Int. J. Devl Neuroscience 30 (2012) 267–276

Contents lists available at SciVerse ScienceDirect

International Journal of Developmental Neuroscience

journal homepage: www.elsevier.com/locate/ijdevneu

Longitudinal changes in cortical thickness in children after traumatic brain injury and their relation to behavioral regulation and emotional control

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ARTICLE INFO

Article history:
Received 13 September 2011
Received in revised form 4 January 2012
Accepted 4 January 2012

Keywords:
Traumatic brain injury
Child
Imaging
Volumetrics
Longitudinal
Behavior
Emotion
Frontal lobes
Cortical thickness

ABSTRACT

The purpose of this study was to assess patterns of cortical development over time in children who had sustained traumatic brain injury (TBI) as compared to children with orthopedic injury (OI), and to examine how these patterns related to emotional control and behavioral dysregulation, two common post-TBI symptoms. Cortical thickness was measured at approximately 3 and 18 months post-injury in 20 children aged 8.2–17.5 years who had sustained moderate-to-severe closed head injury and 21 children aged 7.4–16.7 years who had sustained OI. At approximately 3 months post-injury, the TBI group evidenced decreased cortical thickness bilaterally in aspects of the superior frontal, dorsolateral frontal, orbital frontal, and anterior cingulate regions compared to the control cohort, areas of anticipated vulnerability to TBI-induced change. At 18 months post-injury, some of the regions previously evident at 3 months post-injury remained significantly decreased in the TBI group, including bilateral frontal, fusiform, and lingual regions. Additional regions of significant cortical thinning emerged at this time interval (bilateral frontal regions and fusiform gyrus and left parietal regions). However, differences in other regions appeared attenuated (no longer areas of significant cortical thinning) by 18 months post-injury including large bilateral regions of the medial aspects of the frontal lobes and anterior cingulate. Cortical thinning within the OI group was evident over time in dorsolateral frontal and temporal regions bilaterally and aspects of the left medial frontal and precuneus, and right inferior parietal regions. Longitudinal analyses within the TBI group revealed decreases in cortical thickness over time in numerous aspects throughout the right and left cortical surface, but with notable "sparing" of the right and left frontal and temporal poles, the medial aspects of both the frontal lobes, the left fusiform gyrus, and the cingulate bilaterally. An analysis of longitudinal changes in cortical thickness over time (18 months–3 months) in the TBI versus OI group demonstrated regions of relative cortical thinning in the TBI group in bilateral superior parietal and right paracentral regions, but relative cortical thickness increases in aspects of the medial orbital frontal lobes and bilateral cingulate and in the right lateral orbital frontal lobe. Finally, findings from analyses correlating the longitudinal cortical thickness changes in TBI with symptom report on the Emotional Control subscale of the Behavior Rating Inventory of Executive Function (BRIEF) demonstrated a region of significant correlation in the right medial frontal and right anterior cingulate gyrus. A region of significant correlation between the longitudinal cortical thickness changes in the TBI group and symptom report on the Behavioral Regulation Index was also seen in the medial aspect of the left frontal lobe.

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doi:10.1016/j.ijdevneu.2012.01.003

Longitudinal analyses of cortical thickness highlight an important deviation from the expected pattern of developmental change in children and adolescents with TBI, particularly in the medial frontal lobes, where typical patterns of thinning fail to occur over time. Regions which fail to undergo expected cortical thinning in the medial aspects of the frontal lobes correlate with difficulties in emotional control and behavioral regulation, common problems for youth with TBI. Examination of post-TBI brain development in children may be critical to identification of children that may be at risk for persistent problems with executive functioning deficits and the development of interventions to address these issues.

1. Introduction

Traumatic brain injury (TBI) is the leading cause of injury-related morbidity and mortality among children and young adults (Kraus et al., 1990; Thurman et al., 2007). Every year in the United States alone, an estimated half a million children under the age of 14 sustain a TBI (Langlois et al., 2003), and in the 15–19-year old age range, the incidence for TBI-related visits to the emergency department is 757 per 100,000, with 120 per 100,000 hospitalized for these injuries (Faul et al., 2010). The neurocognitive and neurobehavioral morbidity is particularly significant with acquired child brain injury because, at least theoretically, the injury disrupts neural maturation and development (Catroppa et al., 2008). Teasdale and colleagues have shown substantial percentages of disability across all levels of TBI severity, but especially at the moderate-to-severe levels (Whitnall et al., 2006; McMillan et al., 2011).

In addition to various cognitive and social deficits, children who sustain a TBI frequently exhibit significant disruptions in behavioral and emotional functioning (Max et al., 2011). Attention-deficit/hyperactivity disorder (ADHD) is classified as a disruptive behavior disorder and its symptomatology is that of behavioral dysregulation. Lesion correlates have been identified in studies of children and adolescents who have developed ADHD after TBI (Gerring et al., 2000; Herskovits et al., 1999; Max et al., 2005b). Specifically, lesions of the orbital gyrus and basal ganglia have been implicated in the development of ADHD, suggesting that injury to components of the cortico (orbitofrontal)–striatal–pallidal–thalamic loop may increase the likelihood for a child to develop ADHD after TBI. The prototype disorder of emotional control related to pediatric TBI is "Personality change due to TBI" characterized by clinical significant affective lability (Max et al., 2001). Lesion correlates of this disorder include frontal lobe areas, especially the superior frontal gyrus, within the first postinjury year and then frontal white matter injury in the second postinjury year (Max et al., 2005a, 2006). Cole et al. (2008) have also found significant increases in post-injury aggressive behavior in a group of children who had sustained a severe TBI one year earlier. Research using parent report measures of behavioral and emotional functioning indicates continued disruptions in these areas one and even five years after injury (Donders et al., 2010; Gioia and Isquith, 2004; Mangeot et al., 2002; Sesma et al., 2008; Vriezen and Pigott, 2002). Executive deficits can be vexing for rehabilitation professionals as they may detrimentally impact adaptive skills, coping strategies, and functioning within a number of neurocognitive domains and social settings (Cole et al., 2008; Gerring et al., 2009; Krpan et al., 2007; Mangeot et al., 2002).

