

# Prospective Study of Gray Matter Atrophy Following Pediatric Mild Traumatic Brain Injury

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## Abstract

### Background and Objectives

The clinical and physiologic time course for recovery following pediatric mild traumatic brain injury (pmTBI) remains actively debated. The primary objective of the current study was to prospectively examine structural brain changes (cortical thickness and subcortical volumes) and age-at-injury effects. A priori study hypotheses predicted reduced cortical thickness and hippocampal volumes up to 4 months postinjury, which would be inversely associated with age at injury.

### Methods

Prospective cohort study design with consecutive recruitment. Study inclusion adapted from American Congress of Rehabilitation Medicine (upper threshold) and Zurich Concussion in Sport Group (minimal threshold) and diagnosed by Emergency Department and Urgent Care clinicians. Major neurologic, psychiatric, or developmental disorders were exclusionary. Clinical (Common Data Element) and structural (3 T MRI) evaluations within 11 days (subacute visit [SA]) and at 4 months (early chronic visit [EC]) postinjury. Age- and sex-matched healthy controls (HC) to control for repeat testing/neurodevelopment. Clinical outcomes based on self-report and cognitive testing. Structural images quantified with FreeSurfer (version 7.1.1).

### Results

A total of 208 patients with pmTBI (age =  $14.4 \pm 2.9$ ; 40.4% female) and 176 HC (age =  $14.2 \pm 2.9$ ; 42.0% female) were included in the final analyses (>80% retention). Reduced cortical thickness (right rostral middle frontal gyrus;  $d = -0.49$ ) and hippocampal volumes ( $d = -0.24$ ) observed for pmTBI, but not associated with age at injury. Hippocampal volume recovery was mediated by loss of consciousness/posttraumatic amnesia. Significantly greater postconcussive symptoms and cognitive deficits were observed at SA and EC visits, but were not associated with the structural abnormalities. Structural abnormalities slightly improved balanced classification accuracy above and beyond clinical gold standards ( $\Delta+3.9\%$ ), with a greater increase in specificity ( $\Delta+7.5\%$ ) relative to sensitivity ( $\Delta+0.3\%$ ).

### Discussion

Current findings indicate that structural brain abnormalities may persist up to 4 months post-pmTBI and are partially mediated by initial markers of injury severity. These results contribute to a growing body of evidence suggesting prolonged physiologic recovery post-pmTBI. In contrast, there was no evidence for age-at-injury effects or physiologic correlates of persistent symptoms in our sample.

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## Glossary

AFNI = Analysis of Functional NeuroImages; EC = early chronic; GEE = generalized estimating equation; GM = gray matter; HC = healthy controls; LOC = loss of consciousness; PCS = postconcussive symptoms; PCSI = Post-Concussion Symptom Inventory; pmTBI = pediatric mild traumatic brain injury; PPCS = persistent PCS; PTA = posttraumatic amnesia; ROI = region of interest; SA = subacute.

Pediatric mild traumatic brain injury (pmTBI; used synonymously herein with concussion) is a major public health concern that negatively affects hundreds of thousands of children each year in terms of quality of life, normal development, and social and cognitive functioning.<sup>1</sup> Emerging biomarker evidence suggests multifaceted pathologies following pmTBI that evolve over different timescales.<sup>2-4</sup> Macroscopic changes in gray matter (GM; volume or cortical thickness) have been reported in some but not all adult mTBI studies, potentially reflective of atrophy or cortical reorganization. Deep GM structures may be particularly sensitive to the effects of mTBI due to the accumulation of shear strain forces in these regions,<sup>5</sup> with the potential of increased adverse effects for hippocampi due to the spatial proximity of large, fluid-filled cavities (temporal horn).<sup>6</sup> Two studies have prospectively assessed changes in GM following pmTBI,<sup>7,8</sup> while others examined the potential effect of acute injury severity characteristics<sup>9,10</sup> or age-at-injury effects<sup>11</sup> on the expression of structural pathology.

The spectrum of TBI is renowned for heterogeneity both in terms of pathology and clinical presentation. Patients present with varying degrees of loss of consciousness [LOC], posttraumatic amnesia [PTA], and self-reported symptoms. These are then used to diagnose concussion, the presence of persistent postconcussive symptoms (PPCS), and even grade injury severity based on various expert consensus panel criteria.<sup>12,13</sup> For example, approximately 20%–35% of patients with pmTBI experience PPCS, and there is great interest in identifying the physiologic underpinnings of prolonged recovery.<sup>1,2,14</sup> However, self-reported postconcussive symptoms (PCS) temporally fluctuate in both patients with pmTBI and healthy controls (HC),<sup>15,16</sup> which may decrease prediction ability for more objective injury markers. Similarly, LOC and PTA have traditionally not been predictive of subjective symptom resolution post-mTBI,<sup>17,18</sup> but 2 recent studies independently replicated a dose-dependent relationship between LOC/PTA and glial fibrillary acidic protein levels in blood following sport-related concussion.<sup>9,10</sup>

Complicating matters further, there is also a need to disentangle the effects of injury on brain morphometry from the known reorganization of GM that occurs through typical neurodevelopment from middle childhood through adolescence.<sup>19,20</sup> Preclinical data suggest that age at injury could moderate potential effects of pmTBI due to either age-related differences in plasticity or by adversely affecting

critical periods of development.<sup>21</sup> One study investigating the effect of age at injury on GM atrophy in a mixed injury severity sample reported both decreased injury severity and prolonged recovery for adolescents relative to younger children.<sup>11</sup>

The primary objective of the current study was therefore to determine whether pmTBI resulted in macroscopic changes in GM as a function of age at injury, potentially due to either neurodegeneration or altered neurodevelopmental trajectories. A total of 208 patients with pmTBI (age 8–18) and 176 age- and sex-matched HC were studied in a prospective cohort design. Patients were assessed at subacute (SA: within 11 days postinjury) and early chronic (EC: 4 months postinjury) injury phases. Based on previous work, it was hypothesized that pmTBI would exhibit reduced cortical thickness and hippocampal volume. It was also predicted that more objective injury severity characteristics (LOC and/or PTA) would be associated with cortical thickness changes and hippocampal volume loss, whereas null findings would be observed for total PPCS burden. Finally, we predicted that age at injury would be inversely associated with both clinical recovery<sup>1</sup> and volume loss.<sup>11</sup>

## Methods

### Participants

Patients with pmTBI (age 8–18 years) were consecutively recruited from local emergency department and urgent care settings between July 2016 and February 2020 as part of an ongoing study. Enrollment criteria included a closed head injury with Glasgow Coma Score  $\geq 13$ , LOC (if present) limited to 30 minutes, PTA (if present) limited to 24 hours, alteration in mental status at the time of injury, or at least 2 new PCSs. Inclusion criteria therefore represented a blend of the American Congress of Rehabilitation Medicine (upper injury limit threshold) and the Zurich Concussion in Sport Group (minimal criteria threshold). Age- and sex-matched HC, recruited through flyers posted in high foot traffic areas, staffing of community events, and word-of-mouth from existing participants (including pmTBI sibling recruitment), underwent identical assessments at similar time intervals to control for neurodevelopmental confounds and/or effects associated with repeat assessment.

