2012-02-25

Imaging and Behavioral Correlates of the Anterior Cingulate in Pediatric Traumatic Brain Injury

Tricia L. Merkley
Brigham Young University - Provo

Imaging and Behavioral Correlates of the Anterior Cingulate in Pediatric Traumatic Brain Injury

Tricia L. Merkley

A dissertation submitted to the faculty of
Brigham Young University
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Erin D. Bigler, PhD, Chair
Elisabeth A. Wilde, PhD
Dawson W. Hedges, MD
Mark D. Allen, PhD
E. Shannon Neeley, PhD

Department of Psychology

Brigham Young University

August 2012

ABSTRACT

Imaging and Behavioral Correlates of the Anterior Cingulate in
Pediatric Traumatic Brain Injury

Tricia L. Merkley
Department of Psychology, BYU
Doctor of Philosophy

The anterior cingulate has been implicated in a number of cognitive processes that are at risk following traumatic brain injury (TBI), such as executive function and emotional processing. While the cingulate is believed to play a role in the above-mentioned cognitive processes, the relative roles of gray and white matter in functional outcomes post-TBI are not fully understood. The current study investigated various quantifiable brain properties (e.g., cortical thickness and volume, volume of underlying white matter, and white matter integrity) of the caudal anterior cingulate (CAC) gyrus and their relationships with behavioral measures of cognitive control following pediatric TBI. Parent ratings at three months post-injury indicated that TBI children demonstrated greater difficulty inhibiting inappropriate behavior and effectively transitioning between tasks. Reductions of CAC white matter integrity were observed in TBI participants, in the absence of significant morphometric group differences in this region. Neither CAC morphometrics nor fractional anisotropy (FA) were associated with experimental measures of cognitive control. The current findings indicate that DTI metrics may be more sensitive to brain changes in the region of the CAC following TBI. While strong relationships were not observed between CAC properties and measures of cognitive control, it is possible that study limitations may have obscured potential findings.

Keywords: anterior cingulate, pediatric traumatic brain injury, MRI, DTI, cognitive control

ACKNOWLEDGMENTS

I would like to express my sincere appreciation to each member of my dissertation committee for their unique perspectives and the guidance they provided throughout the process of the dissertation project. Specifically, I would like to thank Dr. Shannon Neeley and Xiaoqi Li for their expertise and much appreciated assistance in statistical analysis, Dr. Dawson Hedges for his insights regarding demographic variables of the research participants, and Dr. Mark Allen for his background knowledge of related fMRI studies and their implications for the current project. Also, I will be forever indebted to my wonderful mentors, Dr. Erin Bigler and Dr. Lisa Wilde, who have created so many incredible learning opportunities for me. I am truly grateful for all they have taught me (both formally, and by example) during my years of graduate study. Their unfailing support and unquenchable optimism always give me the motivation to continue when things do not turn out as anticipated. Finally, I want to express my deep gratitude to my dear parents for their continued love and support throughout the years.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Imaging and Behavioral Correlates of the Anterior Cingulate in Pediatric Traumatic Brain Injury

Introduction

Traumatic brain injury (TBI) is recognized as an important public health problem in the United States (Langlois, Rutland-Brown, & Thomas, 2006), both in terms of high incidence rates and also severity of functional outcomes for TBI victims. Data from the year 2003 indicates that each year in the United States at least 1.4 million people sustain a TBI. Approximately 50,000 of these injuries result in death, 235,000 TBI victims are hospitalized, and 1.1 million are treated and released from the emergency department. It is likely that a significant number of other individuals with TBI receive only minimal or no medical care. Children represent a large proportion of TBI victims. Indeed, young children (ages 0-4), older adolescents (ages 15-19), and adults ages 75 years and older are the age groups most likely to sustain a TBI. Approximately 475,000 traumatic brain injuries (TBIs) occur annually in the United States among children 0-14 years of age, 90% of which result in a visit to the emergency department. It is estimated that 129,000 TBIs occur among adolescents 15-19 years of age (Langlois, et al., 2006). In addition to age, other common risk factors include gender (males have a higher TBI rate in almost every age group) and premorbid diagnosis of attention-deficit hyperactive disorder (possibly related to the fact that behavioral inattentiveness and impulsivity contribute to risky behavior) (Gerring et al., 1998). Unfortunately, many individuals with TBI may not receive adequate information about the nature of their injury, and thus may be unprepared to deal with the long-term consequences.

Traumatic brain injury is cited as a common cause of death and disability among children, and is a serious concern in view of the fact that survivors of childhood TBI may face relatively more years of reduced quality of productive life, as compared to older TBI survivors (Meyer, 1998). A number of studies indicate that the majority of post-injury onset behavior disorders appear soon after the injury, and they generally persist long-term (Schwartz et al., 2003). However, TBI has been referred to as the "silent epidemic", because the problems that result from the injury are not always physical in nature but include neurobehavioral changes, and thus the morbidity may not be immediately apparent (Rutland-Brown, Langlois, Thomas, & Xi, 2006). Unfortunately, the general public is largely unaware of the implications of TBI-related morbidity. The observed neurobehavioral sequelae may differ based on length of time post-injury, with certain symptoms improving with time, and other symptoms emerging in the chronic phase.

There is marked heterogeneity in the type and severity of traumatic brain injuries that are experienced by children and older individuals, and the degree of the injury generally corresponds with the severity of functional impairments that the individual will suffer. The severity of TBI is generally evaluated by means of the Glasgow Coma Scale, which rates the individual on depth and duration of impaired consciousness and coma following the injury (Teasdale & Jennett, 1974). The scale ranges from 3 to 15, with a score of 3 corresponding to deep coma and 15 representing full consciousness. In general, TBI severity is classified as 3-8 signifying severe injury, 9-12 representing moderate injury, and 13-15 corresponding to mild injury. Other factors such as loss of consciousness and post-traumatic amnesia are also considered when assessing injury severity.

TBI victims have great heterogeneity in the type and severity of neurocognitive and behavioral symptoms, however, common neurobehavioral sequelae involve impairments of attention, memory, processing speed, and executive functions (Gioia & Isquith, 2004). Executive functions that are commonly affected by TBI include the cognitive domains of working memory, inhibition, set shifting, planning, behavior monitoring, decision making, language processing, social cognition, and behavioral self-regulation (Levin & Hanten, 2005). Emotion regulation difficulties are also common following TBI. Case studies of individuals who have sustained traumatic brain injuries suggest common features including irritability, impatience, shallow emotions, and emotional lability (Eslinger, Flaherty-Craig, & Benton, 2004). It is thought that the symptoms of executive function deficits and emotional dysregulation may be due to disrupted development of distributed frontal white matter networks (Levin & Hanten, 2005). In daily life, these impairments have a significant impact on psychosocial functioning, communication skills, adaptive functioning, and overall health-related quality of life (H. G. Taylor et al., 2002). In addition, pediatric TBI affects not only the child, but also the child's family members as they often experience a significant increase in caregiver burden following the injury (Aitken et al., 2009). Unfortunately, adverse family reactions to a child's traumatic brain injury may in turn exacerbate the child's problematic behavior (Schwartz, et al., 2003).

Not only does TBI affect the level of previously achieved functioning, but it can also impact the course and rate of future behavioral development. Initially, it was thought that younger age at injury was a protective factor, due to the enhanced plasticity of the developing brain early in life (known as the "Kennard effect") (Kennard, 1940). However, more recent research indicates generally poorer functional outcomes of injuries acquired earlier in life, including poorer cognitive abilities, neuropsychological functioning (e.g. memory, attention,

executive functioning) and academic performance (Gil, 2003). It is hypothesized that this pattern of poor outcomes is associated with earlier injury due to increased vulnerability of skills in process of development at the time of injury, and additionally the injury may also impede the acquisition of new skills.

Global Brain Changes Following TBI

Despite the heterogeneity of injury severity and location of impact, common areas of residual injury have been observed across individual patients (Gale, Baxter, Roundy, & Johnson, 2005). An understanding of the functional role of TBI-vulnerable brain regions gives a measure of insight into the common functional impairments that are observed subsequent to TBI. Previous neuroimaging studies have shown that the frontal and temporal lobes appear to be especially susceptible to diffuse brain injury and focal brain lesions as a result of moderate to severe traumatic brain injury (Wilde et al., 2005). This is due to the concavities of the skull structure which create surface areas of contact between dura, brain and skull, particularly in the frontal and temporal lobes (Bigler, 2007). In addition, while the dura mater of the falx cerebri tethers and suspends the brain at the midline under normal conditions, it mediates strain fields in the brain under head impact conditions (Sabet, Christoforou, Zatlin, Genin, & Bayly, 2008), and the resulting mechanical deformations frequently damage the brain.

From a developmental perspective, the cerebral regions that are most vulnerable to primary damage are also those which are developing throughout childhood (Anderson & Pentland, 1998), which has implications for more severe adverse functional outcomes of pediatric TBI as compared to adult TBI. It has been proposed that children may also be more vulnerable to TBI from a physiological standpoint, due to their larger ratio of head to body size, with thinner cranial bones which provide less protection of the brain, less-developed myelination

which leads to more susceptibility to axonal damage, and a greater likelihood of sustaining diffuse injury and cerebral edema as compared to adults (Sookplung & Vavilala, 2009).

There is evidence that white matter structures may be more likely to be affected than are gray matter structures following TBI (Gale, Johnson, Bigler, & Blatter, 1995a, 1995b). However, diffuse cerebral atrophy in the post-acute phase is common, therefore gray and white matter changes are likely not mutually exclusive (Bigler, 2001; Blatter et al., 1997; Gale, et al., 1995a). Indeed, Merkley, et al. observed global cortical thinning in moderate-to-severe pediatric TBI patients compared to controls (2008). Histological findings have recently corroborated MRI indications of global cortical thinning after TBI (Maxwell, MacKinnon, Stewart, & Graham, 2010). These global changes in both gray and white matter are likely due to various underlying etiologies, including the focal injury associated with impact (coup and contra coup injuries) as well as processes secondary to diffuse axonal injury (DAI) and Wallerian degeneration (Bigler, 2007). DAI results in widespread microstructural damage, and is the result of the shearing and stretching caused by the abrupt rotational acceleration and deceleration forces which are often powerful enough to separate axons from cell bodies (Gaetz, 2004; Smith, Meaney, & Shull, 2003). Thus, DAI may lead to disrupted communication between cerebral structures which may be observed as behavioral manifestations. It is important to note that the mechanisms of DAI may develop over the course of hours to days after injury, which may explain the often long course of behavioral changes following TBI (Pierce, Smith, Trojanowski, & McIntosh, 1998). Diffuse injury and secondary brain insult are also mediated by processes such as excitotoxicity, inflammation, and apoptosis, all of which further negatively impact brain development of children after TBI (Levin & Hanten, 2005).

Anterior Cingulate Cortex in TBI

In addition to the general frontal and temporal regions cited previously, atrophy as a result of TBI has been observed specifically in the region of the cingulate gyrus, which correlates with poorer attention performance (Gale, et al., 2005).

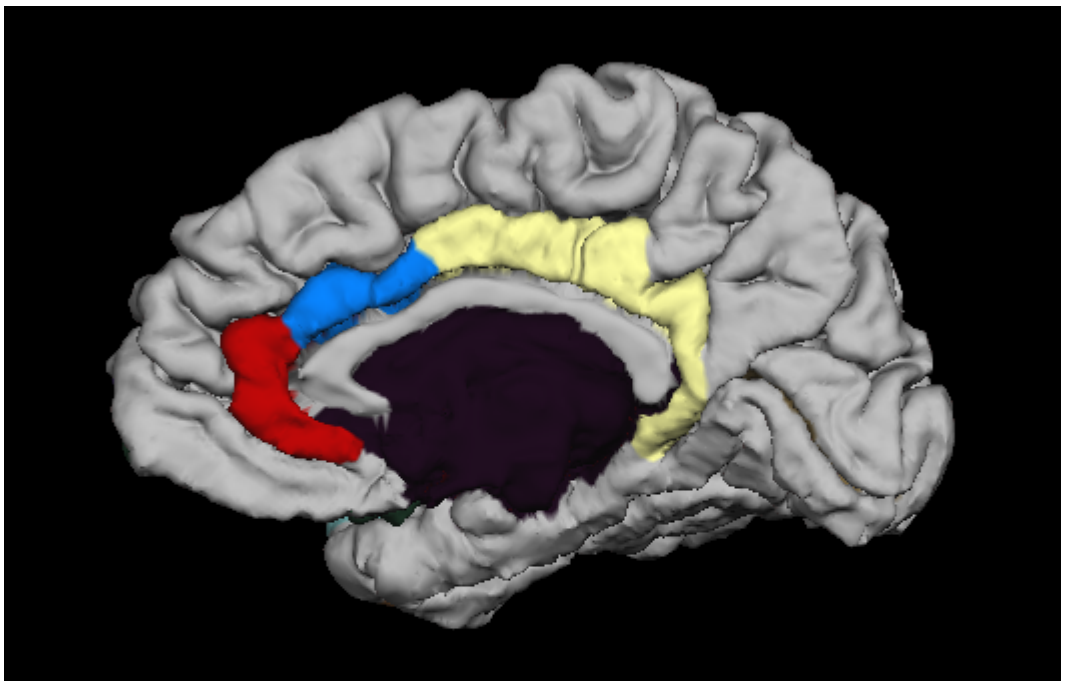

Figure 1. Cingulate gyrus, with rostral anterior cingulate gyrus marked in red, caudal anterior cingulate in blue and the posterior cingulate marked in yellow.

The cingulate cortex is a limbic structure situated along the medial aspect of the brain, surrounding the dorsal, rostral, and caudal regions of the corpus callosum. Given its location deep in the cerebrum and the nature of support it receives from the falx cerebri during lateral movement, it may initially be assumed that the anterior cingulate would be relatively protected from damage due to TBI (Yount et al., 2002). However, this is misleading since the cingulate gyrus is actually susceptible to shearing action in cases of midline shift, if the rough surface of the falx cerebri strikes it (Gean, 1994). Even in cases where the cingulate is spared from focal

cortical damage, it may still be vulnerable to secondary damage by means of diffuse axonal injury and Wallerian degeneration (Bigler, 2007).