In addition to behavioral and emotional deficits, several studies involving conventional or advanced imaging methodologies have established that severe TBI in children results in persistent alterations to both white and gray matter (Bigler et al., 2010; Beauchamp et al., 2011; Fearing et al., 2008; Spanos et al., 2007; Wilde et al., 2007, 2006, 2005; Wu et al., 2010; Merkley et al., 2008; McCauley et al., 2010, 2011), but studies addressing the nature and extent of these changes over time are limited (Ewing-Cobbs et al., 2008; Wu et al., 2010). It has been suggested that injury to the developing brain, particularly during critical periods of development, may alter subsequent maturation and impact neurobehavioral and cognitive development (Catroppa and Anderson, 2005; Suskauer and Huisman, 2009), but little is known regarding the long-term structural and functional consequences of TBI sustained in childhood or adolescence. Long-term perturbations in gray and white matter development following pediatric TBI, especially if these changes are centered upon critical frontal structures, are particularly relevant when considering behavioral outcomes as frontal areas are postulated to underlie many facets important in behavioral and emotional control (Powell and Voeller, 2004; Rosso et al., 2004; Wood and Grafman, 2003).

Using MRI-derived measures of cortical thickness, our aim was to determine the location and extent of change to the cortical mantle following moderate to severe TBI in children and adolescents, to examine the nature of any changes that occurred between 3 and 18 months post-injury, and to examine the extent to which structural change in the cortical mantle related to a measure of parent-reported symptoms of behavioral dysregulation and poor emotional control. We hypothesized that TBI would induce damage to cortical gray matter, particularly in injury-vulnerable regions such as the frontal and temporal lobes, resulting in decreased cortical thickness in TBI patients as compared to a demographically similar group of orthopedically injured (OI) children, and that these changes would be apparent at both 3 and 18 months post-injury. We further hypothesized that deleterious changes observed at 3 months would be increased by 18 months given previous reports of continued degenerative change (Blatter et al., 1997) and also the protracted development of the frontal and temporal brain regions (Westlye et al., 2010). However, we also predicted that a complex interaction likely occurs between age of injury, injury severity and brain maturation changes following TBI. Finally, we hypothesized that children with moderate to severe TBI would evidence more symptoms of behavioral dysregulation than their OI counterparts, and that these changes would be related to imaging-derived evidence of change in the frontal lobes.

2. Materials and methods

2.1. Participants

The TBI group was comprised of twenty children (11 male, 9 female) aged 8.2–17.5 years (mean = 13.6 ± 2.9) who had sustained moderate-to-severe closed head injury, as defined by the presence of abnormalities on acute computed tomography (CT) and a lowest post-resuscitation Glasgow Coma Scale (GCS; Teasdale and Jennett, 1974) score recorded in the emergency department between 3 and 8 (severe) or 9 and 12 (moderate) (mean of 7.9 ± 4.0). Based on a recent finding that children exhibiting focal pathology on acute CT, regardless of having GCS scores in the range of 13–15, demonstrate significant long-term cognitive deficits at 12 months post-injury similar to those with lower GCS scores (Levin et al., 2008), we included participants with a "complicated mild" TBI as well. Based on these criteria, the TBI group was comprised of 13 children with severe TBI, 4 children with moderate TBI, and 3 children with complicated mild TBI. Eligibility criteria for TBI patients included a score less than 4 on an Abbreviated Injury Scale (AIS) (Committee on Injury Scaling, 1990) for areas of the body other than the head and absence of post-resuscitation hypoxia or hypotension exceeding 30 min in duration. The modal injury was sustained via motor vehicle accident.

The comparison group comprised 21 children (15 male, 6 female) aged 7.4–16.7 years (mean 12.1 ± 2.5) who had sustained orthopedic injury (OI). In this study, OI was defined as a traumatic bone fracture or other extracranial injury requiring at

Table 1
Demographic and injury characteristics of TBI and OI groups.

	TBI ($n = 20$) Mean (SD)	OI ($n = 21$) Mean (SD)
Age in years (3 M)	13.6 (2.9); range 8.2–17.5	12.1 (2.5); range 7.4–16.7
Age in years (18 M)	14.8 (2.9); range 9.3–18.7	13.2 (2.6); range 8.8–18.0
Months post-injury (3 M)	4.0 ± 1.0	4.7 ± 2.6
Months post-injury (18 M)	18.5 ± 3.6	18.4 ± 4.2
Gender	11 M/9 F	15 M/6 F
Race/ethnicity	6 W/12 H/2 AA	7 W/6 H/8 AA
SCI (z-score)	−0.16 (0.91); range −1.86 to 1.41	0.11 (0.82); range −1.52 to 1.48
Handedness	19 R/1 L	17 R/4 L
Mechanism of injury	8 MVA/4motorcycle/1 RV-ATV/1 bicycle/4 fall/1 hit by motor vehicle/1 other	0 MVA/1 motorcycle/1 RV-ATV/1 bicycle/6 fall/1 hit by falling object/10 sports-play/1 other
GCS score	7.9 (4.0); range 3–15	N/A
ISS	22.6 (11.6); range 9–50	6.0 (2.5); range 4–9

TBI = traumatic brain injury; OI = orthopedic injury; W = White; H = Hispanic; AA = African American; SCI = Socioeconomic Composite Index; MVA = motor vehicle accident; RV-ATV = recreation vehicle or all-terrain vehicle accident; GCS = Glasgow Coma Scale; ISS = Injury Severity Scale.

least an overnight hospitalization provided that the AIS score was 1–3, indicating relatively mild injury. The modal injury for participants in this study was a fracture to an upper or lower extremity. The rationale for an OI comparison group is to control for risk factors (Bijur and Haslum, 1995; Stancin et al., 2001, 1998) that predispose to injury, including preexisting behavioral problems, subtle learning disabilities, and family variables and nonspecific effects of traumatic injury such as stress. The absence of significant previous head trauma in the OI group was confirmed through a detailed developmental questionnaire administered to the parent or legal guardian, and the absence of concurrent head injury was confirmed through medical records and/or physician report of relevant history and physical examination findings and, when available, clinical imaging results (i.e., negative CT).