Participants from both groups were excluded based on the history of (1) previous TBI with greater than 30-minute LOC, (2) any neurologic diagnosis, (3) any psychiatric disorders

other than adjustment disorder, (4) developmental disorders (autism spectrum disorder or intellectual disability), (5) history of substance abuse/dependence, (6) contraindications for MRI including pregnancy, or (7) non-English speaking. Patients with braces were included as part of a nonquantitative study on radiologic common data elements,<sup>22</sup> but were excluded from the current study due to MRI artifacts. Patients with pmTBI were excluded if injury affected the dominant hand or if general anesthesia was administered immediately postinjury for a surgical indication. HC were also excluded for diagnosis of attention-deficit/hyperactivity disorder or a learning disability. A positive urine drug screen (see eMethods, [links.lww.com/WNL/C525](https://links.lww.com/WNL/C525)) also resulted in exclusion.

## Clinical Assessments

A Common Data Elements battery of tests was administered at SA/EC visits along with retrospective ratings (see eMethods and eTable 1, [links.lww.com/WNL/C525](https://links.lww.com/WNL/C525), for status as primary vs secondary outcomes). This included a modified version of the 5P risk score (see eMethods) and a semistructured pediatric interview to ascertain previous history of TBI.<sup>23</sup> The Post-Concussion Symptom Inventory (PCSI; see eMethods), Conflict and Behavioral Questionnaire, and the Pediatric Quality of Life Inventory were selected as primary clinical outcome measures. Symptomatic vs asymptomatic PCS status was calculated based on HC data.<sup>16</sup> Secondary measures consisted of scales from the Patient-Reported Outcomes Measurement Information System (sleep, anxiety, and depression), self-report pain and headache ratings, Glasgow Outcome Scale Extended, and parent-reported Strengths and Difficulties Questionnaire. Parental distress was measured with the Brief Symptom Inventory-18. A battery of neuropsychological tests was also administered to determine potential cognitive deficits in attention, processing speed, working memory, executive functioning, and long-term memory recall and to estimate reading ability and effort (see eMethods).

## Image Acquisition

High-resolution T<sub>1</sub>-weighted (voxel size = 1.0 mm<sup>3</sup>), T<sub>2</sub>-weighted (voxel size = 1.15 × 1.15 × 1.5 mm), susceptibility-weighted (voxel size = 1.0 × 1.0 × 1.5 mm), and fluid-attenuated inversion recovery (voxel size = 0.8 × 0.8 × 3 mm) images were collected on a Siemens 3 T TrioTim scanner with a 32-channel head coil (see eMethods for full sequence details, [links.lww.com/WNL/C525](https://links.lww.com/WNL/C525)). All MRIs were reviewed by a board-certified neuroradiologist blinded to participant group. A subset of patients with pmTBI (N = 99) received CT scans as part of routine care in the hospital.

The FreeSurfer (version 7.1.1) package was used to generate individual cortical thickness surface maps and regions of interest (ROI) volumes using standard segmentation labels.<sup>24</sup> Cortical thickness maps were transformed to the FreeSurfer average template (fsaverage) and spatially smoothed using a 10-mm full-width at half-maximum Gaussian kernel. Primary ROI included the bilateral hippocampi, whereas secondary subcortical regions included the nuclei accumbens, the amygdalae, the thalami, the pallida, the putamina, and the caudate nuclei.

## Statistical Analysis

Primary and secondary clinical data were assessed using age at injury as a covariate and retrospective ratings when available. Clinical analyses were conducted with either generalized linear models (group effect only) or generalized estimating equations (GEE; group and visit effect), using Gaussian, gamma, or negative binomial distributions. Statistical analyses of the cortical thickness surface data were conducted using linear mixed effects (Analysis of Functional NeuroImages [AFNI] 3dLME) with data missing at random. FreeSurfer data were converted to GIFTI format for use in AFNI. A 2 (visit [SA vs EC]) × 2 (group [HC vs pmTBI]) mixed-effects model with a random intercept was selected with age (unit = month) as a covariate. The minimum cortical surface area needed to achieve cluster-wise significance was  $p = 0.025$  per hemisphere (Bonferroni corrected) based on results from the `slow_surf_clustsim.py` AFNI program ( $p = 0.001$ ; 176 mm<sup>2</sup>).

Clinical and cortical thickness results are reported for main effects of group, visit, group × visit, group × age, and group × visit × age interactions. Subcortical models also included significant effects/interactions associated with hemisphere, with total intracranial volume used as an additional nuisance covariate. Analyses examining the effects of injury severity (presence/absence of LOC/PTA or PPCS) were limited to primary outcome measures and group effects to reduce redundancy. Supplemental analyses were repeated with age treated as an integer (unit = year), with all primary imaging findings replicating.

Finally, a random forests approach<sup>25</sup> was used to determine classification accuracy from both clinical (model 1) and structural MRI (model 2) data. The random forests approach was performed using R (randomForestSRC) with 10,000 trees. This statistical approach was selected due to robust external cross-validation, lack of distributional assumptions, protections against data overfitting, and outputs examining variable importance and clinical prediction accuracy (see eMethods, [links.lww.com/WNL/C525](https://links.lww.com/WNL/C525)).

## Standard Protocol Approvals, Registrations, and Patient Consents

All procedures were approved by the University of New Mexico Health Sciences Institutional Review Board (IRB #07-272). All participants provided informed assent and/or consent.