The anterior and posterior segments of the cingulate cortex can be differentiated based on their distinct cytoarchitecture, projections to other brain regions, and functional roles (Bush, Luu, & Posner, 2000). The anterior region is often referred to as being "executive" in function, whereas the posterior cingulate is characterized as being "evaluative" in nature. Due to its anatomical location, the anterior cingulate is more likely to suffer damage due to TBI, and thus only the structure and function of the anterior cingulate will be considered in the current study. The anterior cingulate is thought to be part of a brain circuit involved in a form of attention that regulates both cognitive and emotional processing (Bush, et al., 2000). This midline cortical region plays a key role in executive functions, particularly initiation, motivation, and goal-directed behaviors (Devinsky, Morrell, & Vogt, 1995). In terms of regional organization, emotional control functions appear to be subserved by the rostral anterior cingulate, whereas cognitive control and nociceptive functions appear to be mediated by the caudal anterior cingulate. However, it is possible that the functional separation between the rostral and caudal anterior cingulate may not be as clearly defined as previously thought because there is some evidence that the "affective" rostral anterior cingulate may in fact play a role in the ongoing adjustment of cognitive control (di Pellegrino, Ciaramelli, & Ladavas, 2007). Given its roles in emotion processing and motor initiation, it is not surprising that the rostral anterior cingulate gyrus has extensive connections with the amygdala, periaqueductal gray, nucleus accumbens, and orbitofrontal cortex, while the caudal anterior cingulate projects to premotor and supplementary motor regions including the striatum and spinal cord (Devinsky, et al., 1995).

Yount, et al., observed that cingulate atrophy was associated with severity of TBI (as assessed by GCS) though it was not related to neuropsychological outcome in measures of memory, processing speed, and mood symptoms (2002). Other studies have reported incidents of anterior cingulate damage with corresponding functional deficits. For example, lesions of the anterior cingulate cortex have been associated with symptoms of apathy, inattention, reduction of inhibition and excessive self-concern, alterations of intention and self-initiated action, executive control, and emotional instability (Cohen et al., 1999; Kennard, 1955; Tow & Whitty, 1953). Area measurements of the right anterior cingulate were observed to be associated with children's performance on a go-no-go task, which requires the participant to inhibit pre-potent responses (Bush, et al., 2000). This suggests that volumetric measures of the anterior cingulate may be useful tools for investigating brain-behavior relationships after TBI.

Neuropsychological Assessment

Behavior Rating Inventory of Executive Function (BRIEF). The previously cited TBI-related deficits in executive function can be evaluated by means of traditional neuropsychological measures. However, it has been argued that traditional assessment methods may not adequately characterize the full impact of neuropsychological impairments in daily life, due to the fact that real-world demands require the coordination of a variety of cognitive and behavioral resources (Gioia & Isquith, 2004). In order to address this concern, assessment measures have recently been developed which are specifically designed to be ecologically valid. One such measure with claims of good ecological validity is the Behavior Rating Inventory of Executive Function (BRIEF) (Gioia, Isquith, Guy, & Kenworthy, 2000). The BRIEF provides separate parent and teacher rating forms in order to identify behavioral presentations in both the home and school. The BRIEF is comprised of eight clinical scales of executive function:

Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor. The clinical scales are grouped into the two broad indexes of Behavioral Regulation and Metacognition, as well as an overall score, the Global Executive Composite. It has been proposed that the BRIEF may be a valuable assessment tool for pediatric TBI, which could play a critical role in planning appropriate interventions (Gioia & Isquith, 2004). Indeed, progressive worsening of parent BRIEF ratings at 3-month and 1-year post-injury were observed for childhood victims of TBI as compared to orthopedically injured children (Sesma, Slomine, Ding, McCarthy, & Group, 2008). Specifically, pediatric TBI patients displayed more dysfunction on the Global Executive Composite score at 3-months post-injury, whereas at one year post-injury they differed from orthopedically injured children on the Behavioral Regulation Index, Metacognition Index, and the Global Executive Composite. The BRIEF Working Memory clinical scale was observed to be highly correlated with cortical thickness globally in a TBI sample (Merkley, et al., 2008); however, no studies were found which examined the relationship between BRIEF ratings and properties of the CAC specifically.

Flanker task. While rating scales may be helpful in the assessment of neurobehavioral sequelae following TBI, it is also desirable to directly assess the child's ability using experimental measures. As indicated above, the caudal anterior cingulate has been implicated in tasks of conflict processing and cognitive control. Therefore, the Flanker task was used in the current study as a measure of behavioral outcomes related to anterior cingulate integrity.

Role of Neuroimaging in Assessment and Prognosis of TBI

The various neuroimaging modalities provide unique information about the structural integrity and function of the brain. Therefore, by utilizing multiple types of imaging techniques (e.g., structural magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI)), it may

be possible to better conceptualize the types of brain changes that predict functional outcomes post-TBI. Morphometric brain changes due to TBI are important in light of a recent study which indicates that measures of cerebral integrity (including cortical thickness and fractional anisotropy (FA)) are related to measures of executive function (Kochunov et al., 2009), though it should be noted that the predictive power of brain-based measures was greater in a senescing group as compared to a maturing group of individuals. However, it is possible that the decrease in cerebral integrity following TBI may result in an increase of predictive power of brain-based measures in the pediatric population as well.

Structural imaging. Neuroimaging has traditionally been used clinically to assess for abnormalities such as cerebral contusions and intracerebral hemorrhaging in the acute phase of TBI; however, quantitative research methods may also be used to evaluate the effect of TBI on brain structure and function in the acute and chronic phases. Brain regions are susceptible to atrophy after TBI, and the degree of atrophy is related to the severity of the injury (Bigler, 2001). While CT and MRI scanning are routinely performed after admittance to the hospital to investigate the extent of damage due to TBI, traditional clinical imaging techniques are often insensitive to the extensive range of effects of TBI. In particular, traditional imaging does not detect the full effects of diffuse axonal injury, and therefore the significance of this type of injury is often not fully recognized (Smith, et al., 2003).

Historically, regional atrophic effects of TBI have been identified by manually tracing regions of interest. However, contemporary neuroimaging methods allow for an automated estimation of regional cortical thickness and subcortical volumetric measurements using magnetic resonance imaging data. This procedure has been used for a variety of normal and pathogenic populations, including pediatric traumatic brain injury (Merkley, et al., 2008). Based

on the previous observations of global cortical thinning in pediatric TBI, it is reasonable to assume that the anterior cingulate cortex will show significant cortical thinning after TBI. Automated neuroimage labeling is able to identify the caudal anterior cingulate, which corresponds with the regions subserving the cognitive control functions of the anterior cingulate, as discussed previously. The present study was restricted to the caudal anterior cingulate and the cognitive control functions that it is purported to mediate.

As discussed above, it was previously thought that white matter structures may be relatively more susceptible to atrophic changes following TBI compared to gray matter structures (including the cerebral cortex) (Gale, et al., 1995a, 1995b). Indeed, white matter volume loss is commonly observed following TBI (Bendlin et al., 2008; Ding et al., 2008; Sidaros, Skimminge, et al., 2009), and specifically has been reported in the cingulum (Bendlin, et al., 2008). Automated neuroimage analysis techniques now allow for the quantification of the white matter volume of the caudal anterior cingulum region, which corresponds to the regions underlying the caudal anterior cingulate cortex.

Diffusion tensor imaging. The superiority and utility of diffusion tensor imaging (DTI) over conventional magnetic resonance imaging has been demonstrated by its sensitivity and specificity to both focal and diffuse microscopic cerebral changes. Indeed, DTI is shown to identify abnormalities that go undetected on conventional neuroimaging (Benson et al., 2007). DTI provides an index of the directionality of water molecules and their relative ability to diffuse across axonal membranes, thus giving an indirect measure of white matter integrity. Greater diffusion of water (as represented by lower fractional anisotropy (FA) values suggests a breakdown of the microstructure of white matter (Kochunov, et al., 2009), since the diffusion of water molecules in a healthy brain are constrained to flow parallel to the major axis of the fiber

tracts by the intact myelin sheaths and the integrity of axonal and intracellular structures (Arfanakis et al., 2002; Assaf & Pasternak, 2008; Harsan et al., 2006). FA values range from 0 to 1, with 0 representing isotropic diffusion (where water molecules are able to freely diffuse in all directions) and 1 representing infinite anisotropy (where there is no diffusion in directions perpendicular to the main axis) (Le Bihan et al., 2001). Regional white matter integrity of the caudal anterior cingulum (as indicated by FA values of this region) is predicted to correspond with outcomes of cognitive control.

Hypotheses

The study was designed to address the following hypotheses.

Hypothesis #1. Children in the TBI group will have reduced cortical thickness and cortical volume in regions including the CAC. White matter volume is also likely to be reduced in the caudal anterior cingulum in the TBI group.

Hypothesis #2. Children in the TBI group will have decreased FA in the caudal anterior cingulum, reflecting a decrease in white matter integrity in this region.

Hypothesis #3. If white matter integrity of the tracts underlying the anterior cingulate is a better predictor of behavioral measures of cognitive control (as compared to cortical thickness, cortical volume, and white matter volume of this region), then FA will be more highly correlated with functional outcome measures of cognitive impairment.

Methods

The data used in the present study are part of an ongoing research program on pediatric traumatic brain injury that is being conducted at Baylor College of Medicine. While the raw magnetic resonance imaging data and neuropsychological test data are archival data, the cortical

reconstruction, diffusion tensor imaging processing, and statistical analysis were performed at the BYU Brain Imaging and Behavior Lab. Computing resources of the Fulton Supercomputing Lab were used to speed up processing.

Participants

Participants were recruited prospectively from level-1 trauma centers in Houston, Dallas, and Miami for a longitudinal study of cognitive and behavioral outcome following traumatic brain injury. The informed consent form was approved by the Institutional Review Boards of Baylor College of Medicine, the University of Texas at Dallas, the University of Texas Southwestern Medical Center, and the University of Miami School of Medicine. Parents or guardians of the participants provided informed consent, and child assent was also obtained.

A total of 147 children were recruited for the study. The participants were fluent in English, full-term births (> 37 weeks of gestation and > 2500 g), had no preexisting major neuropsychiatric disorder (e.g., schizophrenia, bipolar disorder), and had not previously been hospitalized for brain injury. Age at injury was 7 to 17 years. Of the recruited participants, 120 underwent MRI scanning and received neuropsychological testing at 3 months post-injury, 65 of which sustained traumatic brain injury (as the result of motor vehicle, pedestrian vs. vehicle, or bicycle accidents), and 55 of which sustained orthopedic injuries (OI) that did not involve the head but which did require emergency room treatment. Children with OI were specifically recruited for this study in an effort to control for risk factors predisposing children to traumatic injury and also to control for general factors associated with trauma and hospitalization post-injury.

The structural MRI and DTI data for each subject were carefully reviewed for artifacts, other acquisition problems, or uncorrectable image processing errors that necessitated the exclusion of subjects. Unfortunately, virtually all of the DTI data had susceptibility artifacts, resulting in a non-linear frontal "warp" which was most prominent near the anterior corpus callosum. Due to the prevalence of this imaging artifact, the data were retained if this was the only artifact present. Of the 120 recruited participants who received both neuropsychological testing and underwent MRI scanning, several were excluded due to a variety of factors, including incomplete scanning (either MRI or DTI sequence was missing), poor scan quality of either MRI and/or DTI (including imaging artifacts), structural abnormalities of the CAC (including one subject whose CAC appeared to "float" largely unattached from the brain and one subject with a bifurcated CAC, which structural abnormality rendered it much larger in volume than other subjects), poor registration between DTI and MRI that was not sufficiently improved by manual intervention, and abnormally long interval between injury and test date (imaging and/or neuropsychological assessment was performed more than 1 year post-injury). The types of problems encountered and the number of subjects excluded from the sample due to the presence of each type of problem are presented in Table 1.

The final sample consisted of 78 children and adolescents evaluated at 3 months post-injury. Demographic details are provided in Table 2. The TBI group was comprised of 36 individuals (25 males, 11 females) who sustained traumatic brain injury as the result of motor vehicle, pedestrian vs. vehicle, or bicycle accidents. TBI severity was defined as the lowest Glasgow Coma Scale (GCS) Score (Teasdale & Jennett, 1974) in the 24 hours following the injury. GCS for the TBI participants ranged from 3-15 (mean=7.27 ± 4.27). GCS scores for 3 participants were not available.

Table 1

Subject exclusion criteria and number of subjects excluded by category

Exclusion criteria	**Examples**	**# of subjects**
Poor DTI scan quality	Change in acquisition protocol, artifacts (motion, dental, susceptibility artifacts, eddy currents)	22
DTI not available	Image not acquired	6
MRI not available	Image not acquired	4
MRI artifacts/ image processing error	Artifacts (metal, motion, wrap-around)	6
Acquisition delay	>1 year neuroimaging acquisition	1
Structural abnormality	"Floating CAC"/bifurcated CAC	1/1
Extremely poor registration	Registration of DTI to anatomical image	1

The control group consisted of 42 individuals (30 males and 12 females) who had sustained orthopedic injuries (OI) which did not involve the head but which did require emergency room treatment. The OI participants had mild to moderate injuries according to the Abbreviated Injury Scale (Committee on Injury Scaling, 1990).

Magnetic Resonance Imaging (MRI)

All locations used scanners that have similar platforms to increase the compatibility of the data across sites.

Anatomical image acquisition. T1-weighted 3D sagittal acquisition series were performed on Philips Intera 1.5T whole body scanners (Philips, Cleveland, OH). Parameters

included 1.0-mm-thick slices, 0mm slice gaps, TE = 4.6ms/TR = 15ms, FOV = 256/RFOV = 100%, and a reconstructed voxel size M/P/S (mm) = 1.0/1.0/1.0.

Diffusion tensor image acquisition. Transverse multislice spin echo, single-shot, echo planar imaging sequences (10,150.5-milli-second repetition time, 90-millisecond echo time, 2.7 mm slices with 0 mm gap) were applied. A 256 mm FOV (RFOV = 100%) was used with a measured voxel size of 2.69 × 2.69 × 2.7 mm. Diffusivities were evaluated along 15 directions (number of b-value = 2, low b-value = 0, and high-b value = 860 s/mm2). Two acquisitions of high-b images were obtained and averaged to ensure better signal to noise ratio. A total number of 55 slices were acquired, and each acquisition took approximately 6 minutes.

MRI analysis. In order to obtain the brain morphometric variables of interest (e.g. cortical thickness, white matter volume, and FA of the anterior cingulate), cortical reconstruction and volumetric segmentation were performed with the Freesurfer image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures are described in prior publications (Dale, Fischl, & Sereno, 1999; Dale & Sereno, 1993; Fischl & Dale, 2000; Fischl, Liu, & Dale, 2001; Fischl, Salat, et al., 2004; Fischl, Sereno, & Dale, 1999; Fischl, Sereno, Tootell, & Dale, 1999; Fischl, van der Kouwe, et al., 2004; Han et al., 2006; Jovicich et al., 2006; Rosas et al., 2002; Segonne et al., 2004). The following description of neuroimaging processing is extracted from the description provided at the Freesurfer website, and is tailored to the specific needs of the current study. Briefly, this processing includes removal of non-brain tissue (Segonne, et al., 2004), automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures (Fischl, Salat, et al., 2004; Rosas, et al., 2002) intensity normalization (Sled, Zijdenbos, & Evans, 1998), tessellation of the gray matter/white matter boundary,

automated topology correction (Fischl, et al., 2001; Segonne, Pacheco, & Fischl, 2007), and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid boundaries (Dale, et al., 1999; Dale & Sereno, 1993; Fischl & Dale, 2000; Gale, et al., 1995a).

