Mild Traumatic Brain Injury: Longitudinal Regional Brain Volume Changes¹

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Purpose:

To investigate longitudinal changes in global and regional brain volume in patients 1 year after mild traumatic brain injury (MTBI) and to correlate such changes with clinical and neurocognitive metrics.

Materials and Methods:

This institutional review board–approved study was HIPAA compliant. Twenty-eight patients with MTBI (with 19 followed up at 1 year) with posttraumatic symptoms after injury and 22 matched control subjects (with 12 followed up at 1 year) were enrolled. Automated segmentation of brain regions to compute regional gray matter (GM) and white matter (WM) volumes was performed by using three-dimensional T1-weighted 3.0-T magnetic resonance imaging, and results were correlated with clinical metrics. Pearson and Spearman rank correlation coefficients were computed between longitudinal brain volume and neurocognitive scores, as well as clinical metrics, over the course of the follow-up period.

Results:

One year after MTBI, there was measurable global brain atrophy, larger than that in control subjects. The anterior cingulate WM bilaterally and the left cingulate gyrus isthmus WM, as well as the right precuneal GM, showed significant decreases in regional volume in patients with MTBI over the 1st year after injury (corrected $P < .05$); this was confirmed by means of cross-sectional comparison with data in control subjects (corrected $P < .05$). Left and right rostral anterior cingulum WM volume loss correlated with changes in neurocognitive measures of memory ($r = 0.65$, $P = .005$) and attention ($r = 0.60$, $P = .01$). At 1-year follow-up, WM volume in the left cingulate gyrus isthmus correlated with clinical scores of anxiety (Spearman rank correlation $r = -0.68$, $P = .007$) and postconcussive symptoms (Spearman rank correlation $r = -0.65$, $P = .01$).

Conclusion:

These observations demonstrate structural changes to the brain 1 year after injury after a single concussive episode. Regional brain atrophy is not exclusive to moderate and severe traumatic brain injury but may be seen after mild injury. In particular, the anterior part of the cingulum and the cingulate gyrus isthmus, as well as the precuneal GM, may be distinctively vulnerable 1 year after MTBI.

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Traumatic brain injury (TBI) is a major cause of morbidity and mortality, with an annual incidence estimated at 1.5 million in the United States (1). Mild TBI (MTBI), characterized by a Glasgow Coma Scale score of 13–15, accounts for 85% of these injuries (2). Thus far, conventional analysis of routine brain imaging studies detects abnormalities in only a tiny minority of these patients (3); however, neurologic and psychologic problems persist in anywhere from 10% to 55% of patients (4,5), suggesting that even mild head injury may have greater consequences than formerly assumed (6,7). Persistent symptoms comprise what is known as postconcussive syndrome (PCS), a variety of somatic, psychologic, and cognitive

complaints, including headache, fatigue, depression, and memory and attention deficits (8,9).

Investigations of moderate and severe TBI have demonstrated brain atrophy in areas remote from direct injury, including the corpus callosum, the cingulate gyrus, the hippocampus, the thalamus, and the fornix (10–14). In chronic traumatic encephalopathy, a neurodegenerative disease resulting from repetitive traumatic head injuries, brain atrophy involves both cerebral gray matter (GM) and white matter (WM) and is associated with tau neurofibrillary degeneration (15,16). Although there is typically no evidence of structural brain abnormality at conventional neuroimaging after MTBI, recent data (17–20) obtained by using a variety of newer techniques, including proton spectroscopy, advanced diffusion techniques, and functional magnetic resonance (MR) imaging, demonstrate postconcussive microstructural, metabolic, and functional changes in the brain. Whether a single concussive episode and the resultant microstructural, metabolic, and functional changes that have been associated with such an injury culminate in long-term brain atrophy is not known. To the best of our knowledge, this is the first longitudinal study involving use of an automated analysis technique to study changes in global and regional brain volume after MTBI.

The purpose of this study was to examine longitudinal changes in global and regional brain volume by using

automated whole-brain parcellation in a well-defined cohort of patients with MTBI and to correlate regions of brain atrophy with quantitative neurocognitive assessment findings, as well as clinical symptom scale measures.