## Data Availability

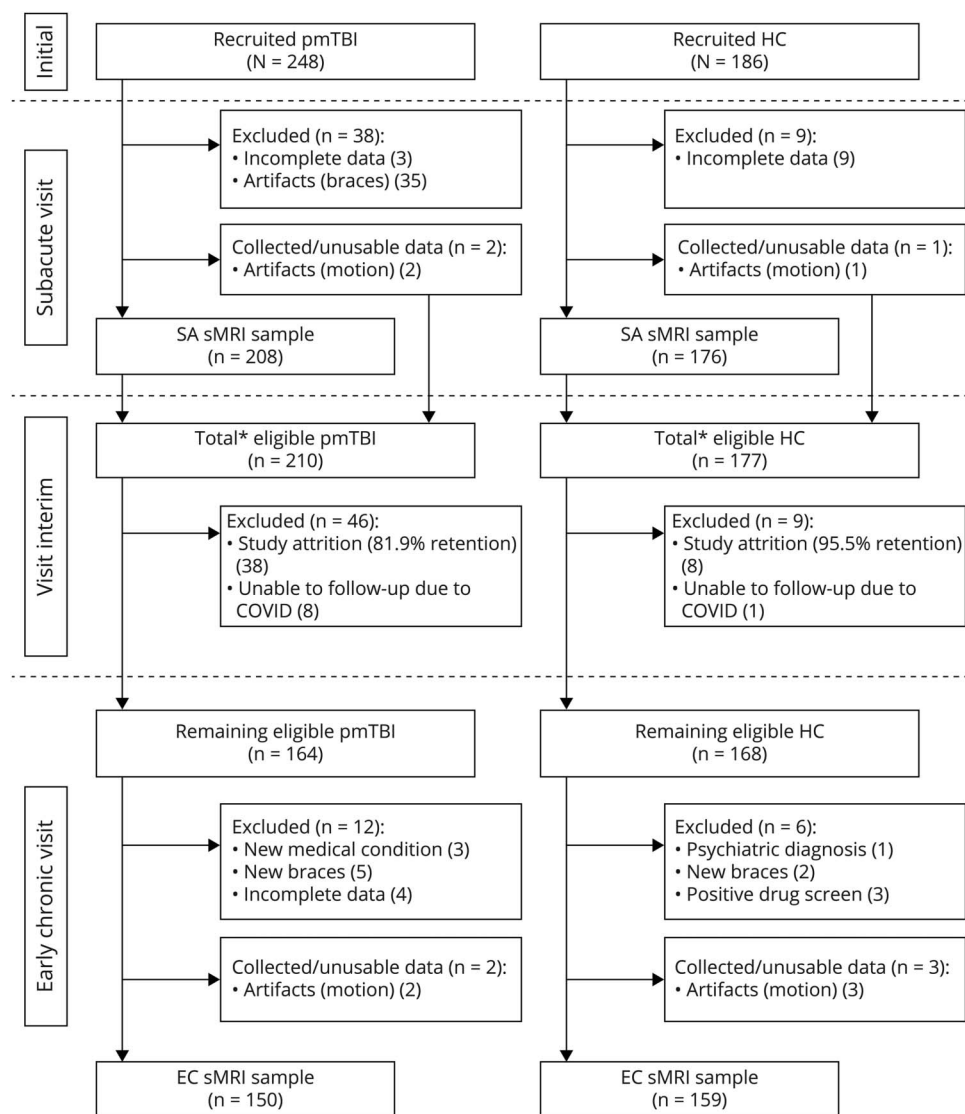
All data will be openly available in FITBIR at [fitbir.nih.gov](https://fitbir.nih.gov), reference number FITBIR-STUDY0000339, at the conclusion of the study.

## Results

### Demographics

The final sample (see eResults, [links.lww.com/WNL/C525](https://links.lww.com/WNL/C525); Figure 1) included 208 patients with pmTBI (84 females; age 14.4 ± 2.9; 7.4 ± 2.2 days postinjury) and 176 HC (74 females;

**Figure 1** Participant Recruitment and Retention



Flowchart of enrollment, inclusion, and data quality control from the subacute (SA) to early chronic (EC) visit for patients with pediatric mild traumatic brain injury (pmTBI) and matched healthy controls (HC). The asterisk denotes the total number of participants who were eligible to return, which is the sum of participants with usable structural MRI (sMRI) data and those whose data were excluded at the SA visit due to quality assurance issues.

age  $14.2 \pm 2.9$ ) for the SA visit and 150 patients with pmTBI (62 females;  $131.1 \pm 14.5$  days postinjury;  $123.7 \pm 14.4$  days between visits; 81.5% retention without study exclusions) and 159 HC (66 females;  $124.6 \pm 15.7$  days between visits; 95.5% retention without study exclusions) for the EC visit.

The pmTBI and HC groups did not differ in terms of handedness, age, self-reported Tanner stage of development, or biological sex (all  $p$ 's  $\geq 0.05$ ; see eTable 2, [links.lww.com/WNL/C525](https://links.lww.com/WNL/C525)). Conversely, significant group differences were observed for self-reported history of previous head injuries ( $\chi^2 = 9.01$ ,  $p = 0.003$ ; pmTBI = 17.6%, HC = 7.3%), parental self-reported psychopathology (Wald  $\chi^2 = 13.55$ ;  $p \leq 0.001$ ; pmTBI > HC), premorbid reading ability (Wald  $\chi^2 = 26.70$ ;  $p \leq 0.001$ ; pmTBI < HC), and effort (Wald  $\chi^2 = 23.17$ ;  $p < 0.001$ ; pmTBI < HC). The latter 2 measures were therefore included as covariates for cognitive analyses.

eTable 2 provides additional information on mechanism of injury and injury characteristics for pmTBI.