Once the cortical models were complete, a number of deformable procedures were performed for further data processing and analysis including registration to a spherical atlas which utilizes individual cortical folding patterns to match cortical geometry across subjects (Fischl, Sereno, Tootell, et al., 1999), and parcellation of the cerebral cortex into regions based on gyral and sulcal structure (Desikan et al., 2006; Fischl, van der Kouwe, et al., 2004). Figure 2 displays the results of the automated cortical parcellation.

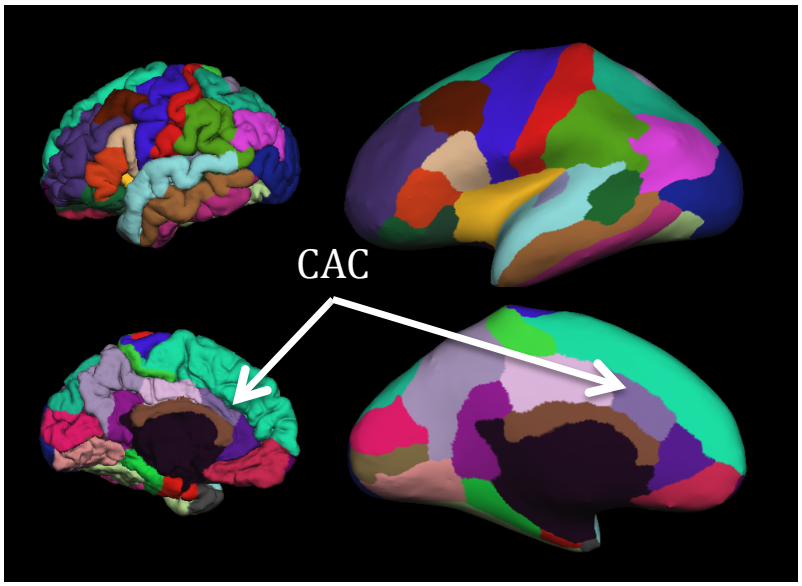

Figure 2. Freesurfer cortical (and inflated) parcellations. The CAC is labeled in purple.

This method uses both intensity and continuity information from the entire three dimensional MR volume to produce representations of cortical thickness, calculated as the

closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the reconstructed surface (Fischl & Dale, 2000). The brain maps are created using spatial intensity gradients across tissue classes and are therefore not simply reliant on absolute signal intensity. The cortical maps produced are not restricted to the voxel resolution of the original data and thus are capable of detecting submillimeter differences between groups. Procedures for the measurement of cortical thickness have been validated against histological analysis (Rosas, et al., 2002) and manual measurements (Kuperberg et al., 2003; Salat et al., 2004). Freesurfer morphometric procedures have been demonstrated to show good test-retest reliability across scanner manufacturers and across field strengths (Han, et al., 2006). Results for each subject were carefully reviewed in order to ensure accuracy of cortical surface reconstruction in the vicinity of the anterior cingulate. Manual editing was performed as needed in order to optimize accuracy of the cortical reconstruction.

Regional white matter volume of the caudal anterior cingulum was derived from the automatically generated cortical labels of the caudal anterior cingulate, in which a distance constraint is imposed that limits the measurement from extending into the centrum semiovale (Salat et al., 2009). Figure 3 displays the results of the white matter parcellation. Total intracranial volume was estimated using the automated atlas-based head size normalization approach (Buckner et al., 2004), which was employed by the Freesurfer workflow.

Freesurfer was also used for processing of native diffusion tensor imaging, with additional select tools provided by FSL (e.g. eddy_correct, flirt). The diffusion data of each subject underwent eddy current and motion correction. The diffusion data was registered to the anatomical image of the same subject. The registration was visually inspected to ensure accuracy, and the bbregister tool was used to automatically register the diffusion data to the

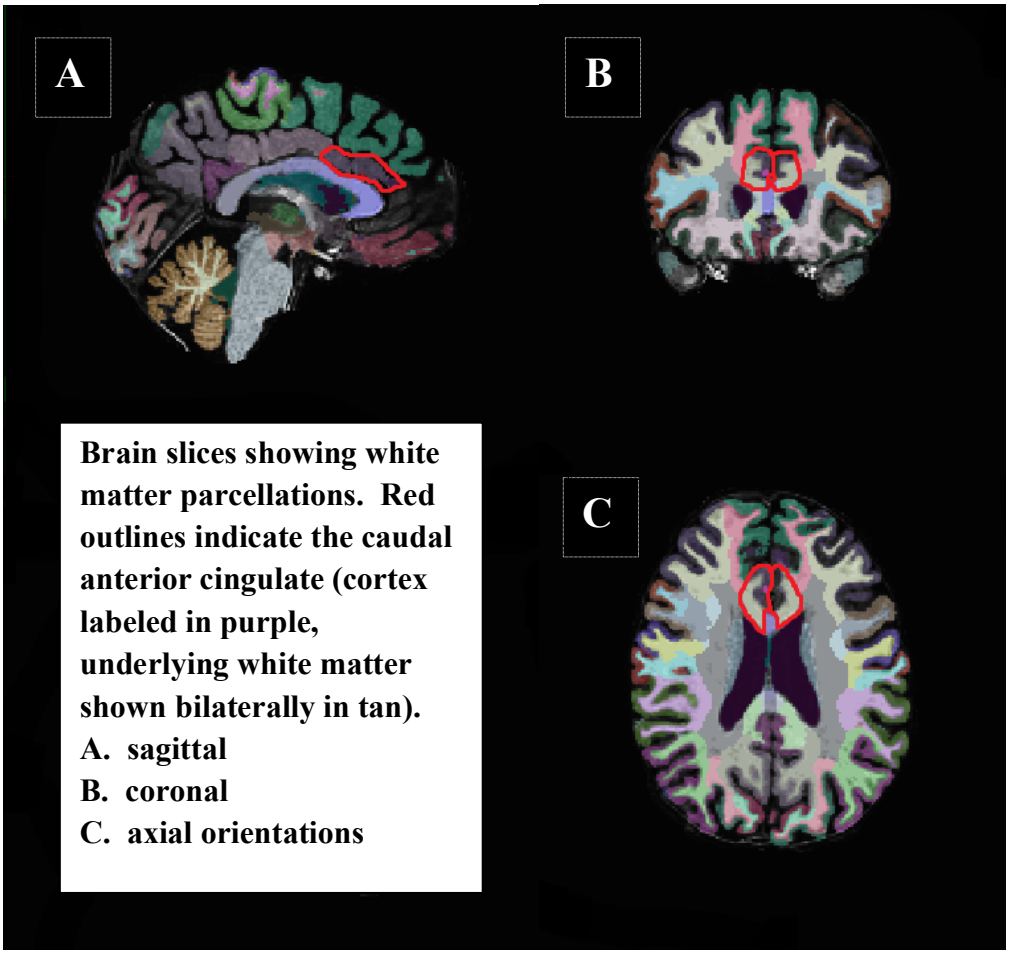

Figure 3. White matter parcellations, as defined by the cortical parcellation regions.

anatomical data as needed. A non-linear warp was observed for the DTI data in the frontal lobe, which was unable to be fully corrected and thus likely affected the registration between the MRI and DTI results. The FA was resampled into the same subject's anatomical space, using nearest neighbor interpolation in order to avoid averaging FA across voxels. The average FA for the left and right anterior cingula were derived from the regional white matter volume of the gyral white matter parcellation associated with the anterior cingulate, as described above.

Behavioral measures

The Behavioral Rating Inventory of Executive Function (BRIEF) (Gioia, et al., 2000) was administered to parents of the participants. The parent rating scale of the BRIEF is a questionnaire that contains 86 items related to executive functioning of children ages 5-18 over the past six months. The measure utilizes a three-point response scale (Never, Sometimes, Often) and takes approximately 10-15 minutes to complete. It was written at a fifth grade reading level to facilitate comprehension. Of the eight clinical scales of the BRIEF (Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor) the Shift and Inhibit clinical scales BRIEF were used as measures of neurobehavioral outcome following injury, since they are likely to be good indices of cognitive control as observed in everyday functioning. In addition, the Inhibit scale is described as likely to be one of the measures most sensitive to difficulties with executive function (personal communication with Peter Isquith). Reliability and validity of the BRIEF were determined to be satisfactory from the authors' technical documentation. Each clinical scale yields a standardized T-score and percentile score, based on the normative tables provided. T-scores greater than 65 are interpreted as representing clinically significant impairment. The T-scores of the Inhibit and Shift scales were used as measures of executive functioning in this sample of participants.

In addition to the rating scales of the BRIEF, the Flanker task was also administered to the participants. In this task, an arrow pointing to the left or right appeared on each trial, and the child was asked to press a button to indicate the direction the arrow was pointing (Levin et al., 2008). The three task conditions include baseline (the arrow is flanked by horizontal dashes), interference (flanker arrows point in the direction opposite to the central arrow), and no-go (the arrow was flanked by "X's", which signaled the child to refrain from responding to the central

arrow). Performance on the interference and no-go conditions were considered in this study, due to the assumed role of the CAC in these aspects of the task. Percent accuracy was the primary performance measure on the no-go condition of the Flanker task. Reaction time difference between the interference and baseline conditions was used as a measure of the child's ability to process conflicting information efficiently, with increased difference scores indicating poorer conflict processing ability. The expectation was that childhood TBI participants would perform more poorly on this task, especially on the interference and no-go conditions. Figure 4 is a diagram of the various task conditions.

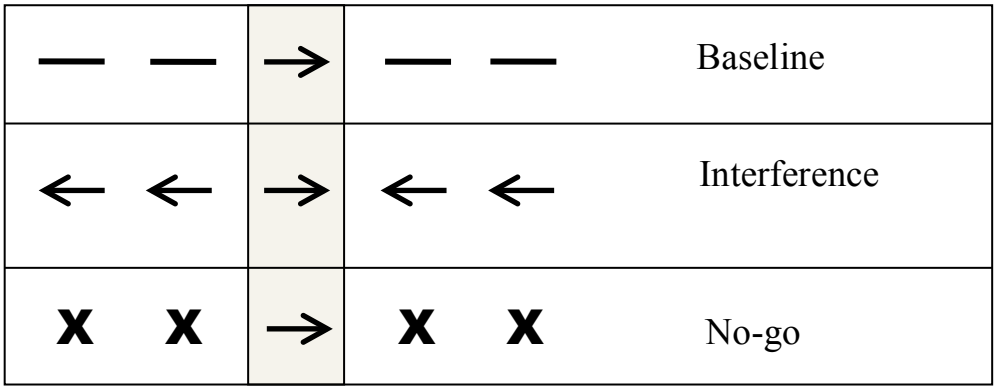

Figure 4. Display of the Flanker task conditions.

Adapted from Levin, H. S., Wilde, E. A., Chu, Z., Yallampalli, R., Hanten, G. R., Li, X., et al. (2008). Diffusion tensor imaging in relation to cognitive and functional outcome of traumatic brain injury in children. *J Head Trauma Rehabil, 23*(4), 197-208. Used with permission.

Statistical Analysis

Between-group differences on demographic characteristics were investigated by means of independent sample *t*-test for continuous variables and χ^2 for categorical variables. Age at injury, gender and Social Composite Index (SCIz) were used as covariates in the subsequent correlations with behavioral measures and between-group tests of CAC properties. Age at injury

was included as a covariate because the TBI participants were significantly older than the OI participants, and progressive cortical thinning is known to start at about the age of puberty (Gogtay et al., 2004). Gender and SCIz were included as covariates due to the likelihood that these factors contribute to brain development and achieved brain volume, in addition to the fact that they were significantly correlated with many of the morphometric properties and Flanker measures in the current sample. Intracranial volume (ICV) was used as a covariate for volume-based CAC measures (cortical volume and white matter volume) only, in order to correct for variability in head size.

Freesurfer's QDEC application was used to perform a general linear model analysis comparing the cortical thickness for the two groups, controlling for age. This procedure displays a statistical parametric map of group differences in cortical thickness globally, and was also used to investigate the relative group differences in cortical thickness of the anterior cingulate specifically. Cluster-wise correction for multiple comparisons (vertex-wise threshold of $p < 0.05$, 10,000 iterations) was performed using a Monte Carlo simulation (Hagler, Saygin, & Sereno, 2006). Cluster-wise probabilities represent the likelihood of finding a maximum cluster that size or larger during simulation. Previous studies indicated that global cortical thinning in the TBI group would likely be present (Merkley, et al., 2008), and the statistical mapping would make it possible to evaluate the relative impact on the CAC in addition to the rest of the brain.

It was expected that children in the TBI group would have reduced cortical thickness and cortical volume in the anterior cingulate, and decreased FA and white matter volume in the anterior cingulum, as compared to children in the OI group. These measures of the CAC (right and left separately) were compared between the two groups using ANCOVA with the CAC

measures as the dependent variable and with age, gender, and SCIz (and ICV where appropriate) as covariates.

The relationships between CAC properties (i.e. cortical thickness and volume, white matter volume, and FA) and behavioral measures of cognitive control (BRIEF Inhibit and Shift t-scores, Flanker interference reaction time difference score, and Flanker no-go accuracy) were investigated by means of partial correlation, controlling for age at injury, gender, and SCIz (and ICV for volume-based measures). This was examined for each group separately, since TBI may alter the magnitude and direction of the brain-behavior relationships.

Power analysis

For the independent samples t-tests, it was calculated that a minimum of 21 subjects per group would be needed in order to observe a large effect (Cohen's $d \geq 0.8$), with $\alpha=0.05$ and power=0.80 for a one-tailed t-test. In order to detect a medium effect ($d \geq 0.5$), a minimum of 51 subjects per group would be needed, and in order to detect a small effect ($d \geq 0.5$), a minimum of 310 subjects per group would be required.

For the partial correlations, it was calculated that 86 subjects would be needed in order to detect a large effect size (Cohen's $f \geq 0.4$), with $\alpha = 0.05$, power = 0.80, and 5 numerator degrees of freedom. At least 211 subjects would be needed to detect a medium effect size (Cohen's $f \geq 0.25$), and at least 1289 subjects would be required in order to detect a small effect size (Cohen's $f \geq 0.10$), with the same parameters.

Results

Demographic characteristics

The participants were well-matched for demographic variables with the exception of age at injury, where the TBI participants (mean age = 13.80 ± 2.57) were older than their OI counterparts (mean age = 11.53 ± 2.34; $t(75) = 4.081$; $p < 0.001$). Demographic and clinical characteristics of the TBI and OI groups are presented in Table 2.