For both groups, participants were recruited as consecutive admissions to the trauma centers of participating hospitals, generally in the emergency department. All children included in the study were English-speaking, right-handed, had no pre-existing head injury involving loss of consciousness or post-concussive symptoms, neurologic disorder associated with cerebral dysfunction or cognitive deficit (e.g., cerebral palsy, seizure disorder), diagnosed learning disability, psychiatric disorders such as autism or schizophrenia, or history of child abuse. Additionally, inclusion criteria included a minimum birth weight of 2500 g (5 lb, 8 oz) and 37-week gestational age at birth, verified by parent report on a detailed developmental questionnaire. Of the eligible patients that were approached for inclusion in this study (in both groups), an estimated 30–50% at each site agreed to participate. The most frequently stated reasons for declining to participate in the study included time constraints and scheduling difficulties. There was no apparent systematic bias in injury severity or age for subjects who elected to participate versus those who declined participation.

As part of the study design, neuroimaging, outcome and cognitive assessments were planned for three and eighteen months post-injury. Demographic and injury-related characteristics for both groups, including age at injury, race/ethnicity, gender, handedness, socioeconomic status as measured by SCI, time post-injury for both time intervals, injury severity as measured by GCS score, Injury Severity Score (ISS), and mechanism of injury appear in Table 1. Data presented in this report is derived from a larger project investigating the long-term consequences of pediatric TBI (Levin et al., 2011; McCauley et al., 2011, 2010; Oni et al., 2010; Wilde et al., 2011, 2010; Wu et al., 2010).

2.2. MRI acquisition and analysis

All subjects underwent MRI without sedation at Texas Children's Hospital (Houston), the Rogers MRI Center, University of Texas Southwestern Medical Center (Dallas), Jackson Memorial Hospital (Miami) or Miami Children's Hospital (Miami) using similar software release versions and quality assurance protocols.

2.2.1. Volumetric data acquisition

T_1-weighted 3D sagittal acquisition series were performed on Philips Intera 1.5 T whole body scanners (Philips, Cleveland, OH). Parameters included 1.0-mm thick slices, 0 mm slice gaps, echo time (TE) = 4.6 ms, repetition time (TR) = 15 ms, field of view (FOV) = 256, reconstructed FOV = 100%, and a reconstructed voxel size M/P/S (mm) = 1.0/1.0/1.0.

2.2.2. Cortical thickness analysis

Cortical reconstruction was performed with the FreeSurfer image analysis suite version 4.5.0 (Athinoula A. Martinos Center for Biomedical Imaging, 2005). The following details of morphometric processing are extracted from the written description provided at the Freesurfer website, and tailored for the needs of this study. Briefly, the cross-sectional processing was first performed as described in previous publications (Bigler et al., 2010; Merkley et al., 2008). Longitudinal processing was then performed with the longitudinal stream in Freesurfer, where an unbiased within-subject template space and average image (Reuter and Fischl, 2011) was created using robust, inverse consistent registration (Reuter et al., 2010). Information from this subject template was used to initialize the longitudinal image processing to increase repeatability and statistical power. Results for each subject were visually inspected by a single rater to ensure accuracy of the cortical surface reconstruction, and manual editing was performed to optimize accuracy as needed. A customized pediatric average subject was created using the results of children with OI. The data for each participant was resampled to this pediatric average subject and surface smoothing was performed, using a 10 mm full-width half-maximum Gaussian kernel, prior to statistical analysis.

2.3. Socioeconomic Composite Index

The SCI provides a measure of a family's socioeconomic status and has been shown to moderate the effects of severe TBI on long-term outcome (Yeates et al., 1997). The index is calculated by deriving z-scores based on the combined distributions of the OI and TBI groups for three variables including: (1) an 8-point scale rating family income, (2) a 7-point scale of parent/guardian education, and (3) a rating of occupational prestige using the Total Socioeconomic Index (TSEI) (Hauser and Warren, 1999). The z-scores for these variables were summed and standardized (mean = 0, SD = 1) based on the aggregate sample of participants (OI and TBI groups) to form the SCI score.

2.4. Behavioral Rating Inventory of Executive Functioning

We selected simple parent-report measures of behavioral dysregulation and emotional control from the Behavioral Rating Inventory of Executive Functioning (BRIEF). Data for these measures was available for 33 subjects at 18 months post-injury (data was missing for 8 participants on this task, including 3 from the OI group and 5 from the TBI group). Missing data was due to failure to return the questionnaire, or time constraints of the parent or guardian which precluded administration. There did not appear to be any source of systematic bias for the subjects with missing data such as greater injury severity, age difference, and missing data was distributed across the three sites. Variables used in this study were Behavioral Regulation Index (T-score) and Emotional Control subscale (T-score).

2.5. Design and statistical analysis

Demographic and injury severity data were tested using chi-square analysis for gender and race/ethnicity, Fisher's exact test for mechanism of injury, and independent samples t-test for age at testing, time post-injury, and Socioeconomic Composite Index (SCI) score. The Kolmogorov–Smirnov test was used to test for between-group distribution differences. Changes in cortical thickness were assessed by fitting a between-subject general linear model at each surface vertex for (1) cortical thickness differences between groups at each time point separately, (2) longitudinal cortical thickness differences within groups, (3) longitudinal cortical thickness differences between groups and (4) the relation of longitudinal changes in cortical thickness to the BRIEF variables. Statistical parametric maps of the entire cortical mantle were generated to show group differences as well as the relation of cortical thickness to BRIEF variables. The results were displayed on a customized pediatric template that was created using data from the children with OI. A Monte Carlo simulation (Hagler et al., 2006) was used to perform cluster-wise correction for multiple comparisons (vertex-wise threshold of $p < 0.05$, 5000 iterations). Cluster-wise probabilities are reported, which represent the likelihood of finding a maximum cluster that size or larger during simulation.