Materials and Methods

Participants

This institutional review board–approved study was in compliance with the Health Insurance Portability and Accountability Act. All study subjects, including control subjects, signed written informed consent forms prior to participation in a multimodality MR imaging study of TBI conducted at our institution. All study subjects were examined between June 2005 and September 2012. The inclusion criteria used to identify patients with MTBI were those defined by the American Congress of Rehabilitation Medicine (21) and are as

Advances in Knowledge

- At 1 year after mild traumatic brain injury (MTBI), there is measurable global brain atrophy, larger than that in control subjects; specifically, there is white matter (WM) atrophy that affects the anterior cingulate WM bilaterally and the cingulate gyrus isthmus WM, as well as gray matter atrophy affecting the right precuneus (corrected $P < .05$).
- These longitudinal changes at 1-year follow-up for MTBI were further validated by means of cross-sectional comparison (with normalization for brain size) with control subjects (corrected $P < .05$).
- Longitudinal volume changes in the left and right rostral anterior cingulate WM correlated with scores at neuropsychologic testing in the memory ($r = 0.65$, $P = .005$) and attention ($r = 0.60$, $P = .01$) domains.
- Reduced volume in the left cingulate gyrus isthmus WM demonstrated negative correlation with postconcussive anxiety ($r = -0.68$, $P = .007$) and postconcussive symptoms ($r = -0.65$, $P = .01$) in patients with MTBI.

Implications for Patient Care

- A single concussive episode can result in global and regional brain atrophy 1 year after injury.
- Correlations between cingulate WM loss and neurocognitive performance and clinical symptom scales, including the Beck Anxiety Inventory and the Post Concussion Symptom Scale, support the notion that chronic pathophysiologic changes occur to the brain that may manifest as persistent symptoms after mild head injury.

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Abbreviations:

ANOVA = analysis of variance
BSI = boundary shift integral
CVLT = California Verbal Learning Test
GM = gray matter
MTBI = mild TBI
PASAT = Paced Auditory Serial Addition Test
PCS = postconcussive syndrome
rAC = rostral anterior cingulum
TBI = traumatic brain injury
VBM = voxel-based morphometry
WM = white matter

Author contributions:

Guarantors of integrity of entire study, Y.G., Y.W.L.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, Y.Z., A.K., Y.G., J. Rath, R.I.G., Y.W.L.; clinical studies, Y.Z., Y.G., J. Rath, J. Reaume, Y.W.L.; statistical analysis, Y.Z., D.K., Y.W.L.; and manuscript editing, Y.Z., A.K., D.K., Y.G., Y.W.L.

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Conflicts of interest are listed at the end of this article.

follows: closed head injury with either posttraumatic amnesia of less than 24 hours or loss of consciousness of approximately 30 minutes or less, with a Glasgow Coma Scale score of between 13 and 15. Exclusion criteria included a history of alcohol or drug abuse; a preexisting psychiatric disorder; a prior brain injury other than the current episode; and a history of other neurologic disease, including stroke, epilepsy, and somatic disorders.

For this study, we identified 32 patients with well-documented MTBI, recruited between June 2005 and September 2012 from the emergency department of a university-affiliated Level I trauma center. Among these patients, two were excluded because their MR imaging examinations were performed with a 1.5-T MR imaging unit, one was excluded because of excessive motion artifact, and one was excluded because of abnormal intracranial findings at conventional MR imaging. Twenty-eight patients with well-documented MTBI (22) (22 men and six women; mean age, 34 years $\pm$ 11.5 [standard deviation]; age range, 18–56 years; mean educational attainment, 15 years $\pm$ 2.6) were thus prospectively recruited from the emergency department of the university-affiliated Level I trauma center and hospital, with a mean interval between trauma and MR imaging of 23 days (range, 3–53 days). At the time of MR imaging, all patients reported at least one posttraumatic symptom, such as headache, insomnia, fatigue, sensitivity to light, irritability, and deficits in attention and memory. Nineteen of 28 patients with MTBI were followed up for 1 year, with repeat imaging and neurocognitive assessment. The average follow-up time for 19 revisits for MTBI was 1 year 1 month.

Twenty-two healthy control subjects matched for sex, age, education level, and handedness were also examined (mean age, 35.1 years $\pm$ 11.3; mean educational attainment, 16 years $\pm$ 2.1). Control subjects were also confirmed to have no history of psychiatric, neurologic, or central nervous system diseases and had normal conventional MR imaging findings. For test-retest

reliability and to document any expected changes after 1 year, 12 longitudinal control-subject comparisons were also performed (average follow-up time, 1 year 2 months).

MR Imaging and Data Processing

All MR imaging examinations were performed with a 3.0-T body MR imaging unit (Tim Trio; Siemens, Erlangen, Germany) and a 12-channel head coil. A three-dimensional T1-weighted magnetization-prepared rapid acquisition gradient-echo protocol (repetition time msec/echo time msec/inversion time msec, 2300/2.98/900; flip angle, 9°; and spatial resolution, $1 \times 1 \times 1$ mm) was used to obtain structural images. In addition, T2-weighted fast spin-echo and high-spatial-resolution susceptibility-weighted imaging sequences were also performed to depict hemorrhagic or other lesions. All images were reviewed by an expert in neuroradiology (Y.W.L., with 13 years of experience in diagnostic MR imaging), and lesions, if present, were documented.