Cortical thickness statistical maps

The parametric maps displaying group differences in cortical thickness revealed several regions where the TBI group demonstrated reduced cortical thickness as compared to the OI group, predominantly in frontal regions, with less extensive regions of significance in the temporal and parietal lobes ($0.01 < p < 0.00001$; see Figure 5). After correction for multiple comparisons, the cluster-thresholded results revealed a similar pattern of reduced cortical thickness in the TBI group ($0.01 < p < 0.00001$; see Figure 6), with frontal regions demonstrating extensive areas of cortical thinning. For the analysis both with and without correction for multiple comparisons, the CAC did not demonstrate group differences, although regions bordering on the CAC were significantly thinner in the TBI group. However, after controlling for age at injury, there were no remaining regions of significant cortical thinning in the TBI group. In contrast, after controlling for multiple comparisons the TBI group demonstrated relative *increase* in cortical thickness as compared to the OI group, in tiny regions of the parietal lobes and medial frontal lobes ($p < 0.01$; see Figure 7). No clusters survived correction for multiple comparisons when controlling for age at injury.

Table 2

Demographic and clinical characteristics of TBI and OI groups

Variables	Groups		Statistics
	TBI (n = 36)	OI (n = 42)	
Age (years)	13.80 (2.57)	11.53 (2.34)	$t(76) = 4.081$; $p < 0.001$
Gender (M/F)	25/11	30/12	$\chi^2(1) = 0.037$, $p = 0.848$
Post-injury interval (yrs.)	0.35 (0.09)	0.33 (0.06)	$t(76) = 0.971$; $p = 0.335$
Social Composite Index	0.07 (0.84)	0.11 (0.78)	$t(71) = -0.242$; $p = 0.810$
Handedness (R/L)	34/2	36/6	$\chi^2(1) = 1.605$; $p = 0.205$
GCS	7.27 (4.27)	N/A	N/A
Ethnicity	4 AA, 1 AI, 18 C, 13 H, 2 BI	12 AA, 0 AI, 14 C, 14 H, 2 BI	$\chi^2(4) = 7.678$; $p = 0.104$

Values are reported as mean (standard deviation). For gender, M = male, F = female; For handedness, R = right, L = left; GCS = Lowest Glasgow Coma Scale score within 24 hours post-injury; NR = not reported; N/A = data not applicable; For Ethnicity, AA = African American, AI = Asian, C = Caucasian, H = Hispanic, BI = biracial.

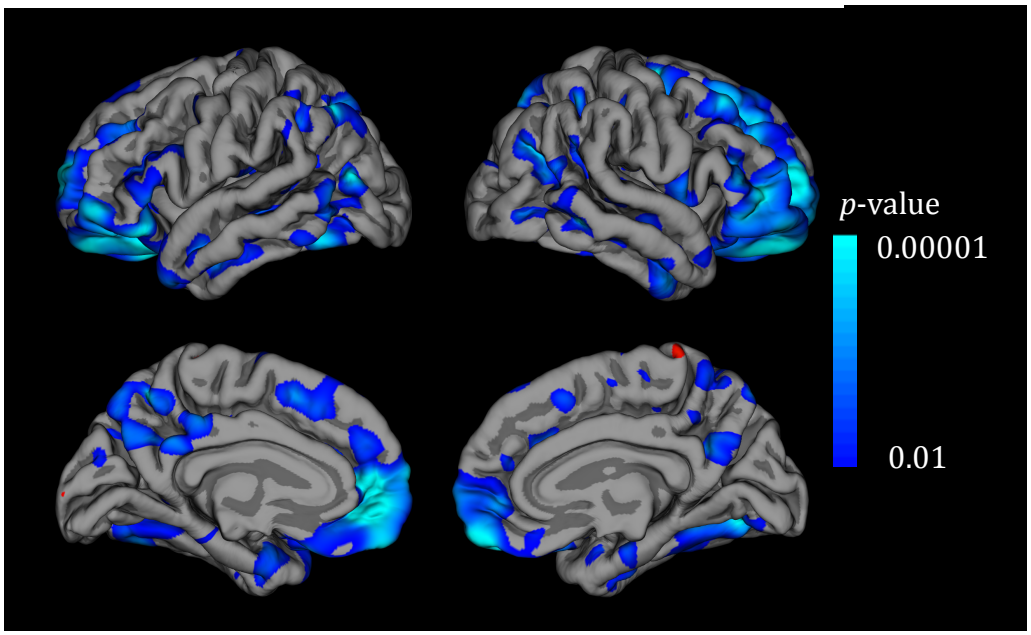

Figure 5. Cortical thickness group differences, uncorrected for multiple comparisons. Blue regions indicate significantly reduced cortical thickness in the TBI group as compared to the OI group.

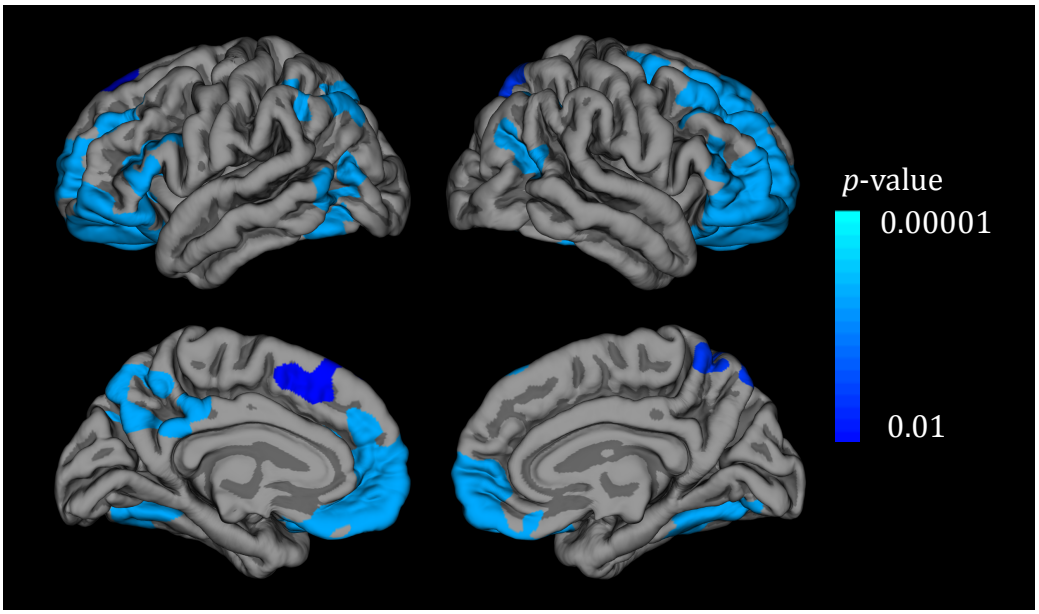

Figure 6. Cortical thickness group difference, corrected for multiple comparisons (vertex-wise threshold of $p < 0.05$, 10,000 iterations). Blue regions indicate significantly reduced cortical thickness in the TBI group as compared to the OI group.

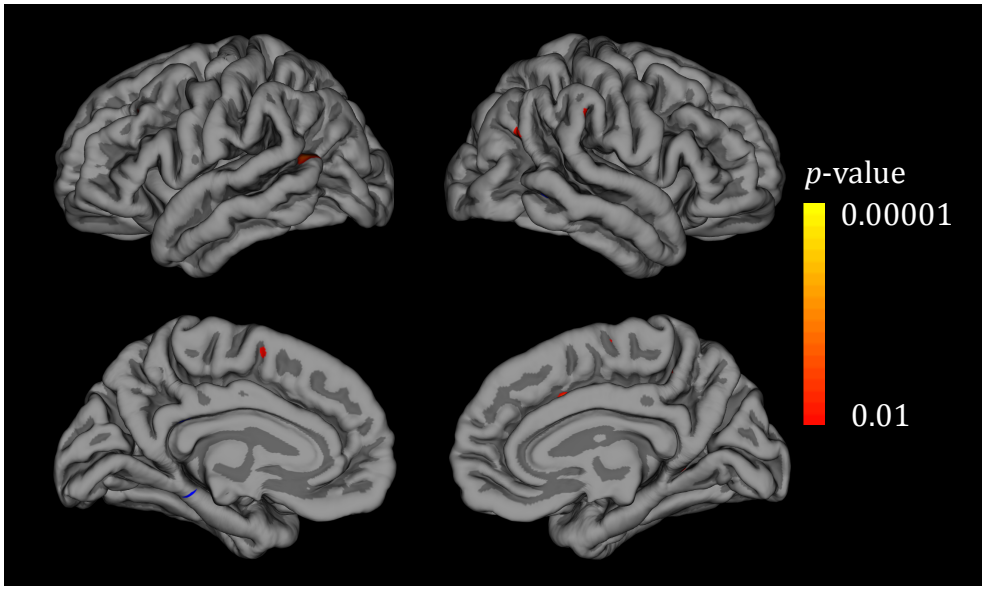

Figure 7. Cortical thickness group differences, uncorrected for multiple comparisons, statistically controlling for age at injury. Red regions indicate relative *increase* in cortical thickness in the TBI group as compared to the OI group.

Group comparisons of morphometry and DTI metrics

Between-group differences were not observed for any of the morphometric properties of the CAC, although a small effect size was observed for reduced left cortical thickness (d = -0.34) and left cortical volume (d = -0.35) in the TBI group. However, significant between-group differences were observed bilaterally for FA. Compared to the OI group, the TBI group demonstrated reduced FA for the right hemisphere ($F(1,68) = 14.291$, $p < 0.001$) and for the left hemisphere ($F(1,68) = 11.997$, $p = 0.001$). After Bonferroni correction for the eight comparisons ($\alpha = 0.05/8 = 0.00625$), the FA comparisons remained significant. Table 3 presents the comparison of morphometric and DTI properties of the CAC for the TBI and OI groups.

Table 3

CAC measures for TBI and OI groups

Variables	Groups		Statistics	
	TBI	OI	*p*-value	Cohen's *d*
Cortical thickness (mm)				
Right	2.80 (0.29)	2.85 (0.22)	0.657	-0.19
Left	2.86 (0.36)	2.97 (0.29)	0.836	-0.34
Cortical volume (mm^3)				
Right	2280.5 (476.8)	2302.6 (599.4)	0.959	-0.04
Left	1904.2 (459.1)	2068.5 (491.5)	0.346	-0.35
White matter volume (mm^3)				
Right	2270.9 (332.5)	2292.4 (484.0)	0.374	-0.05
Left	2156.2 (366.5)	2191.5 (371.1)	0.461	-0.18
FA				
Right	0.426 (0.078)	0.490 (0.044)	<0.001	-1.01
Left	0.437 (0.058)	0.480 (0.044)	0.001	-0.84

Brain metrics are expressed as mean (standard deviation). Age, gender, and SCIz were included as covariates, with ICV included as a covariate for volume-based measures. FA = fractional anisostropy. Cohen's $d \geq 0.80$ indicates a large effect size; 0.50 – 0.79 indicates a moderate effect size, 0.20 - 0.49 indicates a small effect size (Cohen, 1988).

Group comparisons of cognitive control performance

BRIEF scores were missing for 2 TBI participants and 5 OI participants. The TBI group was rated higher on the BRIEF Inhibit ($t(62) = 6.706$, $p = 0.012$) and Shift ($t(62) = 6.706$ $p = 0.012$) scales, indicating that their parents rated them as being lower functioning in these executive domains, as compared to the OI group. The average parent rating for both the Inhibit and Shift scales was less than the recommended cut-off score (T-score = 65) for clinically significant impairment. The BRIEF score comparisons did not survive Bonferroni correction ($\alpha = 0.05/6 = 0.00833$)

Flanker data were missing for 4 TBI participants and 6 OI participants for baseline reaction time and accuracy on the no-go condition. For the interference time and difference between interference reaction time and baseline reaction time on the Flanker task, 4 TBI and 8 OI participants were missing data. Significant group differences were not observed for baseline reaction time, interference reaction time, or the difference between interference reaction time and baseline reaction time (conflict processing measure) on the Flanker task. There was a trend for increased errors committed by the TBI group on the Flanker task, however this did not attain a level of significance ($t(64) = 3.396$ $p = 0.070$). There was a small effect size ($d = 0.28$) for increased error commission rates on the Flanker task in the TBI group as compared to the OI group. Results of the cognitive control performance for the TBI and OI groups are presented in Table 4.

Table 4

Cognitive control performance of TBI and OI groups

Variables	Groups		Statistics	
	TBI	Control	*p*-value	Cohen's *d*
BRIEF Inhibit (T-score)	59.2 (12.4)	51.0 (9.7)	0.015	0.74
BRIEF Shift (T-score)	56.2 (10.5)	49.5 (9.0)	0.012	0.69
Flanker task				
Baseline RT (milliseconds)	737.5 (160.4)	761.5 (193.5)	0.627	-0.14
Interference RT (milliseconds)	830.4 (186.5)	841.4 (200.2)	0.667	-0.06
(Interference - Baseline) RT (milliseconds)	85.0 (66.6)	93.7 (71.3)	0.658	-0.13
No-Go (% errors)	15.8 (23.7)	10.6 (10.9)	0.070	0.28

Values are reported as mean (standard deviation). Age, gender, and SCIz were included as covariates. Cohen's $d \geq 0.80$ indicates a large effect size; 0.50 – 0.79 indicates a moderate effect size, 0.20 - 0.49 indicates a small effect size (Cohen, 1988).

Correlations between cognitive control and brain-based measures

There were no significant relationships between cognitive control and brain-based measures in the TBI group, although the relationship between FA and the Flanker reaction time difference score approached significance, such that increased FA tended to be associated with

increased discrepancy between reaction time on the Flanker interference and baseline trials (left ($F(4,24) = 5.172$, $p = 0.058$; right ($F(4,24) = 5.141$, $p = 0.060$). The results of the correlations between cognitive control and brain-based measures for the TBI group are reported in Table 5.

For the OI group, several CAC properties in the right (but not left) hemisphere were observed to be associated with accuracy on the Flanker no-go task, including right cortical thickness ($F(4,32) = 2.809$, $p = 0.025$), right cortical volume ($F(5,31) = 3.307$, $p = 0.003$) and right white matter volume ($F(5,31) = 2.655$, $p = 0.011$). In all cases, increased error commission on the Flanker no-go trial was associated with increased thickness or volume. Right white matter volume of the CAC was also related to the Flanker interference difference score, such that increased white matter volume was associated with reduced discrepancy between reaction time performance on the Flanker trials ($F(5,29) = 2.011$, $p = 0.036$). These associations were not significant after Bonferroni correction for multiple comparisons (adjusted $\alpha = 0.05/32 = 0.0016$), however the actual p values are reported in Table 6 for direct comparison. The scatterplots of the significant brain-behavior relations are displayed in Figure 8 (A-D).