### Clinical Measures

Table 1 presents clinical and neuropsychological results. Significant group  $\times$  visit  $\times$  age (Wald  $\chi^2 = 6.58$ ;  $p = 0.010$ ), group  $\times$  visit (Wald  $\chi^2 = 21.24$ ;  $p < 0.001$ ), and group  $\times$  age (Wald  $\chi^2 = 7.73$ ;  $p = 0.005$ ) interactions were observed for self-reported PCS severity. Follow-up tests conducted indicated that PCS severity was greater (pmTBI > HC) at the SA (Wald  $\chi^2 = 126.38$ ;  $p < 0.001$ ; 36.1% symptomatic) relative to EC visit (Wald  $\chi^2 = 11.50$ ;  $p = 0.001$ ; 20.7% symptomatic), suggesting partial but not full recovery. Moreover, the group  $\times$  age interaction was significant at the SA (Wald  $\chi^2 = 27.40$ ;  $p < 0.001$ ) but not EC ( $p > 0.10$ ) visit, with a positive association between PCS and age at injury within pmTBI at the SA visit ( $\beta = 0.061$ ;  $p = 0.011$ ) contrasted to a negative

**Table 1** Clinical and Neuropsychological Data

Metric	Outcome	SA pmTBI (N = 208)	SA HC (N = 176)	EC pmTBI (N = 150)	EC HC (N = 159)
<b>Symptom measures</b>					
PCSI (% max) <sup>a,b</sup>	P	11.1 (3.6–29.5)	2.4 (0–8.3)	3.6 (0–13.1)	2.8 (0.6–6.5)
PROMIS sleep <sup>a</sup>	S	19 (13.5–24)	13 (11–16)	18 (12–23)	14 (11–17)
PROMIS anxiety <sup>a</sup>	S	3 (0–8)	1 (0–4)	2 (0–6)	1 (0–5)
PROMIS depression <sup>c</sup>	S	2 (0–8)	0 (0–3)	1 (0–6)	1 (0–3)
Pain scale <sup>a</sup>	S	3 (1–5)	0 (0–1)	0 (0–2)	0 (0–1)
HIT-6 <sup>a</sup>	S	52 (44–59)	40 (36–47)	44 (40–55)	42 (38–47)
<b>Behavioral and outcome measures</b>					
CBQ	P	1 (0–3)	1 (0–2)	1 (0–3)	1 (0–2)
PedsQL	P	—	—	85.9 (76.1–94.6)	90.2 (82.6–95.7)
SDQ <sup>c</sup>	S	—	—	7 (4–10)	4 (2–8)
GOS-E <sup>c</sup>	S	1 (1–4)	1 (1–1)	1 (1–2)	1 (1–1)
<b>Cognitive measures</b>					
TOMMe10 <sup>c</sup>	S	10 (9–10)	10 (10–10)	10 (10–10)	10 (10–10)
WRAT-IV <sup>c</sup>	S	49.3 (43.3–54.7)	54.0 (47.7–62.7)	49.3 (44.0–57.3)	55.3 (49.3–62.7)
PS <sup>c</sup>	P	46.8 ± 7.5	50.3 ± 8.1	50.3 ± 8.4	52.4 ± 8.8
AT <sup>a</sup>	P	47.8 (42.2–53.3)	52.2 (46.7–55.6)	50.0 (44.5–55.5)	53.3 (47.8–56.7)
WM	S	46.9 ± 7.9	50.2 ± 10.6	48.2 ± 9.3	50.5 ± 11.0
EF <sup>c</sup>	S	47.3 ± 7.1	50.3 ± 6.7	50.4 ± 6.8	53.0 ± 6.4
HVLT delay <sup>c</sup>	S	8 (6–10)	9 (7–10)	7 (6–9)	9 (7–10)

Abbreviations: AT = attention; CBQ = Conflict Behavior Questionnaire; EC = early chronic; EF = executive function; GOS-E = Glasgow Outcome Scale–Extended; HC = healthy control; HIT-6 = Headache Impact Test; HVLT Delay = Delayed recall on Hopkins Verbal Learning Task (measure of long-term memory); PCSI = Post-Concussion Symptom Inventory (presented as percent of maximum score to account for age-related scale differences); PedsQL = Pediatric Quality of Life Inventory; pmTBI = pediatric mild traumatic brain injury; PROMIS = Patient-Reported Outcomes Measurement Information System; PS = processing speed; SA = subacute; SDQ = Strengths and Difficulties Questionnaire; TOMMe10 = Test of Memory Malingering–10-item short version; WM = working memory; WRAT-IV = Wide Range Achievement Test 4.

Data are either formatted at mean ± SD or median (interquartile range).

<sup>a</sup> Group × visit interaction.

<sup>b</sup> Group × age interaction.

<sup>c</sup> Group main effect.

association in HC ( $\beta = -0.095$ ;  $p < 0.001$ ). Both primary quality of life and self-reported behavioral disturbances were not significant for group main effects or interactions (all  $p$ 's > 0.0167 following Bonferroni correction).

Tests examining secondary clinical measures (Bonferroni correction  $0.05/7 = 0.007$ ) demonstrated significant group × visit interactions for anxiety, sleep complaints, pain, and headaches (all  $p$ 's ≤ 0.002), characterized by increased symptoms (pmTBI > HC) at the SA visit (all  $p$ 's ≤ 0.001). There were no group-wise differences for anxiety, pain, and headache (all  $p$ 's > 0.05) at the EC visit, with sleep complaints still higher for pmTBI but at a lower magnitude ( $p = 0.004$ ). Worse outcomes (all  $p$ 's ≤ 0.001) were also present for pmTBI for secondary measures of depression, a parent-rated multidimensional measure of behavioral

functioning, and trauma-related functional outcome, but these effects did not statistically vary as a function of visit (i.e., main effect).

### Cognitive Testing

Results for primary cognitive measures indicated a significant (Wald  $\chi^2 = 8.67$ ;  $p = 0.003$ ) main effect for group (HC > pmTBI) for processing speed and a significant group × visit interaction for attention (Wald  $\chi^2 = 6.17$ ;  $p = 0.013$ ) after controlling for effort and reading ability (Bonferroni corrected  $p$ 's < 0.025). As expected, attentional performance deficits were observed at the SA ( $p = 0.012$ ; HC > pmTBI) but not EC ( $p = 0.482$ ) visit. Secondary analyses were significant for the main effect of group (HC > pmTBI) for both executive dysfunction ( $p = 0.007$ ) and long-term memory deficits ( $p < 0.001$ ). All group effects and

interactions were null for working memory after correcting for multiple comparisons (all  $p$ 's > 0.0167).

