the small sample size of Cohort 2, heterogeneity in the nature, degree, location, and severity of focal TBI-related injury, a relatively wide age-range where dynamic developmental changes are likely occurring and may impact white matter and gray matter differently, the visual nature of the SIRT fMRI paradigm used (as opposed to an auditory task which may activate additional temporal regions), inability to measure *exactly* the same regions across modalities, and the cross-sectional design. Although co-registered and normalized fMRI data were checked against the individuals' high resolution anatomical images and the MNI template, respectively, in several locations for each dataset, using an adult template with young adolescent subjects may have introduced error.

Future directions may include exploration of the relation of other advanced forms of imaging with WM, including arterial spin-tag labeling and magnetic source imaging as well as additional forms of analysis of DTI data from a larger sample. Longer-term changes in the brain that may be influenced by injury and developmental factors will be also explored in future longitudinal studies.

¹Two of the regions, left cingulate and left parietal lobe, showed nonsignificant trends of being reduced, but the fact that other regions that also tended to be reduced were not related to reaction time, along with the nonsignificance of the trends, suggests information about trends may be dismissed from consideration.

5 Conclusion

In conclusion, this investigation demonstrates how a multi-modality approach to image analysis aids in determining critical structure/function relationships related to WM. Had only one of the imaging analysis methods employed in this investigation been used, a very incomplete picture of neural correlates of WM would have emerged. The current findings support the hypothesis that WM deficits in TBI are more a consequence of damaged white matter connections than cortical atrophy.

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Abbreviations

WM	working memory
SIRT	Sternberg Item Recognition Task
TBI	traumatic brain injury
OI	orthopedic injury
MRI	magnetic resonance imaging
fMRI	functional magnetic resonance imaging
DTI	diffusion tensor imaging
RT	reaction time
MFG	middle frontal gyrus
GCS	Glasgow Coma Scale
CT	computed tomography
AIS	abbreviated injury scale
SCI	Socioeconomic Composite Index
ACR	American College of Radiology
TR	repetition time
TE	echo time
SENSE	sensitivity encoding
FOV	field of view
EPI	echo planar imaging
BOLD	blood oxygen level dependent
FDR	false discovery rate
SD	standard deviation
ACC	anterior cingulate cortex
TICV	total intracranial volume
FWHM	full width-half maximum
FA	fractional anisotropy

ADC	apparent diffusion coefficient
IFOF	inferior longitudinal fasciculus
ILF	inferior longitudinal fasciculus
UF	uncinate fasciculus
AIC	anterior limb of the internal capsule
PIC	posterior limb of the internal capsule
CB	cingulum bundle
ROI	region of interest
GLM	general linear model
BA	Brodmann's area
TAI	traumatic axonal injury
PFC	prefrontal cortex
PASAT	Paced Auditory Serial Addition Task

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Figure 1. Freesurfer cortical parcellation depicting regions of interest in the study: frontal lobes (yellow), parietal lobes (red), middle frontal gyrus (green), and cingulate gyrus (blue).

Figure 2.

Composite of white matter fiber tracts and regions utilized for analyses of fractional anisotropy (FA) and apparent diffusion coefficient (ADC) for diffusion tensor imaging (DTI), including the frontal lobes, the cingulum bundle, the inferior frontal occipital fasciculus and the inferior longitudinal fasciculus. Note the connectivity of these regions between frontal, temporal and parietal regions. Consistent with convention, green color indicates fibers coursing in an anterior to posterior direction, blue color in a superior to inferior direction, and red color in a right to left direction.

Figure 3.
Schematic of Sternberg Item Recognition Task paradigm.

Figure 4.

Group differences on cortical thickness measures. Areas of greater cortical thinning in TBI patients relative to OI control subjects are rendered upon the lateral and medial brain surfaces in warm colors (e.g., red, orange, yellow), primarily in the frontal and temporal lobes. Areas of increased cortical thickness in the TBI relative to the OI subjects are indicated in blue.

Figure 5. Relation of reaction time to cortical thickness in both groups. Longer reaction time in OI subjects is associated with greater cortical thickness in several regions, including the right precuneus and paracentral lobule, and in the left superior frontal gyrus. Less correlation is seen for the subjects with TBI.