Selected age-matched subsample

As reported previously, the groups were well-matched on all demographic variables, with the exception of age at injury. When age at injury was included in the parametric brain map model demonstrating group differences in cortical thickness, the extensive regions of significant cortical thinning in the TBI group disappeared. It is possible that statistically controlling for age at injury may in fact be over-controlling and thus masking significant group differences. For this reason, a subsample of age-matched participants (28 TBI and 32 OI) was selected in order to investigate this possibility. The statistical analyses as described in the methods section were

Table 5

Associations between cognitive control and CAC properties, TBI group

Behavioral measures	CAC measures							
	Cortical thickness		Cortical volume		WM volume		FA	
	Right	Left	Right	Left	Right	Left	Right	Left
BRIEF Inhibit								
r	-0.05	0.12	-0.15	0.04	0.05	-0.18	-0.18	-0.22
p	ns	ns	ns	ns	ns	ns	ns	ns
BRIEF Shift								
r	0.02	0.16	-0.20	0.03	-0.16	-0.12	-0.18	-0.30
p	ns	ns	ns	ns	ns	ns	ns	ns
Flanker Interference - Baseline RT								
r	-0.06	-0.06	0.24	0.04	0.22	0.20	-0.37	-0.38
p	ns	ns	ns	ns	ns	ns	0.060	0.058
Flanker No-Go Accuracy (% error)								
r	0.12	-0.05	0.16	-0.05	-0.24	-0.15	-0.21	-0.12
p	ns	ns	ns	ns	ns	ns	ns	ns

Age, gender, and SCIz were included as covariates, with ICV included as a covariate for volume-based measures. Partial correlation coefficients are reported. ns = not significant; RT = reaction time

Table 6

Associations between cognitive control and CAC properties, OI group

Behavioral measures	CAC measures							
	Cortical thickness		Cortical volume		WM volume		FA	
	Right	Left	Right	Left	Right	Left	Right	Left
BRIEF Inhibit								
r	-0.14	0.01	-0.33	0.32	-0.28	0.34	0.16	-0.09
p	ns	ns	0.068	0.081	ns	0.059	ns	ns
BRIEF Shift								
r	0.09	0.17	-0.27	0.09	-0.15	0.03	0.26	0.10
p	ns	ns	ns	ns	ns	ns	ns	ns
Flanker Interference - Baseline RT								
r	0.10	0.03	-0.35	-0.11	-0.38	0.05	0.212	-0.21
p	ns	ns	0.057	ns	0.036	ns	ns	ns
Flanker No-Go Accuracy (% error)								
r	0.39	0.17	0.50	0.05	0.44	0.108	-0.14	0.09
p	0.025	ns	0.003	ns	0.011	ns	ns	ns

Age, gender, and SCIz were included as covariates, with ICV included as a covariate for volume-based measures. Partial correlation coefficients are reported. ns = not significant; RT = reaction time

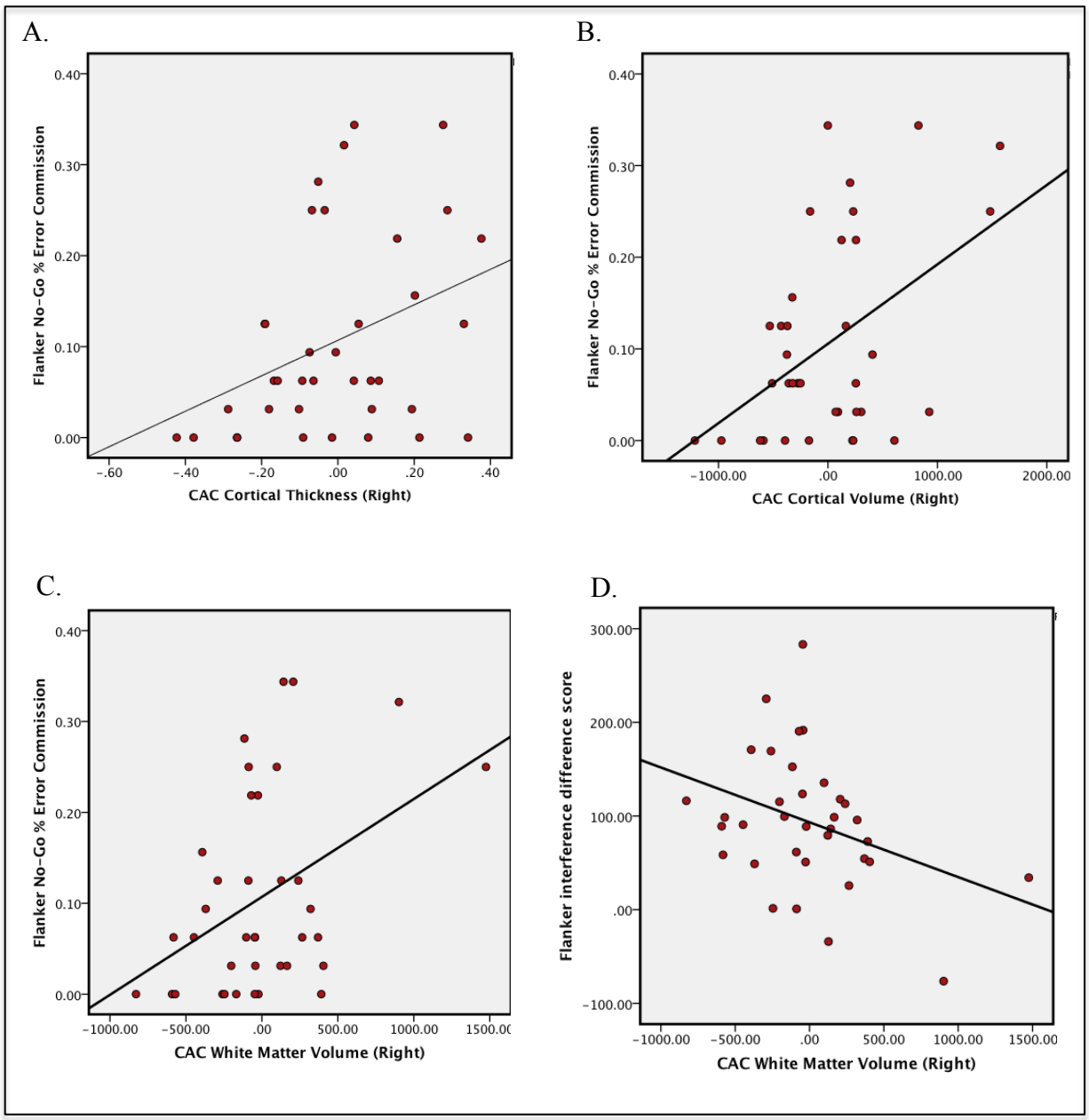

Figure 8A-D. OI group scatterplots for relationships between A. right CAC cortical thickness and Flanker No-Go Error Commission Rate, B. right CAC cortical volume and Flanker No-Go Error Commission Rate, C. right CAC white matter volume and Flanker No-Go Error Commission Rate, and D. right CAC white matter volume and the discrepancy between Flanker interference and baseline reaction time scores. Cortical thickness results are adjusted for age at injury, gender, and SCIz, and volume results are adjusted for age at injury, gender, SCIz, and ICV.

performed on this smaller sample, with the exception that age at injury was not included as a covariate in the analyses.

Demographic characteristics (age-matched subsample). As shown in Table 7, there were no significant group differences in demographic factors in the selected age-matched sample. In the selected subsample, mean age for the TBI group was 12.94 and mean age for the OI group was 12.46. The Kolmogorov-Smirnov test did not reveal a significant difference for the distributions of age at injury between groups ($p = 0.108$, two-tailed).

Cortical thickness statistical maps (age-matched sample). Similar to the results obtained from the larger subject sample, the parametric maps displaying group differences in cortical thickness in the age-matched subsample revealed several regions where the TBI group demonstrated reduced cortical thickness as compared to the OI group, predominantly in frontal regions, with less extensive regions of significance in the temporal and parietal lobes ($0.01 < p < 0.00001$; see Figure 9). After correction for multiple comparisons, the cluster-thresholded results revealed a similar pattern of reduced cortical thickness in the TBI group ($0.01 < p < 0.00001$; see Figure 10), with frontal regions demonstrating extensive areas of cortical thinning. As in the cortical thickness maps for the larger sample, the CAC did not demonstrate group differences, although regions bordering on the CAC were significantly thinner in the TBI group.

Table 7

Demographic and clinical characteristics of selected age-matched sample of 60 participants

Variables	Groups		Statistics
	TBI (n = 28)	OI (n = 32)	
Age (years)	12.94 (2.26)	12.46 (1.81)	$t(58) = 0.913$; $p = 0.365$
Gender (M/F)	19/9	24/8	$\chi^2(1) = 0.037$, $p = 0.540$
Post-injury interval (yrs.)	0.35 (0.08)	0.33 (0.06)	$t(58) = 0.820$; $p = 0.416$
Social Composite Index	0.02 (0.87)	0.05 (0.77)	$t(56) = -0.163$; $p = 0.871$
Handedness (R/L)	26/2	28/4	$\chi^2(1) = 0.476$; $p = 0.490$
GCS	7.58 (4.55)	N/A	N/A
Ethnicity	4 AA, 1 AI, 12 C, 11 H, 0 BI	11 AA, 0 AI, 9 C, 10 H, 2 BI	$\chi^2(4) = 6.505$; p = 0.164

Values are reported as mean (standard deviation). For gender, M = male, F = female; For handedness, R = right, L = left; GCS = Lowest Glasgow Coma Scale score within 24 hours post-injury; NR = not reported; N/A = data not applicable; For Ethnicity, AA = African American, AI = Asian, C = Caucasian, H = Hispanic, BI = biracial.

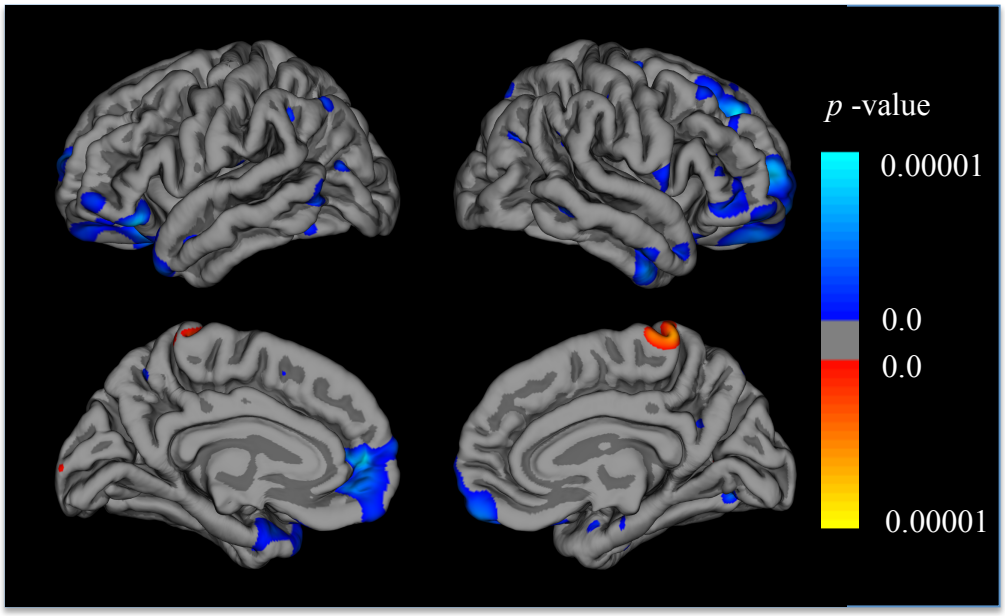

Figure 9. Cortical thickness group differences of age-matched subsample (28 TBI/32 OI), uncorrected for multiple comparisons. Blue regions indicate significant reductions, and red/yellow regions indicate significant increases in cortical thickness in the TBI group compared to the OI group.

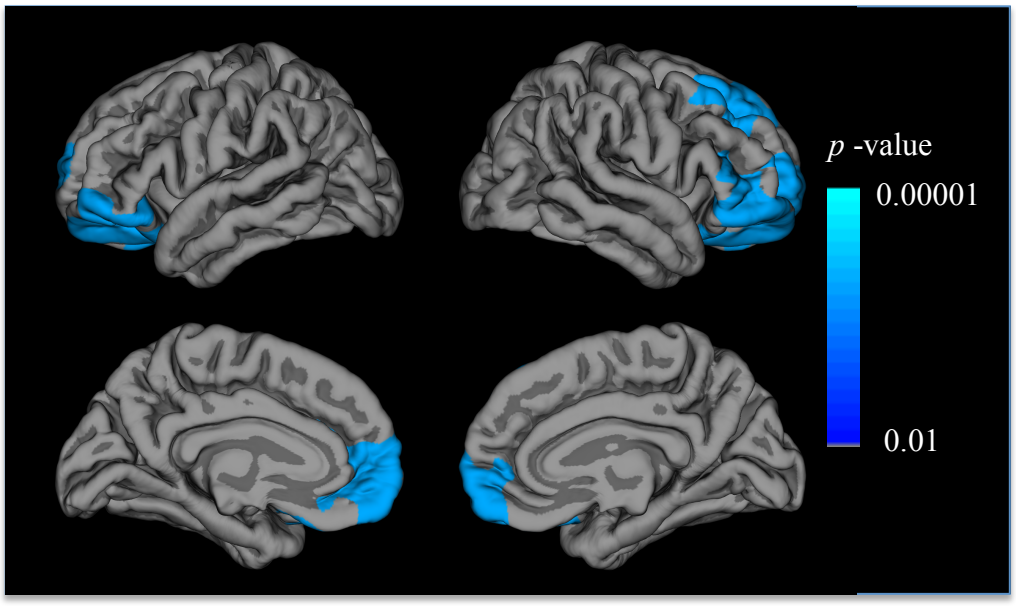

Figure 10. Cortical thickness group differences of age-matched subsample (28 TBI/32 OI), corrected for multiple comparisons (vertex-wise threshold of $p < 0.05$, 10,000 iterations). Blue regions indicate significantly reduced cortical thickness in the TBI group as compared to the OI group.

Group comparisons of morphometry and DTI metrics (age-matched subsample). Between-group differences were not observed for any of the morphometric properties of the CAC. However, as with the larger sample, significant between-group differences were observed bilaterally for FA. Compared to the OI group, the TBI group demonstrated reduced FA for the right hemisphere ($F(1,54) = 12.472$, $p = 0.001$) and for the left hemisphere ($F(1,54) = 10.644$, $p = 0.002$). After Bonferroni correction for the eight comparisons ($\alpha = 0.05/8 = 0.00625$), the FA comparisons remained significant. Table 8 presents the comparison of morphometric and DTI properties of the CAC for the TBI and OI groups.