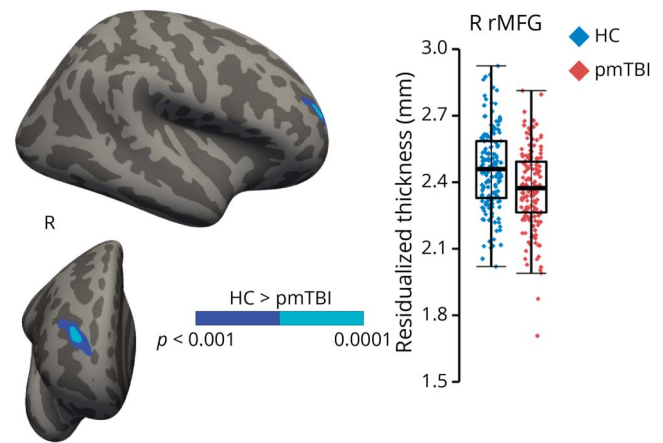
## Radiologic Findings

A total of 8/99 (8.1%) pmTBI had positive day-of-injury CT scans for intracranial pathology or skull fracture (complicated pmTBI). Four pmTBI had negative CT scans but were diagnosed with probable trauma-related findings on MRI (eTable 2, [links.lww.com/WNL/C525](https://links.lww.com/WNL/C525)).<sup>22</sup> Primary group findings were unchanged when these individuals were eliminated from analyses.

## Cortical Thickness Analyses for Effects of Group

Results from the  $2 \times 2$  (group [HC vs pmTBI]  $\times$  visit [SA vs EC]) 3dLME indicated significant main effects of group, visit, and age, with no significant interactions. The main effect of group was significant for the right rostral middle frontal gyrus (Figure 2; Table 2), with pmTBI exhibiting reduced cortical thickness compared with HC (Cohen  $d = -0.49$ ). Group effect size maps are presented in eFigure 1 ([links.lww.com/WNL/C525](https://links.lww.com/WNL/C525)). The main effect of visit was significant for 7 cortical areas on the left and 4 regions in the right hemisphere (summarized in Table 2; eFigure 2). All regions demonstrated reduced cortical thickness for the EC visit compared with the SA visit. The effect of age was widespread in both hemispheres (eFigure 3) and indicated decreased cortical thickness as a function of increasing age.

**Figure 2** Group Effects in Cortical Thickness Analysis



Main effect of group from the cortical thickness analysis for patients with pediatric mild traumatic brain injury (pmTBI; red diamonds) and healthy controls (HCs; blue diamonds). An inflated brain rendering presents a significant cluster within the right (R) rostral middle frontal gyrus (rMFG), with pmTBI exhibiting decreased cortical thickness relative to HC (dark blue:  $p < 0.001$ ; cyan:  $p < 0.0001$ ). Data points in the box-and-scatter plot have been residualized (Resid.) to remove the effect of age.

## Subcortical Volumetric Analyses for Effects of Group

Separate  $2 \times 2 \times 2$  (group [HC vs pmTBI]  $\times$  visit [SA vs EC]  $\times$  hemisphere [right vs left]) GEE models examined subcortical volume loss with age at injury and total intracranial

**Table 2** Statistical Results for the Main Effects of Group and Visit on Cortical Thickness

Region	Laterality	MNI x, y, z (mm)	Peak F statistic <sup>a</sup>	Area (mm <sup>2</sup> ) <sup>b</sup>
<b>Effect of group</b>				
Rostral middle frontal gyrus	R	24, 49, 18	19.2	301
<b>Effect of visit</b>				
Pars triangularis and rostral middle frontal gyrus	L	-51, 31, 7	21.2	444
Pars orbitalis and lateral orbitofrontal cortex	R	35, 31, -14	19.1	471
Lateral orbitofrontal cortex and anterior insula	L	-31, 20, 2	28.7	358
Pars opercularis and precentral gyrus	R	50, 9, 2	26.4	450
Superior temporal gyrus	R	51, -13, -3	19.1	273
Postcentral/supramarginal gyrus	R	62, -16, 20	32.1	421
Transverse/superior temporal gyrus	L	-58, -17, 2	22.7	272
Posterior cingulate and paracentral gyrus	L	-17, -25, 38	22.3	283
Superior temporal gyrus	L	-60, -25, -2	15.2	229
Parahippocampal/fusiform gyrus	L	-36, -44, -12	18.5	319
Inferior parietal lobule	L	-32, -74, 37	19.6	346

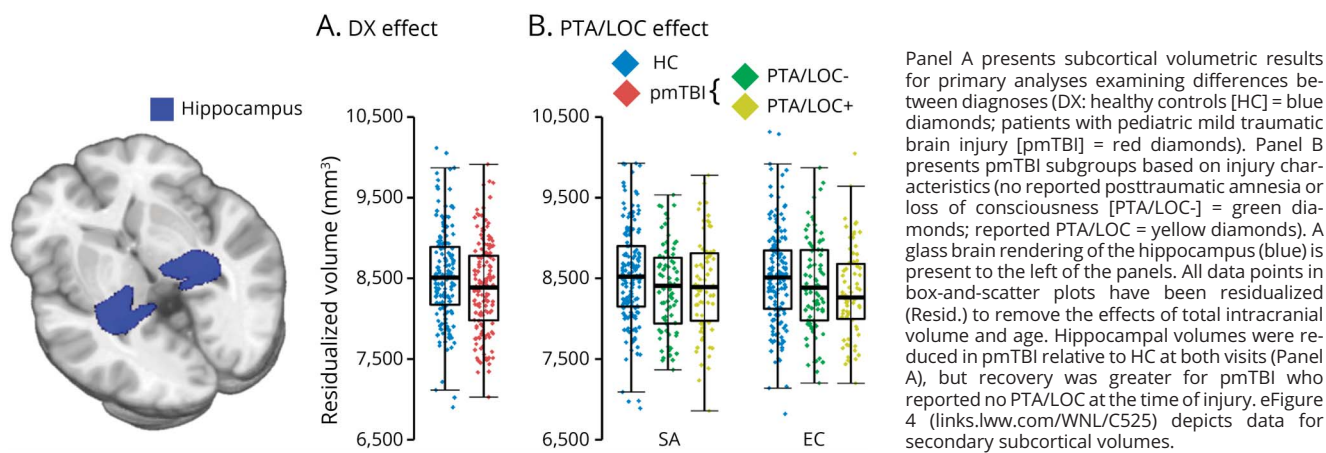
Abbreviations: L/R = left/right; MNI = Montreal Neurological Institute.