For longitudinal comparison of global brain volume at initial and follow-up MR imaging, after we removed extracranial tissues by using the AFNI software (<http://afni.nimh.nih.gov/afni/>) and coregistered magnetization-prepared rapid acquisition gradient-echo images from two time points by using FSL (www.fmrib.ox.ac.uk/fsl), we applied the boundary shift integral (BSI) method (23,24) to measure the global atrophy rate. The BSI measures the longitudinal cerebral volume changes directly from voxel intensity projections, on the basis of the volume change of the boundaries of a given cerebral structure or the whole brain on repeated registered structural images. The BSI has been shown to be a robust measure of changes in overall brain volume that is tightly correlated with changes in whole-brain volumetric segmentation and has even higher accuracy and less variability.

Magnetization-prepared rapid acquisition gradient-echo images in each subject were also analyzed by using the Freesurfer software (version 5.1.ss0) (<http://surfer.nmr.mgh.harvard.edu/>)

to derive whole-brain volumes and subcortical volumes (45 regions), WM volumes (70 regions), and cortical GM volumes (148 regions). The reproducibility of Freesurfer for the same subject has been previously documented; additional details can be obtained at <http://surfer.nmr.mgh.harvard.edu/fswiki/Publications>. Subcortical parcellation was performed with multiple local feature-based statistical classification techniques accounting for individual anatomic variability (25). Cortical parcellation was performed by using the fully automated Freesurfer tool, and data were ascertained from the Destrieux cortical atlas (26). The construction of the brain atlas was done by first segmenting the cortex into gyral and sulcal regions on the basis of local mean curvature and average convexity, then further dividing each hemisphere into 74 structures by means of a manually drawn healthy brain template. A Bayesian maximum a posteriori algorithm with high flexibility was used to incorporate the observed individual surface geometry and the atlas function (27). Subsequently, WM was parcellated by means of the construction of a Voronoi diagram in the WM on the basis of the distance from the WM voxel to the nearest cortical parcellation label (28). All regional volume results are reported in units of cubic millimeters or microliter. To account for individual differences, normalization of regional volume to the supratentorial volume (GM plus WM) was also performed between patients with MTBI and control subjects. To extract reliable volume estimates, images were automatically processed with the longitudinal stream (29) in Freesurfer. Specifically, an unbiased within-subject template space and image (30) was created by using robust, inverse consistent registration (31). Several processing steps, such as skull stripping, Talairach transforms, and atlas registration, as well as spherical surface maps and parcellations, were then initialized with common information from the within-subject template, markedly increasing reliability and statistical power (29). Longitudinal analysis was performed in Freesurfer with the longitudinal reconstruction and QDEC toolbox to

investigate the symmetrical percentage of atrophy rate (defined as the difference in volume between follow-up and initial visits, divided by the average of volumes at two time points and by the time interval in years between initial and follow-up visits). All data processing was performed by an imaging scientist (Y.Z., with 12 years of experience in functional MR imaging data analysis and interpretation).

Clinical Assessment

Clinical assessment included two main components: neurocognitive testing results and scores from an array of established clinical symptom scales. Clinical assessment was performed within 12 hours of MR imaging for all participants, including control subjects, at both time points. Neurocognitive testing was performed by a trained neuropsychologist who was blinded to MR imaging results. The neurocognitive battery comprised the following tests: (a) the Symbol Digit Modalities Test (32), a measure of information processing speed; (b) the Digit Span subtest of the Wechsler Adult Intelligence Scale III (33), a measure of verbal attention, concentration, and working memory; (c) Trail-Making Test A, which is used to assess speed and visual attention; Trail-Making Test B (34), a measure of mental flexibility (specifically, the ability to shift rapidly between cognitive sets) (Both Trail-Making Tests are measures of attention.); (d) the California Verbal Learning Test (CVLT) II (35) to assess verbal learning and immediate and delayed verbal memory; (e) the Rey-Osterrieth Complex Figure Test to assess visuospatial ability and immediate and delayed visual memory (36); and (f) the Paced Auditory Serial Addition Test (PASAT) with four trials (37) to assess sustained attention and concentration, working memory, and information processing ability. These test results were reported in z scores after standardization with the control data and were normalized with the study subject's age and education level; higher z scores indicate better performance.