Group comparisons of cognitive control performance (age-matched sample). In the age-matched subsample, BRIEF scores were missing for 1 TBI participant and 4 OI participants. Similar to the results of the larger sample, the TBI group was rated higher on the BRIEF Inhibit ($F(1,49) = 6.857$, $p = 0.012$) and Shift ($F(1,549) = 7.093$ $p = 0.010$) scales, indicating that their parents rated them as being lower functioning in these executive domains, as compared to the OI group. For the TBI group, the average parent ratings for both the Inhibit and Shift scales were less than the recommended cut-off score (T-score = 65) for clinically significant impairment. The BRIEF score comparisons did not survive Bonferroni correction ($\alpha = 0.05/6 = 0.00833$).

Flanker data were missing for 3 TBI participants and 2 OI participants for baseline reaction time and accuracy on the no-go condition. For the Flanker interference reaction time, 3 TBI participants and 3 OI participants were missing data. For the difference between interference reaction time and baseline reaction time on the Flanker task, 6 TBI and 3 OI participants were missing data. Significant group differences were not observed for baseline reaction time, interference reaction time, or the difference between interference reaction time and

Table 8

CAC measures for TBI and OI groups (age-matched subsample)

Variables	Groups		Statistics	
	TBI	OI	*p*-value	Cohen's *d*
Cortical thickness (mm)				
Right	2.84 (0.29)	2.82 (0.20)	0.969	0.08
Left	2.90 (0.38)	2.93 (0.29)	0.897	-0.09
Cortical volume (mm^3)				
Right	2309.3 (466.3)	2308.2 (664.0)	0.733	<0.01
Left	1936.2 (504.2)	2028.7 (430.6)	0.306	-0.20
White matter volume (mm^3)				
Right	2292.2 (339.7)	2317.4 (539.4)	0.531	-0.06
Left	2191.1 (371.8)	2187.3 (377.3)	0.504	0.01
FA				
Right	0.428 (0.076)	0.489 (0.047)	0.001	-0.97
Left	0.438 (0.051)	0.478 (0.043)	0.002	-0.84

Brain metrics are expressed as mean (standard deviation). Gender and SCIz were included as covariates, with ICV included as a covariate for volume-based measures. FA = fractional anisotropy. Cohen's *d* > 0.80 indicates a large effect size; 0.50 – 0.79 indicates a moderate effect size, 0.20 - 0.49 indicates a small effect size (Cohen, 1988).

baseline reaction time (conflict processing measure) on the Flanker task. The trend for increased errors committed by the TBI group on the Flanker task (as observed in the larger sample) was not evident in the age-matched sample. There was a small effect size (d = 0.36) for increased error commission rates on the Flanker task in the TBI group as compared to the OI group. Results of the cognitive control performance for the TBI and OI groups are presented in Table 9.

Correlations between cognitive control and brain-based measures. There were no significant relationships between cognitive control and brain-based measures in the TBI group of the age-matched sample, although the relationship between right cortical thickness and the Flanker reaction time difference score approached significance, such that decreased cortical thickness tended to be associated with increased discrepancy between reaction time on the Flanker interference and baseline trials (p = 0.088). The results of the correlations between cognitive control and brain-based measures between cognitive control and brain-based measures for the TBI group are reported in Table 10.

For the OI group of the selected age-matched sample, CAC properties in the right hemisphere were observed to be associated with the Flanker reaction time difference score, including right cortical volume (F(4,24) = 2.383, p = 0.036), trend for right white matter volume (F(4,24) = 4.010, p = 0.057), and trend for right FA (F(3,25) = 2.413, p = 0.064. Increased volume was associated with reduced discrepancy between reaction time performance on the Flanker. Also, certain CAC properties in the right hemisphere were associated with accuracy on the Flanker no-go task, including right cortical volume (F(4,25) = 3.307, p = 0.006), right white matter volume (F(4,25) = 6.128, p = 0.020), and trend for right cortical thickness (F(3,26) = 2.249, p = 0.063). In all cases, increased error commission on the Flanker no-go trial

Table 9

Cognitive control performance of TBI and OI groups (age-matched subsample)

Variables	Groups		Statistics	
	TBI	Control	*p*-value	Cohen's *d*
BRIEF Inhibit (T-score)	60.0 (13.1)	51.5 (9.4)	0.012	0.75
BRIEF Shift (T-score)	55.6 (9.4)	50.0 (8.8)	0.010	0.62
Flanker task				
Baseline RT (milliseconds)	728.7 (163.9)	727.4 (179.4)	0.963	0.01
Interference RT (milliseconds)	832.7 (196.1)	817.7 (190.6)	0.940	0.08
(Interference - Baseline) RT (milliseconds)	95.2 (71.2)	95.8 (71.4)	0.844	-0.01
No-Go (% errors)	17.3 (26.3)	9.9 (11.5)	0.196	0.36

Values are reported as mean (standard deviation). Gender and SCIz were included as covariates. Cohen's $d > 0.80$ indicates a large effect size; 0.50 – 0.79 indicates a moderate effect size, 0.20 - 0.49 indicates a small effect size (Cohen, 1988).

was associated with increased thickness or volume. As was observed for the larger sample, these associations were not significant after Bonferroni correction for multiple comparisons (adjusted $\alpha = 0.05/32 = 0.0016$), however the actual *p* values are reported in Table 11 for direct comparison.

Table 10

Associations between cognitive control and CAC properties, TBI group (age-matched sample, n=28)

Behavioral measures	CAC measures							
	Cortical thickness		Cortical volume		WM volume		FA	
	Right	Left	Right	Left	Right	Left	Right	Left
BRIEF Inhibit								
r	-0.12	-0.02	-0.20	-0.07	-0.01	-0.32	-0.16	-0.19
p	ns	ns	ns	ns	ns	ns	ns	ns
BRIEF Shift								
r	-0.13	0.12	-0.34	0.05	-0.09	-0.16	-0.07	-0.17
p	ns	ns	ns	ns	ns	ns	ns	ns
Flanker Interference - Baseline RT								
r	-0.25	-0.20	-0.21	-0.19	-0.17	0.01	0.16	-0.20
p	0.088	ns	ns	ns	ns	ns	ns	ns
Flanker No-Go Accuracy (% error)								
r	0.17	0.07	0.22	-0.02	-0.19	-0.20	-0.21	-0.18
p	ns	ns	ns	ns	ns	ns	ns	ns

Gender and SCIz were included as covariates, with ICV included as a covariate for volume-based measures. Partial correlation coefficients are reported. ns = not significant; RT = reaction time

Table 11

Associations between cognitive control and CAC properties, OI group (age-matched sample, n=32)

Behavioral measures	CAC measures							
	Cortical thickness		Cortical volume		WM volume		FA	
	Right	Left	Right	Left	Right	Left	Right	Left
BRIEF Inhibit								
r	-0.05	-0.01	-0.35	0.19	-0.36	0.24	0.17	-0.05
p	ns	ns	0.058	ns	0.082	ns	ns	ns
BRIEF Shift								
r	0.16	0.10	-0.34	-0.19	-0.21	-0.14	0.33	0.21
p	ns	ns	0.068	ns	ns	ns	0.089	ns
Flanker Interference - Baseline RT								
r	-0.01	0.02	-0.39	-0.03	-0.38	0.09	0.34	-0.07
p	ns	ns	0.036	ns	0.057	ns	0.064	ns
Flanker No-Go Accuracy (% error)								
r	0.34	0.17	0.49	0.15	0.44	0.17	-0.08	0.17
p	0.063	ns	0.006	ns	0.020	ns	ns	ns

Gender and SCIz were included as covariates, with ICV included as a covariate for volume-based measures. Partial correlation coefficients are reported. ns = not significant; RT = reaction time

Discussion

Neuroimaging has traditionally been used clinically to assess for abnormalities such as cerebral contusions and intracerebral hemorrhaging in the acute phase of TBI; however, quantitative research methods also may be used to evaluate the effects of TBI on brain structure and function in the acute and chronic phases. While CT and MRI scanning are routinely performed after admittance to the hospital to investigate the extent of damage due to TBI, traditional clinical imaging is often insensitive to the extensive range of effects of TBI. In particular, traditional imaging does not detect the full effects of traumatic axonal injury, and therefore the significance of this type of injury is often not fully recognized (Smith, et al., 2003).

Observed between-group differences post-TBI

Group comparisons of CAC properties. The current study investigated brain changes that are assumed to occur on a much smaller scale (as compared to gross brain lesions), which would be related to the effects of traumatic axonal injury, excitotoxicity, Wallerian degeneration, etc. Such processes are understood to continue months and perhaps even years into the chronic phase post-injury (Sidaros, Skimmings, et al., 2009), and thus the full impact of these changes would not be appreciated on an acute brain scan even if they could be identified by the unaided human eye. In the current study, at 3 months post-injury the TBI group demonstrated reduced cortical thickness predominantly in frontal regions. Statistical brain maps demonstrated significant cortical thinning in medial regions of the brain near the CAC; however, cortical thickness of the CAC itself was not significantly reduced in the TBI group. On average, regional cortical thickness, cortical volume, and cortical white matter volume of the CAC were reduced in the TBI group at 3 months post-injury, however these reductions were not statistically significant. This was contrary to expectation, since previous studies generally report significant

reductions in brain matter globally and in the CAC specifically. One possible explanation for the observed lack of significant CAC atrophy post-TBI is that the processes that result in atrophy were likely still underway at 3 months post-injury. Indeed, post-injury intervals exceeding a year are commonly reported for studies where atrophy of the CAC was identified (Bendlin, et al., 2008; Gale, et al., 2005; Levine et al., 2008).

White matter volume loss is commonly observed following TBI (Bendlin, et al., 2008; Ding, et al., 2008; Sidaros, Skimminge, et al., 2009), and specifically has been reported in the cingulum (Bendlin, et al., 2008). In spite of the fact that white matter volume loss was not observed for the CAC in the present study, there were significant between-group differences in the white matter structural integrity of the cingula. The relatively reduced FA demonstrated by the TBI group indicates a decrease of white matter integrity following TBI. Greater diffusion of water, as represented by lower FA values, suggests a breakdown of the microstructure of white matter (Kochunov, et al., 2009), since the diffusion of water molecules in a healthy brain are constrained to flow parallel to the major axis of the fiber tracts by the intact myelin sheaths and the integrity of axonal and intracellular structures (Arfanakis, et al., 2002; Assaf & Pasternak, 2008; Harsan, et al., 2006). It should be noted that the current findings indicate that degradations of white matter integrity are possible even in the absence of morphometric alterations after TBI. These results seem to confirm previous claims that DTI may be more sensitive to pathology that remains undetected on conventional imaging (Benson, et al., 2007; Kou et al., 2010).

Group comparisons of measures of cognitive control. As expected, there were significant between-group differences in parent ratings on the BRIEF Inhibit and Shift scales. Parents of the TBI participants rated their children as exhibiting greater difficulty on tasks that require controlling impulses (Inhibit scale) and shifting or transitioning freely from one

activity/situation to another (Shift scale). However, the actual discrepancies between the groups on the BRIEF scores were fairly modest (8.2 T-score units difference for the Inhibit scale, 6.7 units difference for the Shift scale). Additionally, the average parent rating for the TBI group did not exceed the recommended cut-off score for determining clinically significant impairment (T-score = 65). Therefore, while it appears that children with TBI demonstrated relatively increased difficulty with behavioral inhibition and effective task shifting in everyday life, it is unclear whether these differences were clinically significant.

Contrary to expectations, the TBI group did not perform the Flanker task more slowly for any of the trials considered herein, and the error commission rates on the Flanker no-go task approached but did not attain significance. It is possible that the Flanker task is not sensitive to aspects of inhibitory control that are often disrupted following TBI. An alternate explanation may be that the full extent of inhibitory control disruption presents in closer temporal proximity to the injury and then may resolve due to brain plasticity by 3 months post-injury.

Relationships between CAC properties and cognitive control

Previous research has indicated that the CAC is implicated in cognitive control performance. Left cingulate activation was previously observed in an fMRI task that involved attentional shifting and inhibitory filtering (Thomsen, Specht, Ersland, & Hugdahl, 2005). Anterior cingulate activation on fMRI studies involving tasks of error monitoring and conflict processing (such as the Eriksen Flanker task) has been repeatedly observed (Carter, Botvinick, & Cohen, 1999; Casey et al., 1997; Hester, Fassbender, & Garavan, 2004). In the present study, accuracy on the Flanker task did not significantly differ between the TBI and OI groups, although there was a trend for the TBI group to commit more errors. Nevertheless, decreased morphometric properties (i.e. reduced cortical thickness, cortical volume, and white matter

volume) of the right CAC in particular was associated with improved accuracy on the no-go condition of the Flanker task in the OI group only, although after correction for multiple tests these associations were no longer significant. A similar relationship was not observed for the TBI group. This finding of a trend relationship between CAC volume and inhibitory control in the OI group is not consistent with the results of a study by Elderkin-Thompson and colleagues (2008), in which they observed that better performance on a response inhibition task (i.e. Stroop) was associated with *larger* volume of the anterior cingulate in adults. However, participants in the current study were children and adolescents, and thus were likely in the process of undergoing a characteristic pattern of cortical thinning (Gogtay, et al., 2004; Shaw et al., 2008) which would be associated with reduced cortical volumes as they mature. Therefore, the observation that improved inhibition of incorrect responses on the Flanker task was associated with reduced cortical volume of the CAC may indicate that the maturationally-dependent pruning process may facilitate error monitoring.

Significance and limitations of the current study

One aim of the current study was to investigate the relative impact of TBI on quantifiable properties of the CAC, given that its location renders it susceptible to damage from TBI. Contrary to expectations, there were no significant between-group differences for cortical thickness, cortical volume, or white matter volume of the CAC, although the TBI group tended to show reductions on average. However, significant group differences were observed bilaterally for FA, suggesting that white matter integrity may be compromised in this region, even in the absence of gross atrophy. Indeed, DTI has been shown to identify abnormalities that go undetected on conventional neuroimaging (Benson, et al., 2007), therefore it is not surprising that it is sensitive to regional reductions in white matter integrity as well.

Another aim of the current study was to further elucidate the relative contributions to behavior made by the various quantifiable CAC properties. Contrary to expectations, no significant relationships between cognitive control and morphometrics/DTI metrics of the CAC were observed. However, it cannot be assumed that volume and/or white matter integrity of the CAC make no contributions to behavior. A number of factors could potentially have contributed to reduced sensitivity, which are described in detail hereafter.

Neuroimaging data quality. The ability to make valid inferences based on the neuroimaging data in the current study may have been limited by the quality of the MRI data. The efficiency of automated quantitative image analysis algorithms can be very adversely affected by image artifacts (Mortamet et al., 2009), which in turn can limit the ability to make inferences from neuroimaging data in general. The MRI data in the present study were acquired with field strength of 1.5T, whereas using 3T data would likely have contributed to a higher signal-to-noise ratio and spatial resolution, thereby enabling more accurate automated brain segmentation and parcellation results. By visual inspection, the automated CAC segmentation and parcellation of the imaging data of the current study looked reasonable, although cortical reconstruction errors were noted in other brain regions (predominantly the temporal lobes). Nevertheless, it would be preferable to use data with higher resolution in order to optimize automated neuroimage processing.