The table entries are arranged in the anterior-posterior order.

<sup>a</sup>  $F(1,383)$  for the effect of group,  $F(1,302)$  for the effect of visit.

<sup>b</sup> Family-wise error  $p < 0.025$  for cluster areas  $>176$  mm<sup>2</sup>.

**Figure 3** Group Effects in Subcortical Volume Analysis



volume as covariates. There were no outliers for any of the subcortical volume measurements. Primary analyses (Figure 3A) indicated significantly reduced hippocampal volumes for pmTBI relative to HC (Wald  $\chi^2 = 7.32$ ;  $p = 0.007$ ; Cohen  $d = -0.24$ ), along with a main effect for hemisphere (Wald  $\chi^2 = 552.73$ ;  $p < 0.001$ ; right > left).

Secondary analyses for amygdalae, thalami, pallida, putamina, and caudate nuclei (eFigure 4, [links.lww.com/WNL/C525](https://links.lww.com/WNL/C525)) were nonsignificant for any main effects of group or interactions with group following Bonferroni correction ( $0.05/6 = 0.008$ ). The nuclei accumbens indicated a significant group  $\times$  visit  $\times$  age  $\times$  hemisphere interaction (Wald  $\chi^2 = 21.72$ ;  $p < 0.001$ ), but none of the main effects or interactions with group were significant when a follow-up GEE was performed examining each hemisphere separately. Age exhibited significant negative associations with amygdalae ( $\beta = -0.005$ ; Wald  $\chi^2 = 8.74$ ;  $p = 0.003$ ), caudate nuclei ( $\beta = -0.007$ ; Wald  $\chi^2 = 12.96$ ;  $p < 0.001$ ), and nuclei accumbens ( $\beta = -0.007$ ; Wald  $\chi^2 = 34.03$ ;  $p < 0.001$ ) volume. See eResults for main effects associated with hemisphere and visit.

### Cortical Thickness and Volumetric Analyses for Effects of Injury Characteristics

Primary analyses were repeated with the pmTBI group further divided by more traditional injury severity characteristics (positive LOC and/or PTA; full sample) and the presence of PPCS at 4 months postinjury (limited to participants who returned for the EC visit). Results from a  $3 \times 2$  (group [HC vs pmTBI+LOC/PTA vs pmTBI-LOC/PTA]  $\times$  visit [SA vs EC]) cortical thickness analyses indicated null findings for the main effect of group and nonsignificant group  $\times$  visit and group  $\times$  visit  $\times$  age interactions. Null results were also obtained from a  $3 \times 2$  (group [HC vs pmTBI+PPCS vs pmTBI-PPCS]  $\times$  visit [SA vs EC]) PPCS analysis for PPCS cortical thickness analyses.

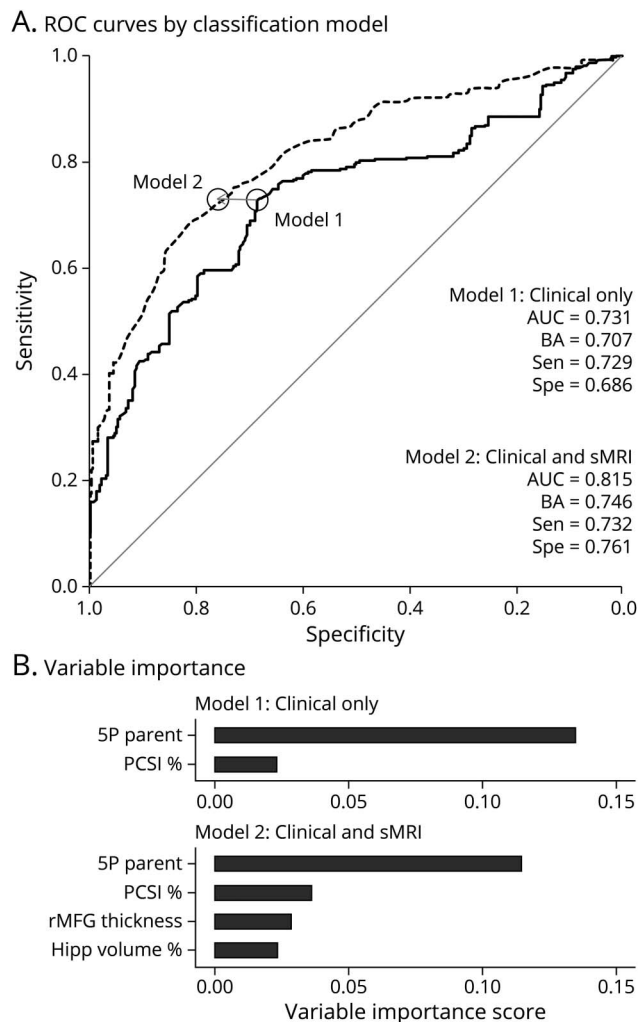
Results for hippocampi indicated a significant group  $\times$  visit interaction (Wald  $\chi^2 = 6.02$ ;  $p = 0.049$ ) for the presence of LOC/PTA (Figure 3B). The main effect of group was significant at the SA visit ( $p = 0.038$ ) but only a trend at the EC ( $p = 0.078$ ) visit. Simple effect testing indicated that the pmTBI-LOC/PTA group exhibited reduced hippocampal volumes at the SA ( $p = 0.019$ ) but not EC ( $p = 0.176$ ) visit, whereas in pmTBI+LOC/PTA demonstrated a trend for reduced hippocampal volume at the SA visit ( $p = 0.061$ ) that remained significantly decreased at the EC ( $p = 0.033$ ) visit. There were no differences between the 2 pmTBI groups at either visit ( $p$ 's  $\geq 0.384$ ). No interactions or main effect of interest were significant (all  $p$ 's  $> 0.05$ ) for hippocampi analyses examining PPCS.

### Structural Abnormalities and Clinical Correlations

The next set of analyses examined the relationship between clinical indices of cognitive dysfunction (independent variables: measures of attention, processing speed, working memory, executive functioning, and long-term memory recall) and structural abnormalities (cortical thickness and hippocampi volumes) and was limited to the pmTBI group. However, both regression models were nonsignificant (Bonferroni corrected  $p$ 's  $> 0.025$ ).