Posttraumatic clinical symptoms, including anxiety, depression, and fatigue, were assessed by using self-report questionnaires and were also reported in z scores, for which higher scores indicated greater symptoms. The Beck Anxiety Inventory (38) and the Beck Depression Inventory (39) were used to assess anxious and depressive symptoms separately. Fatigue was measured by using the Fatigue Severity Scale (40), and subjective symptoms associated with the postconcussive state were assessed by using the Post Concussion Symptom Scale (PCSS) (41). The PCSS assesses the severity of 19 symptoms (eg, dizziness, balance problems, headache, sensitivity to light, perceived cognitive impairments). Items were rated on a Likert scale indicating the severity of the symptom from 0 (none) to 6 (severe). Past research has validated the use of these inventories in assessing individuals after minor head injury (42).

Validation of Imaging Results

To validate the regional volumetry derived from Freesurfer cross-sectional and longitudinal analysis, as well as for cross-sectional comparison between patients with MTBI and control subjects, the whole-brain voxel-based morphometry (VBM) package in FSL (www.fmrib.ox.ac.uk/fsl/vbm) was used for segmentation and GM density analysis based on magnetization-prepared rapid acquisition gradient-echo data. Statistical comparisons of VBM morphologic differences between groups were further corrected for multiple comparisons by implementing threshold-free cluster enhancement (43).

Statistical Analysis

Statistical comparisons were performed by using MATLAB software (release 2010b; MathWorks, Natick, Mass) on the Freesurfer results. A one-sample paired t test was used to compare the first and second visits of patients with MTBI to identify significant changes in regional brain volumes at MTBI follow-up compared with those at initial visits. For groupwise comparison, the paired t test was also applied to the longitudinal brain volume measure of

the control group. All P values were adjusted with Bonferroni correction for multiple-region comparisons (45 subcortical, 70 WM, and 148 GM); a significance level of .05 after correction was used. The longitudinal mean regional volume difference was further compared by using a post-hoc two-way analysis of variance (ANOVA) (the Friedman test with Tukey-Kramer critical value), with study subject age and time between injury and MR imaging as covariates, as these two variables differed between follow-up times. A one-sample t test was also used to assess volume differences, targeting those regions found to have significant changes over time between two patient subgroups (those who were imaged within 1 week of injury and those in whom initial imaging was performed more than 1 week after injury).

A two-sample t test was used to assess cross-sectional volume differences between patient and control groups at both initial and follow-up times for patients in the regions that were found to be longitudinally different. All P values were adjusted with Bonferroni correction for multiple-region comparisons. Statistical correlation between Freesurfer longitudinal results (eg, relative supratentorial volumetric change) and BSI results (in cubic centimeters or milliliters) was also performed. Correlations between regional volume measures (volumes at initial or follow-up visits, as well as volume change between two visits) and clinical injury metrics (eg, site of injury, duration of loss of consciousness, time between injury and MR imaging) in patients were further examined to test whether there were any direct associations between MR imaging volumetric variables and subject injury variables.

Two-sample t tests were used to compare patients and control subjects with respect to scores on neuropsychologic tests and clinical symptom scales. One-sample t tests were implemented to compare the differences between the initial and follow-up visits in patients with MTBI with respect to their scores on neuropsychologic tests and clinical symptom scales. An ANOVA with

Friedman testing was performed to compare neurocognitive status between initial and follow-up visits in patients with MTBI after accounting for six non-image-related confounding factors (age, sex, site of injury, mechanisms of injury, duration of loss of consciousness, and time between injury and imaging). The Pearson correlation coefficient was computed between longitudinal brain volume changes and changes in neurocognitive scores over the course of the follow-up period. The Spearman rank coefficient between regional brain volume and clinical metrics over the same period was also computed.

Results

Patient demographic information, including injury mechanism, injury laterality (when applicable), duration of loss of consciousness, and time between MR imaging and trauma for the first visit, is listed in Table 1. No focal abnormalities, including hemorrhagic brain lesions, were detected at conventional imaging in any of the patients. There were no focal areas of abnormal susceptibility on susceptibility-weighted images.

The average BSI in patients with MTBI from the time of initial assessment to 1-year follow-up showed a loss of 7.6 cm³, larger than two times the change seen in control subjects (3.7 cm³). We also found significant correlation between change in total supratentorial volume as measured by using Freesurfer and whole-brain BSI in patients ($r = 0.54$, $P = .042$). As expected for further validation, for both patients with MTBI and control subjects, the BSI of the whole-brain volume and segmented volume, as well as the BSI of the ventricles and the segmented ventricular volume, were tightly correlated ($r = 0.99$ and $r = 0.96$, respectively).