DTI in particular is susceptible to noise and artifacts (Tournier, Mori, & Leemans, 2011). While several subjects were excluded from the statistical analyses due to DTI artifacts, the acquisition parameters of the DTI data as a whole may not have been optimal for making inferences. For example, simulation studies seem to suggest that FA estimation improves with increasing diffusion gradient orientations (up to 30 orientations, whereas the current diffusion

data was acquired with 15 gradient directions). The susceptibility artifact of the DTI data that resulted in the frontal "warp" was another area of concern, especially since it was most noticeable near the anterior corpus callosum and anterior cingulate. The non-linear warp rendered co-registration between each subject's DTI and anatomical image nearly impossible, yet this artifact was present in virtually every subject. Since the problem was pervasive and thus was not expected to affect one group more than the other, the observed FA group differences are assumed to be valid reflections of decreased white matter integrity in the vicinity of the CAC following pediatric TBI. However, the presence of the frontal warp likely limited the ability to draw meaningful inferences about the correlation between the white matter integrity (FA) and cognitive control. Specifically, it is highly likely that the region of interest outlined by the white matter parcellation of the CAC in the anatomical image may have included extraneous white matter from surrounding brain regions, which could have either increased or decreased the observed average FA of the CAC, most likely in a non-uniform manner which could have affected the magnitude of the individual measurements of FA (and thus obscured the results of the correlations with behavioral measures).

Defined boundaries of the CAC. As mentioned previously, fMRI studies to date have demonstrated anterior cingulate activation for tasks of error monitoring and conflict processing (Carter, et al., 1999; Casey, et al., 1997; Hester, et al., 2004). However, while the area of activation in these studies is reported as "anterior cingulate", a careful review of the findings indicates that there is variability in the reported location of the peak activations (e.g., anterior cingulate cortex proper and overlying prefrontal zones) for conflict processing tasks (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004; S. F. Taylor, Stern, & Gehring, 2007), and a number of other regions have also been implicated including anterior insulae, inferior

frontal operculum, dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, and lateral parietal cortex (S. F. Taylor, et al., 2007). Thus, there may be reduced likelihood that measures of the CAC as defined in the current study will reliably be related to performance on measures of inhibitory control.

Reduced power due to final sample size. Related to the imaging quality problem was the fact that several subjects were excluded from the analysis due to either neuroimaging artifacts or missing imaging data. While a sufficient number of participants were recruited for the study, several were missing at least one imaging sequence, had suboptimal neuroimaging data, and/or were missing neuropsychological testing results. It was anticipated that 120 of the recruited subjects would have both neuroimaging and neuropsychological data, however this number was reduced to 78 remaining participants (as described previously in detail in Table 1). This reduced the statistical power and may have obscured potential findings. Indeed, power analyses indicated that the number of remaining subjects would make it possible to detect only large between-group effects for the CAC metrics and measures of cognitive control. The ANCOVAs that were performed to investigate the CAC-cognitive control relationships were underpowered; 86 participants would have been necessary in order to detect a large effect. However, in the present study the TBI and OI groups were considered separately (36 and 42 participants, respectively), due to the concern that TBI likely disrupts networks required for effective response inhibition. Therefore, it would be expected that each group could demonstrate patterns of distinct CAC-cognitive control relationships, which distinct patterns would have been obscured by considering them together as a uniform group. Nevertheless, this strategy resulted in a reduced number of subjects for the CAC-cognitive control analyses, which served to further reduce the likelihood that effects would be identified.

Confounding age effect. Another likely confound is the fact that the groups were not well matched for age, with the TBI participants being significantly older. This was controlled for statistically, but as evidenced by the brain maps of group differences in cortical thickness at three months post-injury, including age in the model may have overcorrected for the discrepancy. The analysis was performed on a selected subsample of age-matched TBI and OI participants; however, the general findings were consistent with the results for the larger sample.

Control sample. Orthopedically injured children were used as control participants for the current study. While there are arguments in favor of including OI participants as appropriate controls for TBI patients, (e.g., to control for risk factors predisposing children to traumatic injury and also to control for general factors associated with trauma and hospitalization post-injury), it is possible that OI children may not truly represent otherwise "typically developing" children. Specifically, there are concerns that children who sustain orthopedic injuries may have predisposing risk factors including attention-deficit hyperactive disorder (either clinically or subclinically) or other psychiatric disorders or tendencies. It is possible that significant differences in morphometric properties of the brain and Flanker task performance were not observed due to the fact that the control subjects may have underlying structural and functional features that are not representative of a normal population. Additionally, the present sample of TBI children did not include patients with lesions specifically in the cingulate (as identifiable by T1- and T2-weighted imaging). It is possible that a more dramatic comparison (for both morphometric properties and behavioral performance) would be between typically developing children (without a history of OI and with no evidence of psychiatric symptoms) and children with identifiable lesions in the cingulate gyrus.

Other limitations. It should also be noted that the current findings may be affected by the length of the post-injury interval of the scanning sessions. At present, it is unclear what the optimal post-injury interval may be for using neuroimagine to predict functional outcomes in the post-acute phase. While acute imaging is often necessary to guide early treatment, it may reflect the effects of edema, which will subside with time. Also, acute imaging will fail to detect the full extent of atrophy, which has been reported well into the chronic phase of TBI. Another confound in the investigation of brain-behavior relationships in pediatric populations is the likelihood that the effects of injury may be masked due to plasticity. Studies involving repeated scanning over the course of recovery may help to identify the optimum window for scanning TBI patients, in order to better predict functional outcomes and guide appropriate treatments long-term.

Future directions

As indicated above, the imaging data quality may have limited the ability to draw valid inferences regarding the relationship between CAC measures and inhibitory control performance. A similar study is currently underway at Baylor College of Medicine and the University of Arkansas, in which imaging data of higher resolution (3T vs. 1.5T, 32 direction vs. 15 direction DTI gradients) is being acquired, which theoretically should yield higher signal to noise ratios and thus increase the ability to make valid inferences from the imaging data. The susceptibility artifact (frontal "warp") is an inherent problem with the DTI echo planar imaging (EPI) sequence, although it may be possible to remove the artifact during post-processing in the future. Efforts are currently underway to address this problem, although an effective solution has not been identified to date.

Another advantage of the new TBI study currently in the recruitment phase is that the neuropsychological tests administered to the participants include a Stroop task, which is commonly used as a measure of selective attention and response inhibition (Beauregard & Levesque, 2006; Vakil, Weisz, Jedwab, Groswasser, & Aberbuch, 1995; Vitale et al., 2005). Activations of the anterior cingulate have been observed during performance of various versions of the task, usually in conjunction with other brain regions that form a neural circuit underlying response inhibition (Beauregard & Levesque, 2006; Bernal & Altman, 2009; Goldstein et al., 2011). It is possible that the Stroop task may be a more appropriate measure of cognitive control, rather than relying on parent report measures of behavior. It is to be expected that ecologically valid measures of executive functions (i.e. BRIEF scales) may recruit slightly different cognitive processes than are involved in experimental fMRI tasks. Indeed, the items on the BRIEF inquire regarding behaviors that require the coordination of a variety of cognitive and behavioral resources (Gioia & Isquith, 2004), which likely recruit a number of different brain systems in addition to the CAC.

Yet another strength of the new TBI study is that the participants recruited to date are very well-matched between the groups. This should reduce the need to control (or potentially over-control) for the age effect statistically in future analyses.

In spite of the cited limitations of the current study, it is hoped that the multimodal MRI approach described herein may eventually provide better understanding of the relationship between brain changes and functional outcomes of TBI. Ideally, this could result in obtaining needed services (such as cognitive rehabilitation, family support services, patient education regarding the injury, and academic services) for the TBI patient in order to reduce the likelihood and severity of TBI-related disability. It is possible that the multimodal MRI approach may be

used in the future to evaluate novel or competing standard of care treatments, by investigating the relative effect of the treatment modality on cortical thickness, cortical volume, white matter volume and/or white matter integrity. Given the fact that children potentially have a longer life ahead of them in which to deal with the consequences of TBI, and also given that the consequences of pediatric TBI are potentially more severe than those of adult TBI, it is of great importance to endeavor to mitigate the negative consequences of injury for pediatric TBI patients.

References

Aitken, M. E., McCarthy, M. L., Slomine, B. S., Ding, R., Durbin, D. R., Jaffe, K. M., …Mackenzie, E.J. (2009). Family burden after traumatic brain injury in children. *Pediatrics, 123*(1), 199-206. doi: 123/1/199 [pii]10.1542/peds.2008-0607

Anderson, V., & Pentland, L. (1998). Residual attention deficits following childhood head injury: Implications for ongoing development. *Neuropyschological Rehabilitiation, 8*(3), 283-300.

Arfanakis, K., Haughton, V. M., Carew, J. D., Rogers, B. P., Dempsey, R. J., & Meyerand, M. E. (2002). Diffusion tensor MR imaging in diffuse axonal injury. *AJNR Am J Neuroradiol, 23*(5), 794-802.

Assaf, Y., & Pasternak, O. (2008). Diffusion tensor imaging (DTI)-based white matter mapping in brain research: A review. *J Mol Neurosci, 34*(1), 51-61.

Beauregard, M., & Levesque, J. (2006). Functional magnetic resonance imaging investigation of the effects of neurofeedback training on the neural bases of selective attention and response inhibition in children with attention-deficit/hyperactivity disorder. *Appl Psychophysiol Biofeedback, 31*(1), 3-20.

Bendlin, B. B., Ries, M. L., Lazar, M., Alexander, A. L., Dempsey, R. J., Rowley, H. A., …Johnson, S.C. (2008). Longitudinal changes in patients with traumatic brain injury assessed with diffusion-tensor and volumetric imaging. *Neuroimage, 42*(2), 503-514. doi: S1053-8119(08)00606-X [pii]10.1016/j.neuroimage.2008.04.254

Benson, R. R., Meda, S. A., Vasudevan, S., Kou, Z., Govindarajan, K. A., Hanks, R. A., …Haacke, E. M. (2007). Global white matter analysis of diffusion tensor images is

predictive of injury severity in traumatic brain injury. *Journal of Neurotrauma, 24*(3), 446-459.

Bernal, B., & Altman, N. (2009). Neural networks of motor and cognitive inhibition are dissociated between brain hemispheres: An fMRI study. *Int J Neurosci, 119*(10), 1848-1880.

Bigler, E. D. (2001). Quantitative magnetic resonance imaging in traumatic brain injury. *J Head Trauma Rehabil, 16*(2), 117-134.

Bigler, E. D. (2007). Anterior and middle cranial fossa in traumatic brain injury: Relevant neuroanatomy and neuropathology in the study of neuropsychological outcome. *Neuropsychology, 21*(5), 515-531.

Blatter, D. D., Bigler, E. D., Gale, S. D., Johnson, S. C., Anderson, C. V., Burnett, B. M., …Bailey, B. J. (1997). MR-based brain and cerebrospinal fluid measurement after traumatic brain injury: Correlation with neuropsychological outcome. *AJNR Am J Neuroradiol, 18*(1), 1-10.

Buckner, R. L., Head, D., Parker, J., Fotenos, A. F., Marcus, D., Morris, J. C., & Snyder, A. Z. (2004). A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: Reliability and validation against manual measurement of total intracranial volume. *Neuroimage, 23*(2), 724-738. doi: S1053811904003271 [pii] 10.1016/ j.neuroimage.2004.06.018

Bush, G., Luu, P., & Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn Sci, 4*(6), 215-222.

Carter, C. S., Botvinick, M. M., & Cohen, J. D. (1999). The contribution of the anterior cingulate cortex to executive processes in cognition. *Rev Neurosci, 10*(1), 49-57.

Casey, B. J., Trainor, R. J., Orendi, J. L., Schubert, A. B., Nystrom, L. E., Giedd, J. N., …Rapoport, J. L. (1997). A developmental functional MRI study of prefrontal activation during performance of a go-no-go task *J Cogn Neurosci., 9*(6), 835-847.

Cohen, R. A., Kaplan, R. F., Zuffante, P., Moser, D. J., Jenkins, M. A., Salloway, S., & Wilkinson, H. (1999). Alteration of intention and self-initiated action associated with bilateral anterior cingulotomy. *The Journal of Neuropsychiatry & Clinical Neurosciences, 11*(4), 444-453.

Dale, A. M., Fischl, B., & Sereno, M. I. (1999). Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage, 9*(2), 179-194.

Dale, A. M., & Sereno, M. I. (1993). Improved localization of cortical activity by combining EEG and MEG with MRI cortical surface reconstruction: A linear approach. *J Cogn Neurosci, 5*, 162-176.

Desikan, R. S., Segonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., …Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage, 31*(3), 968-980.

Devinsky, O., Morrell, M. J., & Vogt, B. A. (1995). Contributions of anterior cingulate cortex to behaviour. *Brain, 118 (Pt 1)*, 279-306.

di Pellegrino, G., Ciaramelli, E., & Ladavas, E. (2007). The regulation of cognitive control following rostral anterior cingulate cortex lesion in humans. *J Cogn Neurosci, 19*(2), 275-286.

Ding, K., Marquez de la Plata, C., Wang, J. Y., Mumphrey, M., Moore, C., Harper, C., Diaz-Arrastia, R. (2008). Cerebral atrophy after traumatic white matter injury: Correlation with

acute neuroimaging and outcome. *J Neurotrauma, 25*(12), 1433-1440. doi: 10.1089/neu.2008.068

Elderkin-Thompson, V., Ballmaier, M., Hellemann, G., Pham, D., & Kumar, A. (2008). Executive function and MRI prefrontal volumes among healthy older adults. *Neuropsychology, 22*(5), 626-637.

Eslinger, P. J., Flaherty-Craig, C. V., & Benton, A. L. (2004). Developmental outcomes after early prefrontal cortex damage. *Brain Cogn, 55*(1), 84-103.

Fischl, B., & Dale, A. M. (2000). Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci U S A, 97*(20), 11050-11055.

Fischl, B., Liu, A., & Dale, A. M. (2001). Automated manifold surgery: Constructing geometrically accurate and topologically correct models of the human cerebral cortex. *IEEE Trans Med Imaging, 20*(1), 70-80.

Fischl, B., Salat, D. H., van der Kouwe, A. J., Makris, N., Segonne, F., Quinn, B. T., & Dale, A. M. (2004). Sequence-independent segmentation of magnetic resonance images. *Neuroimage, 23 Suppl 1*, S69-84.

Fischl, B., Sereno, M. I., & Dale, A. M. (1999). Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. *Neuroimage, 9*(2), 195-207.