3. Results

3.1. Demographics

No significant differences were noted in gender composition, SCI score, post-injury interval, or race/ethnicity between the two groups. The OI group was not significantly younger than the TBI group at both 3 months and 18 months post-injury, but the p-values showed marginal significance (0.073 at 3 months, and 0.066 at 18 months for the mean); however, the Kolmogorov–Smirnov test did

not reveal a significant difference for the distribution of age at test between groups at 3 and 18 months ($p = 0.248$). As expected, the TBI group was more frequently injured as a result of high-speed mechanisms of injury, such as motor vehicle crashes (Fisher's exact test, $p < 0.0001$), and also received high ISS scores ($F(18.43) = -5.92$, $p < 0.0001$).

3.2. Group differences in cortical thickness at 3 months post-injury

Differences between the TBI and OI control groups were evident bilaterally in the rostral middle frontal, superior frontal, lateral and medial orbital frontal, anterior cingulate, and frontal pole, as well as in the right pars orbitalis, right pars triangularis and right pars opercularis (all $ps = 0.0001–0.0003$). In each of these regions, decreased cortical thickness was seen in the TBI group.

3.3. Group differences in cortical thickness at 18 months post-injury

By 18 months post-injury, some of the regions evident at 3 months post-injury remained significantly different between groups including bilateral rostral middle frontal ($p = 0.0001$), caudal middle frontal ($p = 0.0001$), fusiform (left $p = 0.0018$, right $p = 0.0001$), and lingual (left $p = 0.0018$, right $p = 0.0001$). New regions of difference (cortical thinning) between the two groups were also apparent at this time interval including the fusiform gyrus bilaterally (left $p = 0.0018$, right $p = 0.0001$). Additional left hemispheric regions of significance included superior frontal ($0.0046 > p > 0.0001$), precentral gyrus ($p = 0.0046$), precuneus ($p = 0.0001$), isthmus cingulate ($p = 0.0001$), superior parietal ($p = 0.0001$), and inferior parietal ($p = 0.0001$). Additional right hemispheric regions of significance were observed for right pars triangularis ($p = 0.0001$), right pars orbitalis ($p = 0.0001$), and right lateral orbital frontal ($p = 0.0001$), all with decreased cortical thickness in the group with TBI. However, differences in other regions appeared attenuated (no longer areas of significant cortical thinning) by 18 months post-injury including large bilateral regions of the medial aspects of the frontal lobes (bilateral medial orbital frontal and anterior cingulate, and right superior frontal). Areas of significant cortical thinning in the children with TBI in relation to those with OI at both 3 and 18 months are depicted in Fig. 1a and b.

3.4. Longitudinal changes in the OI group

Longitudinal changes in cortical thickness within the OI group were evident bilaterally in dorsolateral frontal areas (rostral and caudal middle frontal, $p = 0.0002$), bilateral aspects of superior and inferior temporal gyri ($p = 0.0002$), the medial aspect of the left frontal lobe (superior frontal and anterior cingulate, $p = 0.0004$), the left postcentral gyrus ($p = 0.0004$), the left precuneus and posterior cingulate ($p = 0.01–0.001$), right inferior parietal ($p = 0.0002$), and right superior frontal ($p = 0.0004$). In all cases, these regions evidenced cortical thinning at 18 months in relation to 3 months.

3.5. Longitudinal changes in the TBI group

Longitudinal changes in cortical thickness within the TBI group were evident in numerous aspects throughout the right and left cortical surface ($p = 0.0002$), with notable sparing of the right and left frontal and temporal poles, the medial aspects of both the frontal lobes, the left fusiform gyrus, and the cingulate bilaterally. In all cases, these regions evidenced significant cortical thinning at 18 months in relation to 3 months. Longitudinal changes in cortical thickness for each group are presented in Fig. 2a and b.

3.6. Longitudinal changes in the OI versus TBI group

Finally, an analysis of longitudinal changes in cortical thickness over time (18 months–3 months) in the TBI versus OI group demonstrated regions of relative cortical thinning in the TBI group in superior parietal (left $p = 0.0002$, right $p = 0.0028$) and right paracentral ($p = 0.0016$) regions, but relative cortical thickness increases in aspects of the medial orbital frontal lobes and cingulate (left $p = 0.0002$, right $p = 0.0004$) and in the right lateral orbital frontal lobe ($p = 0.0004$) (see Fig. 3).

3.7. Group differences on BRIEF

The group of children with TBI demonstrated significantly higher scores on both the Behavioral Regulation Index ($t(31) = -2.08$, $p = 0.046$) and the Emotional Control subscale ($t(31) = -2.62$, $p = 0.013$) than the children with OI, indicating a greater number of reported symptoms of problems in these areas at 18 months post-injury.

3.8. Relation of cortical thickness changes to behavioral dysregulation and emotional control

Findings from analyses correlating the longitudinal cortical thickness changes in TBI with symptom report on the Emotional Control subscale of the BRIEF demonstrated a region of significant correlation in the right medial frontal and right anterior cingulate gyrus ($p = 0.0018$) (see Fig. 4a). A region of significant correlation ($p = 0.0002$) between the longitudinal cortical thickness changes in the TBI group and symptom report on the Behavioral Regulation Index was also seen in the medial aspect of the left frontal lobe (see Fig. 4b).