A supervised machine learning algorithm investigated the diagnostic accuracy of the 5P risk score and PCSI (model 1) vs the diagnostic accuracy when the right rostral frontal gyrus thickness and hippocampal volume were included in the model (model 2). HC served as the reference group. Results from model 1 indicated approximately 70.7% balanced classification accuracy (Figure 4; sensitivity = 72.9%; specificity = 68.6%), with variable importance scores of 13.5% for the 5P risk score and 2.3% for the PCSI. Balanced classification accuracy increased to 74.6% when structural abnormalities were included in model 2, with a greater increase in specificity

**Figure 4** Group Classification Using Random Forest Machine Learning Algorithm



Receiver operating characteristic (ROC; A) results from the random forest supervised machine learning algorithm for classifying patients with pediatric mild traumatic brain injury relative to healthy controls. Diagnostic accuracy was compared based on a model that included current clinical gold standards (model 1: 5P risk score [5P] and Post-Concussion Symptom Inventory total score [PCSI]; solid line) or clinical gold standards in conjunction with significant structural MRI (sMRI) findings (model 2; dashed line). Structural abnormalities included reduced cortical thickness of the rostral middle frontal gyrus [rMFG] and the volume of the hippocampi (Hipp) relative to total intracranial volume. Estimates for area under the curve (AUC), balanced accuracy (BA), sensitivity (Sen), and specificity (Spe) are provided for each model, with the intersection of optimal sensitivity/specificity denoted with a circle for each model. Panel B lists the variable importance score for variables in each model.

(sensitivity = 73.2%; specificity = 76.1%). However, the 5P score maintained the highest variable importance score at 11.4%.

## Discussion

The current study prospectively examined quantitative changes in the GM structure over a 4-month period in a large cohort of patients with pmTBI relative to a sex- and age-matched HC. Results indicated small but significant

differences in postinjury emotional, physical, and cognitive symptoms that persisted up to 4 months post-TBI. In addition, pmTBI was associated with reduced prefrontal cortical thickness in the right hemisphere and smaller hippocampal volumes, with the latter being mediated by traditional indicators of injury severity (LOC/PTA) in concussion research. These structural deficits improved the specificity of injury classification above and beyond clinical gold standards. However, there were no associations between cognitive deficits/symptom burden and structural abnormalities, and age at injury similarly did not account for any significant variance in terms of GM differences or recovery.

Similar to previous studies,<sup>26</sup> results from our extensive clinical battery indicated small but statistically significant residual deficits in multiple emotional, physical, and cognitive domains. Specifically, processing speed, executive functioning, and long-term memory remained below the control group performance at 4 months postinjury even when controlling for premorbid reading abilities, whereas attentional functioning showed evidence of recovery. However, neither cortical thickness nor reduced hippocampal volumes were associated with cognitive deficits, which may be reflective of the small effect sizes observed for both cognitive testing and structural pathology, as well as the potential nonspecific nature of cognitive deficits.<sup>27</sup> Thus, even if pmTBI results in long-standing physiologic changes, it may be challenging to relate physiologic changes to clinical measurements (cognitive, behavioral, or somatic symptoms). Similarly, several (pain, headache, and anxiety) physical and emotional symptoms demonstrated more complete resolution, whereas others (postconcussive symptoms, sleep, and depression) remained elevated at 4 months postinjury in the pmTBI group. Collectively, current and previous findings highlight the need for multidimensional clinical assessments multiple months postinjury.<sup>27</sup>

Current results indicate that hippocampal volume was reduced following pmTBI and that this reduction was further mediated by the presence of LOC/PTA but not PPCS. Smaller hippocampal volumes have been reported in children with mild, moderate, and severe TBI years following injury,<sup>28,29</sup> in young adult athletes with a high exposure (concussions and subconcussive blows) history,<sup>30-32</sup> in retired American football players with a high exposure history,<sup>33</sup> and in adults decades after their most recent mTBI.<sup>34</sup> Recent modeling studies suggest that the hippocampi may be more susceptible to injury due to the proximity of the fluid-filled temporal horns.<sup>6</sup> Null findings for hippocampal volume have also been reported in a previous prospective pmTBI (N = 15) study,<sup>7</sup> but this difference may be a result of the relatively small sample size based on current effect size estimates.

Several earlier (Cantu guidelines, American and Colorado Sports Concussion, American Academy of Neurology; Grade I, II, and III concussion grading) expert consensus panel guidelines recommend grading mTBI severity based on the presence of LOC/PTA or using LOC/PTA to stratify injury



probability (possible, probable, and definitive).<sup>35</sup> However, the inclusion of LOC/PTA for grading injury severity has generally not been adapted by more recent expert consensus panels.<sup>12</sup> A large reason for this is because LOC/PTA has traditionally not been shown to be predictive of functional and symptom-based outcomes in mTBI,<sup>17,18</sup> and LOC/PTA is more infrequent in sport-related concussion. However, LOC and PTA have higher test-retest reliability and specificity relative to postconcussive symptoms<sup>23</sup> and have recently demonstrated a dose-dependent relationship with blood-based biomarkers in 2 independent studies.<sup>9,10</sup> Thus, future research is necessary to determine whether LOC/PTA is a better predictor of objective biomarkers than subjective findings of injury severity (PPCS) across the spectrum of mTBI.