Figure 6.

Figure 6a. OI subjects showed greater activation in frontal areas than did TBI subjects during the Load 4 Retrieval condition of a Sternberg Item Recognition Task. Figure 6b. TBI subjects showed greater activation in posterior areas than did OI subjects during the Load 4 Retrieval condition of a Sternberg Item Recognition Task.

Table 1

Demographic and Injury Variables of Cohort 1

Variable	OI (n=41)	TBI (n=40)	Statistical Comparison
Age-at-Test (years), mean (<i>SD</i>)	13.5 (2.5)	12.1 (2.4)	$t(79) = -2.52, p = 0.014$
Gender (female: male)	13: 28	14: 26	$\chi^2(2) = 0.10, p = 0.753$
SCI, mean (<i>SD</i>)	0.0 (0.8)	0 (0.9)	$t(79) = -0.01, p = 0.994$
Race/Ethnicity, <i>n</i> (%)			
<i>African American</i>	15 (36.6)	5 (12.5)	$\chi^2(2) = 7.15, p = 0.030$
<i>European American/Asian</i>	15 (36.6)	16 (40.0)	
<i>Hispanic</i>	11 (26.8)	19 (47.5)	
Handedness, (right: left)	36: 5	39: 1	$p = 0.201^*$
Time Postinjury (days), mean (<i>SD</i>)	4.0 (0.9)	4.0 (0.9)	$t(79) = -0.12, p = 0.900$
GCS (lowest in 1 st 24 hours) mean (<i>SD</i>)	15.0 (0)	7.7 (4.2)	N/A
ISS score mean (<i>SD</i>)	6.8 (3.9)	21.2 (10.8)	$F(1,39) = 7.8, p < 0.0001$
Mechanism of Injury, <i>n</i> (%)			
<i>MVA</i>	1 (2.4)	13 (32.5)	$p < 0.0001^*$
<i>MCA/Scooter/Moped</i>	4 (9.8)	4 (10.0)	
<i>RV</i>	1 (2.4)	3 (7.5)	
<i>Bicycle</i>	4 (9.8)	3 (7.5)	
<i>Fall</i>	5 (12.2)	8 (20.0)	
<i>Hit by falling object</i>	1 (2.4)	0 (0)	
<i>Sports/Play</i>	20 (48.8)	2 (5.0)	
<i>Hit by motor vehicle</i>	2 (4.9)	6 (15.0)	
<i>Other</i>	3 (7.3)	1 (2.5)	

* Fisher's exact test

SCI = Socioeconomic Composite Index

GCS = Glasgow Coma Scale score

ISS = Injury Severity Score

MVA = motor vehicle accident

MCA = motorcycle accident

RV = recreational or other off-road vehicle

Table 2

Region of Interest Volumes in Cubic Millimeters (gray and white matter combined) for TBI and OI groups

ROI	TBI LSM (SE)	OI LSM (SE)	F	p	Effect size f
Right Cingulate	10117.68 (322.62)	10238.71 (318.56)	1.48	0.227	0.14
Left Cingulate	10216.05 (382.92)	10658.22 (378.10)	5.08	0.027	0.26
Right Frontal	176636.23 (2517.35)	189862.80 (2485.65)	13.62	0.001*	0.42
Left Frontal	176211.26 (2462.38)	187601.04 (2431.38)	10.56	0.002*	0.37
Right MFG	45025.79 (1050.93)	49666.05 (1037.70)	9.62	0.003*	0.35
Left MFG	44902.13 (939.09)	48036.90 (927.26)	4.47	0.038	0.27
Right Parietal	77157.44 (1286.15)	80899.99 (1269.96)	4.18	0.044	0.23
Left Parietal	74738.73 (1218.35)	78383.61 (1203.01)	4.42	0.039	0.24

Note:

* denotes significant group difference after Bonferroni correction ($p < .006$). ROI = region of interest. TBI = traumatic brain injury. OI = orthopedic injury. LSM = least squares mean. SE = standard error. MFG = middle frontal gyrus. For Cohen's f , 0.1 = small, 0.25 = moderate and 0.40 = large effect size.