4. Discussion

4.1. Group differences at 3 and 18 months post-injury

Differences between the group with TBI and OI controls were initially most prominent in dorsolateral and medial frontal areas and the right cingulate at 3 months post-injury, consistent with sites of known predilection for TBI-related injury given the bony protuberances of the skull (Wilde et al., 2005; Bigler, 2007; Graham et al., 1989). By 18 months, some of the regions identified at 3 months post-injury evidenced persistent differences in cortical thickness including bilateral rostral and caudal middle frontal, fusiform and lingual areas, left superior frontal, precentral gyrus, precuneus, cingulate, superior and inferior parietal regions, and right dorsolateral (pars triangularis, pars orbitalis, right lateral orbital frontal) regions. There were also new areas of cortical thinning in the TBI group at 18 months, including the fusiform gyrus bilaterally, left superior and inferior parietal regions, left precuneus, left superior/precentral gyrus, and right lingual gyrus. In each instance, decreased cortical thickness was shown in the group with TBI, consistent with previous reports of MRI-derived measures of cortical thinning in children with TBI (Merkley et al., 2008; McCauley et al., 2010), and at the histological level, with demonstrated thinning of the cortical mantle which reflects trauma-induced neuronal loss (Maxwell et al., 2010).

In addition to regions of persistent and progressive cortical thinning between groups, differences in other brain regions appeared attenuated (no longer areas of significant decrease in cortical thickness) by 18 months post-injury including large bilateral regions of the medial aspects of the frontal lobes (bilateral medial orbital

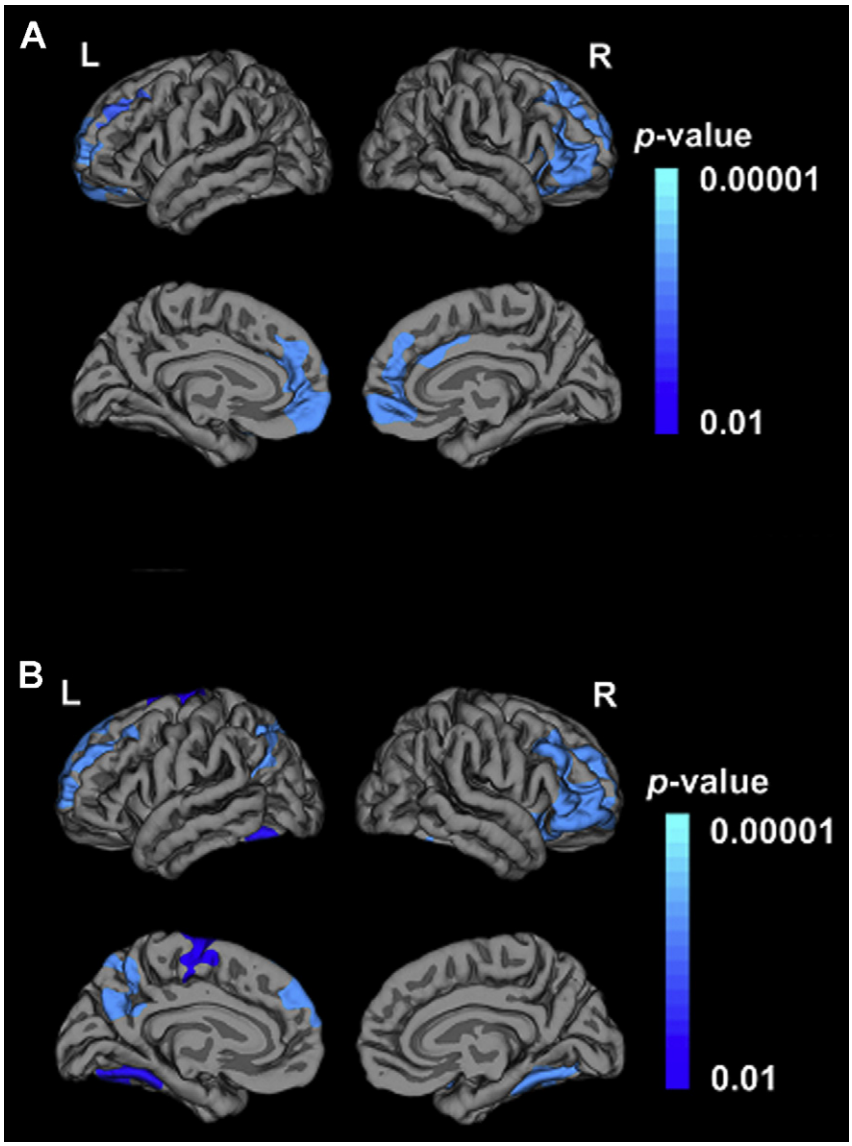

Fig. 1. Between-group cortical thickness differences at 3 months (A) and 18 months (B) post-injury. Blue regions indicate significantly thinner cerebral cortex in the traumatic brain injury (TBI) group. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

frontal and anterior cingulate, and right superior frontal). At least two primary explanations exist. The first explanation invokes the concept of plasticity and adaption whereby children who have experienced TBI early in the course of development may subsequently undergo adaptive developmental changes that ameliorate earlier injury-related effects to gray matter, such that initial injury is no longer as evident later in the course of recovery (Max et al., 2010). Such plasticity has been presumed to occur via mechanisms such as the development of new cortical-to-cortical anastomoses. The alternative explanation is significantly more complex and implicates a fundamental alteration in the pattern of the post-injury developmental trajectory in children who experience TBI. This line of reasoning suggests that the between group differences only appear to have been ameliorated, but are in fact, based on the assumption that cortical thinning is solely injury-induced and/or deleterious. However, neuronal pruning occurs throughout childhood, where some reduction is the norm for typical, non-injured brain development (Jernigan et al., 2011; Landing et al., 2002; Giorgio et al., 2010). In TBI, there is likely an interaction between what would be developmentally programmed apoptosis (Stiles and Jernigan, 2010) and what would be trauma-induced decreases in cortical neurons (Robertson et al., 2009). To address the complexity of this alternative explanation, careful examination of the within-groups effects was required.