Fischl, B., Sereno, M. I., Tootell, R. B., & Dale, A. M. (1999). High-resolution intersubject averaging and a coordinate system for the cortical surface. *Hum Brain Mapp, 8*(4), 272-284.

Fischl, B., van der Kouwe, A., Destrieux, C., Halgren, E., Segonne, F., Salat, D. H., …Dale, A. M. (2004). Automatically parcellating the human cerebral cortex. *Cereb Cortex, 14*(1), 11-22.

Gaetz, M. (2004). The neurophysiology of brain injury. *Clin Neurophysiol, 115*(1), 4-18.

Gale, S. D., Baxter, L., Roundy, N., & Johnson, S. C. (2005). Traumatic brain injury and grey matter concentration: A preliminary voxel based morphometry study. *J Neurol Neurosurg Psychiatry, 76*(7), 984-988.

Gale, S. D., Johnson, S. C., Bigler, E. D., & Blatter, D. D. (1995a). Nonspecific white matter degeneration following traumatic brain injury. *J Int Neuropsychol Soc, 1*(1), 17-28.

Gale, S. D., Johnson, S. C., Bigler, E. D., & Blatter, D. D. (1995b). Trauma-induced degenerative changes in brain injury: A morphometric analysis of three patients with preinjury and postinjury MR scans. *Journal of Neurotrauma, 12*(2), 151-158.

Gean, A. D. (Ed.). (1994). *Imaging of head trauma*. New York: Raven.

Gerring, J. P., Brady, K. D., Chen, A., Vasa, R., Grados, M., Bandeen-Roche, K. J., Denckla, M. B. (1998). Premorbid prevalence of ADHD and development of secondary ADHD after closed head injury. *J Am Acad Child Adolesc Psychiatry, 37*(6), 647-654.

Gil, A. M. (2003). Neurocognitive outcomes following pediatric brain injury: A developmental approach. *Journal of School Psychology, 41*, 337-353.

Gioia, G. A., & Isquith, P. K. (2004). Ecological assessment of executive function in traumatic brain injury. *Dev Neuropsychol, 25*(1-2), 135-158.

Gioia, G. A., Isquith, P. K., Guy, S. C., & Kenworthy, L. (2000). Behavior rating inventory of executive function. *Child Neuropsychol, 6*(3), 235-238.

Gogtay, N., Giedd, J. N., Lusk, L., Hayashi, K. M., Greenstein, D., Vaituzis, A. C., …Thompson, P. M. (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *Proc Natl Acad Sci U S A, 101*(21), 8174-8179. doi: 10.1073/pnas.0402680101 [pii]

Goldstein, L. H., Newsom-Davis, I. C., Bryant, V., Brammer, M., Leigh, P. N., & Simmons, A. (2011). Altered patterns of cortical activation in ALS patients during attention and cognitive response inhibition tasks. *J Neurol*.

Hagler, D. J., Jr., Saygin, A. P., & Sereno, M. I. (2006). Smoothing and cluster thresholding for cortical surface-based group analysis of fMRI data. *Neuroimage, 33*(4), 1093-1103.

Han, X., Jovicich, J., Salat, D., van der Kouwe, A., Quinn, B., Czanner, S., …Fischl, B. (2006). Reliability of MRI-derived measurements of human cerebral cortical thickness: The effects of field strength, scanner upgrade and manufacturer. *Neuroimage, 32*(1), 180-194.

Harsan, L. A., Poulet, P., Guignard, B., Steibel, J., Parizel, N., de Sousa, P. L., Ghandour, M. S. (2006). Brain dysmyelination and recovery assessment by noninvasive in vivo diffusion tensor magnetic resonance imaging. *J Neurosci Res, 83*(3), 392-402. doi: 10.1002/jnr.20742

Hester, R., Fassbender, C., & Garavan, H. (2004). Individual differences in error processing: A review and reanalysis of three event-related fMRI studies using the GO/NOGO task. *Cereb Cortex, 14*(9), 986-994.

Jovicich, J., Czanner, S., Greve, D., Haley, E., van der Kouwe, A., Gollub, R., …Dale, A. (2006). Reliability in multi-site structural MRI studies: Effects of gradient non-linearity correction on phantom and human data. *Neuroimage, 30*(2), 436-443.

Kampel, A., Franz, R., Aichner, F., Pfausler, B., Haring, H., Felber, S., Schmutzhard, E. (1998). The persistent vegetative state after closed head injury: Clinical and magnetic resonance imaging findings in 42 patients. *Journal of Neurosurgery, 88*, 809-816.

Kennard, M. A. (1940). Relation of age to motor impairment in man and subhuman primates. *Archives of Neurology & Psychiatry, 43*, 377-397.

Kennard, M. A. (1955). Effect of bilateral ablation of cingulate area on behaviour of cats. *J Neurophysiol, 18*(2), 159-169.

Kochunov, P., Robin, D. A., Royall, D. R., Coyle, T., Lancaster, J., Kochunov, V., …Fox, P. T. (2009). Can structural MRI indices of cerebral integrity track cognitive trends in executive control function during normal maturation and adulthood? *Hum Brain Mapp, 30*(8), 2581-2594. doi: 10.1002/hbm.20689

Kou, Z., Wu, Z., Tong, K. A., Holshouser, B., Benson, R. R., Hu, J., & Haacke, E. M. (2010). The role of advanced MR imaging findings as biomarkers of traumatic brain injury. *J Head Trauma Rehabil, 25*(4), 267-282. doi: 10.1097/HTR.0b013e3181e54793 00001199-201007000-00005 [pii]

Kuperberg, G. R., Broome, M. R., McGuire, P. K., David, A. S., Eddy, M., Ozawa, F., …Fischl, B. (2003). Regionally localized thinning of the cerebral cortex in schizophrenia. *Arch Gen Psychiatry, 60*(9), 878-888.

Langlois, J. A., Rutland-Brown, W., & Thomas, K. E. (2006). *Traumatic brain injury in the United States: Emergency department visits, hospitalizations, and deaths*. Atlanta (GA): Centers for Disease Control and Prevention, National Center for Injury Prevention and Control.

Le Bihan, D., Mangin, J. F., Poupon, C., Clark, C. A., Pappata, S., Molko, N., & Chabriat, H. (2001). Diffusion tensor imaging: Concepts and applications. *J Magn Reson Imaging, 13*(4), 534-546. doi: 10.1002/jmri.1076 [pii]

Levin, H. S., & Hanten, G. (2005). Executive functions after traumatic brain injury in children. *Pediatr Neurol, 33*(2), 79-93.

Levin, H. S., Wilde, E. A., Chu, Z., Yallampalli, R., Hanten, G. R., Li, X., Hunter, J. V. (2008).

Diffusion tensor imaging in relation to cognitive and functional outcome of traumatic brain injury in children. *J Head Trauma Rehabil, 23*(4), 197-208. doi: 10.1097/01.HTR.0000327252.54128.7c00001199-200807000-00002 [pii]

Levine, B., Kovacevic, N., Nica, E. I., Cheung, G., Gao, F., Schwartz, M. L., & Black, S. E. (2008). The Toronto traumatic brain injury study: Injury severity and quantified MRI. *Neurology, 70*(10), 771-778. doi: 70/10/771 [pii] 10.1212/01.wnl.0000304108.32283.aa

Maxwell, W. L., MacKinnon, M. A., Stewart, J. E., & Graham, D. I. (2010). Stereology of cerebral cortex after traumatic brain injury matched to the Glasgow outcome score. [Comparative Study]. *Brain: A journal of neurology, 133*(Pt 1), 139-160.

Merkley, T. L., Bigler, E. D., Wilde, E. A., McCauley, S. R., Hunter, J. V., & Levin, H. S. (2008). Diffuse changes in cortical thickness in pediatric moderate-to-severe traumatic brain injury. *J Neurotrauma, 25*(11), 1343-1345.

Meyer, A. A. (1998). Death and disability from injury: A global challenge. *J Trauma, 44*(1), 1-12.

Mortamet, B., Bernstein, M. A., Jack, C. R., Jr., Gunter, J. L., Ward, C., Britson, P. J., …Krueger, G. (2009). Automatic quality assessment in structural brain magnetic resonance imaging. [Research Support, N.I.H., Extramural]. *Magnetic resonance in medicine: Official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine, 62*(2), 365-372. doi: 10.1002/mrm.21992

Pierce, J. E., Smith, D. H., Trojanowski, J. Q., & McIntosh, T. K. (1998). Enduring cognitive, neurobehavioral and histopathological changes persist for up to one year following severe experimental brain injury in rats. *Neuroscience, 87*(2), 359-369.

Ridderinkhof, K. R., Ullsperger, M., Crone, E. A., & Nieuwenhuis, S. (2004). The role of the medial frontal cortex in cognitive control. [Research Support, Non-U.S. Gov't Review]. *Science, 306*(5695), 443-447.

Rosas, H. D., Liu, A. K., Hersch, S., Glessner, M., Ferrante, R. J., Salat, D. H., …Fischl, B. (2002). Regional and progressive thinning of the cortical ribbon in Huntington's disease. *Neurology, 58*(5), 695-701.

Rutland-Brown, W., Langlois, J. A., Thomas, K. E., & Xi, Y. L. (2006). Incidence of traumatic brain injury in the United States, 2003. *The Journal of head trauma rehabilitation, 21*(6), 544-548.

Sabet, A. A., Christoforou, E., Zatlin, B., Genin, G. M., & Bayly, P. V. (2008). Deformation of the human brain induced by mild angular head acceleration. *J Biomech, 41*(2), 307-315.

Salat, D. H., Buckner, R. L., Snyder, A. Z., Greve, D. N., Desikan, R. S., Busa, E., …Fischl, B. (2004). Thinning of the cerebral cortex in aging. *Cereb Cortex, 14*(7), 721-730.

Salat, D. H., Greve, D. N., Pacheco, J. L., Quinn, B. T., Helmer, K. G., Buckner, R. L., & Fischl, B. (2009). Regional white matter volume differences in nondemented aging and Alzheimer's disease. *Neuroimage, 44*(4), 1247-1258. doi: S1053-8119(08)01124-5 [pii] 10.1016/j.neuroimage.2008.10.030

Schwartz, L., Taylor, H. G., Drotar, D., Yeates, K. O., Wade, S. L., & Stancin, T. (2003). Long-term behavior problems following pediatric traumatic brain injury: Prevalence, predictors, and correlates. *J Pediatr Psychol, 28*(4), 251-263.

Segonne, F., Dale, A. M., Busa, E., Glessner, M., Salat, D., Hahn, H. K., & Fischl, B. (2004). A hybrid approach to the skull stripping problem in MRI. *Neuroimage, 22*(3), 1060-1075.

Segonne, F., Pacheco, J., & Fischl, B. (2007). Geometrically accurate topology-correction of cortical surfaces using nonseparating loops. *IEEE Trans Med Imaging, 26*(4), 518-529.

Sesma, H. W., Slomine, B. S., Ding, R., McCarthy, M. L., & Group, C. s. H. A. T. C. S. (2008). Executive functioning in the first year after pediatric traumatic brain injury. *Pediatrics, 121*, e1686-e1695.

Shaw, P., Kabani, N. J., Lerch, J. P., Eckstrand, K., Lenroot, R., Gogtay, N., Wise, S. P. (2008). Neurodevelopmental trajectories of the human cerebral cortex. *J Neurosci, 28*(14), 3586-3594. doi: 28/14/3586 [pii]10.1523/JNEUROSCI.5309-07.2008

Sidaros, A., Skimminge, A., Liptrot, M. G., Sidaros, K., Engberg, A. W., Herning, M., …Rostrup, E. (2009). Long-term global and regional brain volume changes following severe traumatic brain injury: A longitudinal study with clinical correlates. *Neuroimage, 44*(1), 1-8. doi: S1053-8119(08)00942-7 [pii]10.1016/j.neuroimage.2008.08.030

Sled, J. G., Zijdenbos, A. P., & Evans, A. C. (1998). A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Trans Med Imaging, 17*(1), 87-97.

Smith, D. H., Meaney, D. F., & Shull, W. H. (2003). Diffuse axonal injury in head trauma. *J Head Trauma Rehabil, 18*(4), 307-316.

Sookplung, P., & Vavilala, M. S. (2009). What is new in pediatric traumatic brain injury? *Curr Opin Anaesthesiol, 22*(5), 572-578.

Taylor, H. G., Yeates, K. O., Wade, S. L., Drotar, D., Stancin, T., & Minich, N. (2002). A prospective study of short-and long-term outcomes after traumatic brain injury in children: Behavior and achievement. *Neuropsychology, 16*, 15-27.

Taylor, S. F., Stern, E. R., & Gehring, W. J. (2007). Neural systems for error monitoring: Recent findings and theoretical perspectives. [Research Support, N.I.H., Extramural Review]. *The Neuroscientist: A review journal bringing neurobiology, neurology and psychiatry, 13*(2), 160-172.

Teasdale, G., & Jennett, B. (1974). Assessment of coma and impaired consciousness. A practical scale. *Lancet, 2*(7872), 81-84.

Thomsen, T., Specht, K., Ersland, L., & Hugdahl, K. (2005). Processing of conflicting cues in an attention-shift paradigm studied with fMRI. *Neurosci Lett, 380*(1-2), 138-142.

Tournier, J. D., Mori, S., & Leemans, A. (2011). Diffusion tensor imaging and beyond. [Research Support, N.I.H., Extramural Review]. *Magnetic resonance in medicine: Official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine, 65*(6), 1532-1556.

Tow, P. M., & Whitty, C. W. (1953). Personality changes after operations on the cingulate gyrus in man. *J Neurol Neurosurg Psychiatry, 16*(3), 186-193.

Vakil, E., Weisz, H., Jedwab, L., Groswasser, Z., & Aberbuch, S. (1995). Stroop color-word task as a measure of selective attention: Efficiency in closed-head-injured patients. *J Clin Exp Neuropsychol, 17*(3), 335-342.

Vitale, J. E., Newman, J. P., Bates, J. E., Goodnight, J., Dodge, K. A., & Pettit, G. S. (2005). Deficient behavioral inhibition and anomalous selective attention in a community sample of adolescents with psychopathic traits and low-anxiety traits. *J Abnorm Child Psychol, 33*(4), 461-470.

Wilde, E. A., Hunter, J. V., Newsome, M. R., Scheibel, R. S., Bigler, E. D., Johnson, J. L., …Levin, H. S. (2005). Frontal and temporal morphometric findings on MRI in children

after moderate to severe traumatic brain injury. *J Neurotrauma, 22*(3), 333-344. doi: 10.1089/neu.2005.22.333

Yount, R., Raschke, K. A., Biru, M., Tate, D. F., Miller, M. J., Abildskov, T., …Bigler, E. D. (2002). Traumatic brain injury and atrophy of the cingulate gyrus. *J Neuropsychiatry Clin Neurosci, 14*(4), 416-423.