Current results indicated reduced cortical thickness in the right rostral middle frontal gyrus for pmTBI, with no evidence of recovery across a 4-month study period. Previous research suggests that neuronal degeneration occurs in the first few months of severe TBI and continues into more chronic injury phases, with rates of tissue loss ranging from 1% to 5% per year<sup>36,37</sup> regardless or not of whether macroscopic lesions are present. In contrast, research on atrophy and/or neuropil loss following adult mTBI is more controversial, with mixed results across multiple adult studies.<sup>37-40</sup> Similarly, previous cross-sectional studies in pmTBI have reported no differences in GM volume at 3 months post-pmTBI (N = 26) relative to sibling controls<sup>41</sup> and at 6 months postinjury (age 8–15; N = 219) relative to orthopedically injured controls.<sup>42</sup> Other cross-sectional studies have reported increased cortical thickness in the left parietal cortex for patients with pmTBI (age 8 to 16; N = 136) relative to orthopedically injured controls.<sup>43</sup>

One other prospective study of emergency department patients (age 10–17; N = 15) also reported reduced thickness values in several cortical regions from 2 weeks to 4 months post-pmTBI.<sup>7</sup> Thus, it is possible that prospective designs may be more sensitive to smaller differences in cortical thinning than cross-sectional designs due to the decreased variance associated with repeat visits.<sup>7,39</sup> Both current and previous<sup>7</sup> prospective pmTBI studies also independently replicated findings of reduced cortical thickness in the right middle frontal gyrus. The prefrontal cortex is commonly affected by TBI pathology across all levels of severity and tended to exhibit the largest effect sizes in the current sample (eFigure 1, [links.lww.com/WNL/C525](https://links.lww.com/WNL/C525)). Importantly, effect size maps indicated that these potential differences are mostly small to moderate in magnitude and may therefore only be observed in large sample sizes. Nonetheless, the findings of reduced cortical thickness and hippocampal volume appeared to be clinically meaningful, as they improved the specificity of patient classification by approximately 8% even when using current clinical gold standards (5P risk score and total symptom burden).

Among the injured, patients with pmTBI with PPCS represent a greater public health burden due to costs associated with prolonged patient care and continued disruptions for

return to normal activities.<sup>1</sup> A minority of patients with pmTBI in the current study self-endorsed significant PCS at the SA visit in the current study (36.1%; N = 75), with 20.7% (N = 31) reporting PPCS at the EC visit. Clinically significant symptoms were determined using normative estimation methods that significantly reduce the rate of false positives.<sup>16</sup> However, there were no significant differences in cortical thickness or hippocampal volumes for pmTBI with PPCS relative to either HC or pmTBI without PPCS.

Although 1 other study reported that adolescents with PPCS (age 10–14; N = 27) had smaller posterior cingulate cortex, caudal anterior cingulate cortex, and total brain volume relative to controls at 1 month postinjury,<sup>44</sup> these findings did not replicate at 6 months postinjury in a similar sample when appropriate corrections for multiple comparisons were enacted.<sup>8</sup> Null findings associated with PPCS may result from the non-specific nature of postconcussive symptoms,<sup>15</sup> their low to moderate test-retest reliability,<sup>16</sup> and/or from reduced statistical power associated with smaller sample size of patients with PPCS (N = 31 in the current sample). Importantly, other recent larger sample studies have reported white matter microstructural abnormalities that varied as a function of PPCS presence (primarily affecting mean diffusivity) or absence (primarily affecting fractional anisotropy) relative to orthopedic injured controls,<sup>45</sup> suggesting that additional work is needed to understand the potential biological basis of PPCS.<sup>14</sup>

In contrast to previous results,<sup>11</sup> age at injury did not significantly interact with diagnosis in terms of cortical thickness or subcortical volume loss. Preclinical models suggest improved outcomes in the very young due to increased plasticity following TBI, although contrary evidence also exists for injuries occurring during critical developmental periods.<sup>21</sup> Clinical studies have also reported worse outcomes for children who were injured before 7 years of age in mixed injury samples,<sup>46</sup> whereas null age-at-injury findings have also been observed for diffusion<sup>47,48</sup> and resting-state metrics of regional homogeneity and low-frequency fluctuations.<sup>49</sup> Thus, current null findings could be the result of the older age range (8–18 years) and associated neurodevelopmental stages investigated in the current study, the highly prescribed subacute postinjury intervals at which participants were assessed, or due to the exclusion of more severely injured patients with TBI. As such, current null age-at-injury effects on structural abnormalities may not generalize to more severely injured or chronic TBI samples or to injuries that occur in the very young.

Cortical thickness was reduced both as a function of increasing age and study visit (SA > EC). Previous large-scale neurodevelopmental studies (N > 1,000) have also reported a reduction in cortical thickness as a function of age.<sup>19,20</sup> However, it was unexpected to observe this effect at such a short time interval between visits (i.e., 4 months) during longitudinal analyses. Age-related reductions in cortical thickness have primarily been attributed to the combination of synaptic pruning of excessive connections in conjunction

with increased myelination.<sup>19</sup> Current findings of reductions in cortical thickness over a 4-month window highlight the relatively short time scale over which these neurodevelopment changes may occur and emphasize the need for large, prospective control samples to reduce the likelihood of spurious conclusions attributed to trauma rather than typical neurodevelopment in pmTBI studies.

Strengths of the current study include a large and homogeneous (same level of injury severity collected at similar time points postinjury) sample collected longitudinally at the same imaging center with a high retention rate for follow-up visits (>80%). This partially mitigates concerns regarding smaller effect sizes associated with pmTBI that may be further obscured by interscanner, intervender, and even intrasoftware variances.<sup>48</sup> However, this single-site recruiting strategy also increases the risk of sampling bias and limits generalization of findings to broader clinical contexts. Second, the current study did not include an orthopedically injured control cohort, which may control for nonspecific injury effects and potential differences in sampling strategies.<sup>42,43</sup> Third, the current study may have had limited power to detect complex, nonlinear interactions between age at injury and quantitative structural abnormalities. Fourth, sexual dimorphisms have been reported as a function of both age<sup>19,20</sup> and mTBI,<sup>50</sup> but were not examined in the current study. Finally, although the current study exclusively focused on GM changes postinjury, several recent studies have also observed white matter pathology post-pmTBI in large samples that also persist multiple months postinjury.<sup>45,47</sup> Thus, future studies that examine pathology from a multimodal perspective are needed, as well as the potential relationship between injury biomarkers and clinical outcomes.

In summary, previous research suggests that pmTBI may result in delays in academic achievement, decreases in overall quality of health, and an increased incidence of neuropsychiatric conditions.<sup>14</sup> Current clinical results suggest an impartial recovery at 4 months postinjury for clinical and cognitive functioning, with additional evidence of structural abnormalities within the right middle frontal gyrus and hippocampi. Recovery of hippocampal volume loss appeared to be partially mediated by injury severity as indexed by LOC/PTA, suggesting the need to reconsider the role of these injury markers in more objective outcomes.<sup>9,10</sup> Current results highlight the need for more extended surveillance intervals to determine the potential long-term, physiologic effects of pmTBI on neurodevelopment.

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Continued

## Appendix (continued)

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