4.2. Longitudinal changes in the OI group

Our findings of longitudinal changes within the OI control group alone revealed areas of significant cortical thinning over the 3–18-month post-injury interval in the dorsolateral frontal, parietal, and temporal regions. These findings are consistent with previously reported longitudinal developmental changes in cortical thickness and other related measures such as cortical volume and surface area (Jernigan et al., 2011), where cortical changes generally follow an inverted U-shaped trajectory over childhood and adolescence. In these studies, cortical thinning appears first in primary sensorimotor areas and is latest in higher order association areas including dorsolateral prefrontal cortex, inferior parietal areas and superior temporal gyrus (Gogtay et al., 2004). Age-related changes have been shown to be particularly prominent in measures of cortical thickness in relation to other MRI-based measures such as cortical volume or cortical surface areas between the ages of 8–22

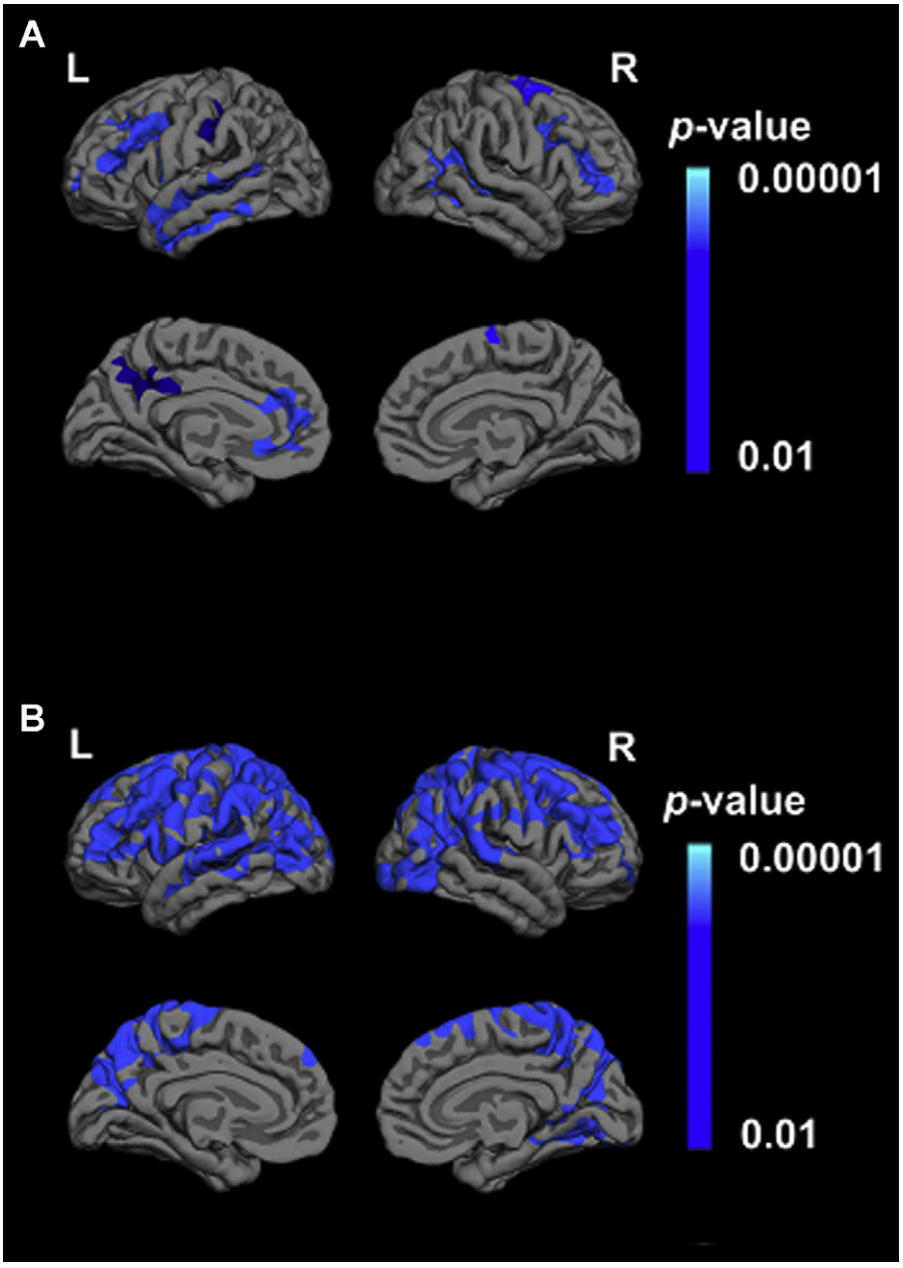

Fig. 2. Within-group longitudinal reductions in cerebral cortex for groups with orthopedic injury (OI; A) and traumatic brain injury (TBI; B) at the 18-month post-injury interval as compared to 3-month assessment.

years (Raznahan et al., 2011). Such changes in cortical gray matter have been presumed to be related to synaptic proliferation and pruning during childhood and adolescence as demonstrated in postmortem studies (Huttenlocher, 1994) and also supported by an MRI/quantified EEG study of older children, adolescents and young adults that found a curvilinear reduction in EEG signals presumably reflecting synaptic activity in frontal and parietal gray matter regions (Whitford et al., 2007). However, Sowell et al. (2001) have also cautioned that the developmental pattern of gray matter loss observed in MRI-derived studies may be influenced by myelination of small axons at the interior aspect of the cortical border which may reflect a technical limitation of MRI resolution and post-processing, i.e., the reclassification of voxels as gray matter to white matter, rather than being solely attributable to changes in cortical thickness per se.

4.3. Longitudinal changes in the TBI group

Examination of longitudinal changes in cortical thickness in the TBI group revealed numerous regions of significant cortical thinning covering large areas of dorsolateral frontal regions and the parietal and occipital lobes. The progression of TBI-induced atrophic change in the cortical mantle between 3 and 18 months is not wholly unexpected, and is consistent with other studies in both animals (Liu et al., 2010) and humans (Porto et al., 2011). These changes have been presumed to be related directly to neuronal loss demonstrated at post-mortem (Maxwell et al., 2010).

Surprisingly, despite evidence for widespread progressive decreases in cortical thickness over time, evidence for significant progressive cortical thinning in the medial frontal, temporal, and cingulate areas was notably absent in the group of children with TBI.

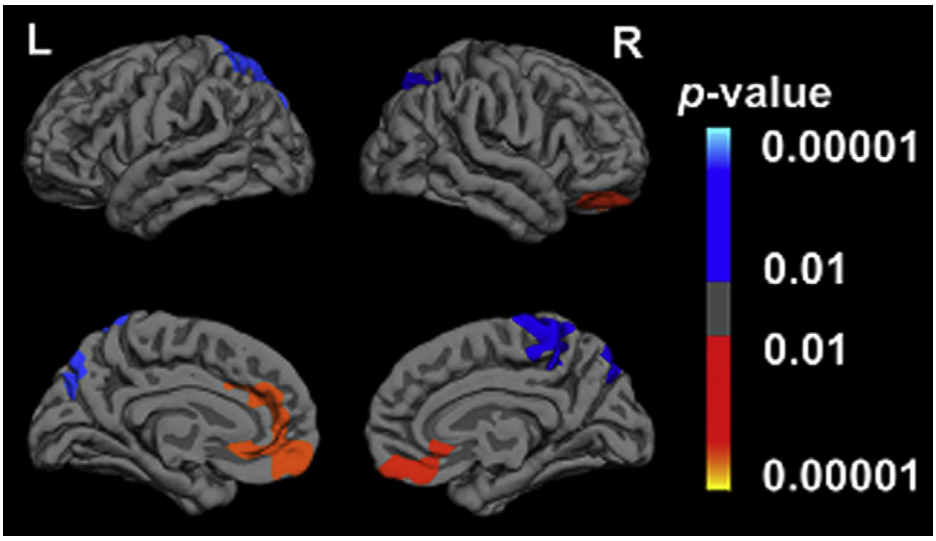

Fig. 3. Between-group longitudinal changes in cortical thickness. Blue regions indicate relative cortical thinning, and red-orange regions indicate relative cortical increase in the traumatic brain injury (TBI) group over the 3-month to 18-month post-injury time interval. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

This was unexpected given the previous demonstration of areas of significant cortical thinning in the frontal regions in the between groups analyses, and particularly the 3 months post-injury group difference analysis. We had hypothesized that cortical changes would be progressive, particularly in areas most injured as a result of TBI. However, this hypothesis was not supported, and, in fact, changes occurred within regions such as the frontal lobes where progressive cortical thinning was almost absent. A possible explanation is that injury alters programmed apoptosis. If injury altered the internal signaling to initiate apoptosis, the observed lack of cortical thinning in frontal cortex might represent a failure of programmed cell death to occur at the developmentally typical stage. In effect, this would appear as greater thickness in the TBI group, because in these regions, the control group would be undergoing programmed pruning and expected reductions in gray matter. Most of what is known about the interaction of cortical development and apoptosis comes from the animal literature (Kim and Sun, 2011), but the above speculation would also be consistent with theories of brain adaptation known to occur with neonatal insults (Ferriero and Miller, 2010).

4.4. Longitudinal changes in the TBI versus OI group

Analyses of longitudinal changes between the groups confirmed this pattern, such that areas of relative cortical thickness increase were evident in the ventromedial and medial aspects of the frontal lobes and portions of the cingulate in TBI as compared to OI groups. Given the combined findings of the longitudinal changes in the OI and TBI groups, we interpret this relative increase in cortical thickness as a failure to undergo normally expected developmental cortical thinning. Gray matter changes are likely influenced by reciprocal connections among neurons, glial cells, inter-neuronal spacing and myelin, all of which may be altered as a result of TBI (Adams et al., 2011; Browne et al., 2011) and these altered connections may lead to behavioral and emotional complications (Goodman, 1989). From a developmental perspective, the cerebral regions that are most vulnerable to primary damage are also those which are developing throughout childhood, with implications for further adverse functional outcomes of pediatric TBI due to abnormal trajectories of brain development. Whether TBI merely delays the timing of normal cortical developmental thinning or more fundamentally disrupts its course remains unknown.

4.5. Relation of cortical thickness changes to behavioral dysregulation and emotional control

Analyses of the relation between longitudinal changes in cortical thickness and increased symptoms of behavioral dysregulation demonstrated regions of correlation in the medial aspect of the left frontal lobe, the region which was identified in the longitudinal group difference analyses as a region failing to undergo significant cortical thinning. Additionally, analysis of the Emotional Control subscale of the BRIEF in relation to longitudinal changes in cortical thickness revealed significant overlap between an increased number of symptoms and failure to undergo cortical thinning in the right medial frontal and right anterior cingulate gyrus.

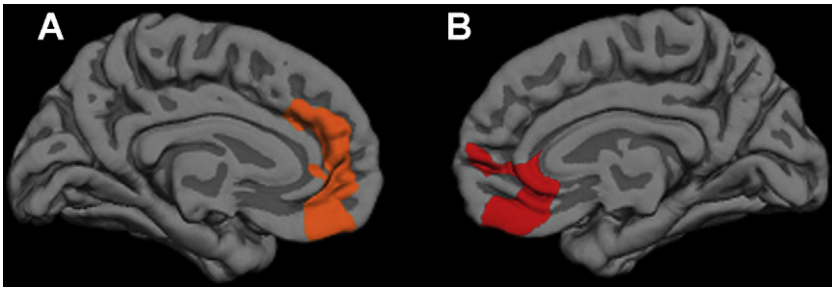

Fig. 4. Positive correlations between longitudinal cortical thickness change and the Behavioral Rating Inventory of Executive Functioning (BRIEF) Behavioral Regulation Index (BRI) (A, $p = 0.0002$) and BRIEF Emotional Control subscale (B, $p = 0.0018$) in the traumatic brain injury (TBI) group.

Parenchymal changes may underlie cognitive abilities and behavior subserved by the frontal lobes, such as emotional control and behavioral regulation. Max et al. has reported the association of frontal lesion findings related to "Personality change due to TBI," the quintessential brain-injury related disorder of emotional control (Max et al., 2005a, 2006). The current findings align well in that frontal gray matter lesions are associated with emotional dyscontrol in the first year and frontal white matter damage (the presumed reason for early postinjury frontal cortical thinning and later maladaptive reduction in pruning) in the second year post TBI. Furthermore, a disorder of behavioral regulation such as ADHD has also been associated with frontal lobe damage (Gerring et al., 2000; Herskovits et al., 1999; Max et al., 2005b). Anderson et al. (2002) reported that children with observable frontal lobe lesions exhibited elevated BRIEF scores compared to healthy children or to children with more diffuse developmental injuries. Similarly, Wozniak et al. (2007) reported a relationship between reduced frontal fractional anisotropy and parent-reported executive dysfunction on the BRIEF in a group of children sustaining either a mild or moderate TBI. In a recent study, Zappala et al. (2011) demonstrated a direct relationship between the clinical manifestations of a TBI and disruption of frontal white matter tracts.

4.6. Limitations and future directions

Our study represents the first to specifically examine longitudinal changes in the cortical thickness of children with TBI. Strengths of the study include its prospective design with imaging performed at a generally uniform post-injury interval, and a comparison group of children with orthopedic injury. Limitations of the study include heterogeneity in injury severity and the location, extent and nature of focal pathology, and the relatively small sample size. An additional limitation involves the potential influence of age in the group comparisons. While the groups did not technically differ in terms of mean age or distribution of age, it should be noted that the difference in mean age was marginally significant, with the mean age of TBI group being slightly higher than the OI group. In the current report, we included all subjects with complete imaging data of sufficient quality for both 3 and 18 month imaging occasions (i.e., no missing imaging data) that were between the ages of 8 and 17 years. Since developmental changes were of primary interest, we elected not to include age as a covariate in the model as this would potentially eliminate some of the expected age-related change we were attempting to examine. However, we do acknowledge that the marginal differences between groups in terms of mean age or the precise distribution of age within each group could also contribute to our findings. Ideally, future studies would examine the impact of TBI in a true longitudinal design with stratification by age. We also acknowledge the significant individual heterogeneity present in brain regional measurements, and the presumed influence of gender, which we could not adequately examine with this sample size. We also acknowledge the limitations of parent-report measures of symptoms of emotional control and behavioral regulation, and the possible role of factors such as parenting style and family functioning in the residual problems with executive functioning manifested by some children with TBI (Potter et al., 2011).

Future studies may include examining the impact of changes in the cortical mantle and their relation to additional standardized and functional cognitive outcome measures and emotional functioning measures. The persistence, timing, and pattern of cortical changes over a longer post-injury interval that may be influenced by injury (in TBI) and developmental factors in both TBI and comparison groups will also be explored in future longitudinal studies.

5. Conclusion

Our findings suggest that changes in cortical gray matter are complex. Injury-induced cortical thinning is evident at 3 and 18 months post-injury, particularly in areas of known vulnerability to TBI such as the frontal and temporal lobes. However, injury-induced changes at more chronic intervals, such as 18 months post-injury and longer, may be masked by the developmentally based cortical thinning which is also occurring during development in children aged 8–17 years in similar areas, rendering the overall difference between groups and also the relation with cognitive or functional measures less obvious or straightforward at these later intervals. At present, it is still unknown whether lack of cortical thinning in the frontal and temporal lobes over time represents a structurally adaptive change or whether this represents failure to undergo expected developmental cortical thinning, which is actually maladaptive in terms of function. In our study, greater cortical thickness (presumably caused by failure to undergo normal cortical thinning) was associated with greater symptom severity on measures of emotional control and behavioral regulation, lending support to the notion that such changes in the developmental trajectory may be deleterious.

The current investigation demonstrates that the quantitative neuroimaging methods measuring cortical thickness are sensitive in detecting pathological as well as developmental changes in gray matter in children with TBI. The current study is one of but a handful that have used these advanced image analysis methods to examine longitudinal changes in child TBI and application of these methods hold great promise of developing a better understanding of the neurobehavioral adaptions that occur in the developing child with TBI. A potential clinical application of these findings would be that by monitoring gray matter growth trajectories following injury may become predictive of the intellectual and executive functioning deficits known to occur in child TBI (Anderson et al., 2011; Beauchamp et al., 2011). Advanced neuroimaging techniques such as those applied in this study are rapidly evolving and the full extent of potential clinical application of these findings is unknown at this time. Future studies confirming that TBI induces persistent changes in the subsequent development of the cortical mantle in children and adolescents, and pinpointing specific periods of vulnerability for these changes, may enable clinicians to better identify children who are at risk for developing specific cognitive or emotional difficulties (see also Max et al., 2011). Additionally, a better understanding of the long-term developmental consequences of TBI may have implications for the timing of treatment initiation in addition to the duration, intensity, and modality of therapeutic interventions in rehabilitation with children during critical stages of brain development.

Conflict of interest

None of the authors have any financial or other relationship(s) that could be construed as a conflict of interest with respect to the content of this manuscript. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Acknowledgments

This work was supported by the National Institute Neurological Disorders and Stroke grant R01-NS21889 ("Neurobehavioral outcome of head injury in children," Levin, PI). We also acknowledge the generous contribution of Mission Connect of the TIRR Foundation. We gratefully acknowledge the contribution of Ana C. Vasquez, Deleene Menefee, PhD., Summer Lane, Lori Cook, Sandra

B. Chapman, Ph.D., and Gillian Hotz, Ph.D. in data collection, and Joshua Cooper and Ragini Yallampalli in manuscript preparation. We thank the participants and their families for their participation in this research.

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