Significant changes in regional WM and GM volume in patients with MTBI over the 1st year after injury are shown in Table 2 (original $P \leq .0005$; Bonferroni-corrected $P < .05$; two-way Friedman nonparametric ANOVA $P < .05$). Specifically, evaluation of longitudinal volume changes in regional WM

Table 1

Demographic Information in Patients with MTBI

Patient No./Age (y)/Sex	Injury Location	Mechanism of Injury	Loss of Consciousness (min)	Time between Injury and MR Imaging (d)
1/23/M	Diffuse	Assaulted	30	18
2/22/M	Back	Assaulted	30	6
3/51/F	Left	Bicycle accident	30	21
4/18/M	NA	Struck by car	15	19
5/28/F	NA	Struck by car	20	29
6/25/M	Right	Sport related (wrestling)	25	10
7/44/M	Forehead	Fell on street	5	5
8/36/M	Back	Sport related (soccer)	<1	25
9/42/M	Forehead	Fell on sidewalk	<1	3
10/24/M	Back	NA	NA	17
11/27/M	Right	Struck by car	<1	12
12/56/M	Forehead	Assaulted	<1	41
13/44/F	Back	Struck by car	<1	56
14/29/M	Left	Bicycle accident	15	52
15/38/M	Right	Fell	<1	31
16/32/F	Right	Fell down stairs	1	45
17/41/M	Back	Hit on head by street sign	<1	55
18/32/M	Left	Assaulted/fight	2	17
19/25/F	Right	Struck by car	<1	14
20/19/M	Back	Assaulted/fight	30	19
21/42/M	Back and crown	Fell down stairs	<1	5
22/51/M	Back and crown	Car accident while driving	30	19
23/18/M	Back	Assaulted	20	10
24/35/M	Right	Sport related (soccer)	<1	24
25/27/F	Right	Motorcycle accident	30	15
26/44/M	Right	Hit pipe and fell	<1	29
27/23/M	Right	Hit light pole and fell	17	10
28/56/M	NA	Fell from scaffolding	2	36

Note.—NA = not applicable.

revealed a decrease in volume in the rostral anterior cingulum (rAC) bilaterally and in the left caudal anterior cingulum, as well as in the left cingulate gyrus isthmus, in patients with MTBI when multiple comparisons were accounted for (Bonferroni-corrected $P < .05$). The evaluation of longitudinal GM changes in patients revealed decreased volume in the right precuneus and the right inferior and medial orbital olfactory frontal regions (Bonferroni-corrected $P < .05$). In these regions, cross-sectional comparison between patients at 1-year follow-up and control subjects with normalization to supratentorial volume also showed differences in volume between patients and control subjects in the rAC bilaterally, in the left caudal

anterior cingulum, in the left cingulate gyrus isthmus WM, and in the right precuneal GM (Bonferroni-corrected $P < .05$) (Table 3). There were no significant differences in the two right frontal regions (inferior and medial orbital olfactory regions) when we compared patients at 1-year follow-up with control subjects. Brain regions that showed significant longitudinal changes in volume in patients with MTBI and significant differences compared with control subjects are shown in Figure 1. The volume loss seen at the time of follow-up was present in both patient subgroups (those imaged within 1 week of injury and those imaged more than 1 week after injury), and there were no significant differences in volume between the two patient

Table 2

Significant Differences in Regional Brain Volume, Accounting for Multiple Comparisons, between Initial and Follow-up Visits in Patients after MTBI

Region and Location	Initial Visit for MTBI*	Follow-up Visit†	Original <i>P</i> Value/ Corrected <i>P</i> Value‡	ANOVA <i>P</i> Value§
Anterior cingulate WM				
Left rostral	2582 ± 486	2222 ± 583	.0005/.033	.015
Right rostral	2151 ± 326	1685 ± 404	.0001/.006	.009
Left caudal	2861 ± 517	2476 ± 435	.0001/.009	.013
Cingulate gyrus isthmus WM—left	3778 ± 689	3295 ± 578	.0003/.022	.005
Frontal GM				
Right inferior	3331 ± 833	2999 ± 853	.0002/.032	.009
Right medial orbital olfactory	1299 ± 258	1059 ± 199	.0001/.011	.013
Cuneal and occipital GM—right precuneus	6143 ± 906	5732 ± 854	.0001/.019	.007

Note.—Data are mean brain volumes in cubic millimeters ± standard deviation.

* Mean time between injury and MR imaging was 23 days.

† Mean follow-up time was 13 months.

‡ The original *P* value was calculated with the one-sample paired *t* test; Bonferroni multiple-region correction was then performed.

§ Calculated by using post hoc two-way Friedman nonparametric ANOVA with Tukey-Kramer critical value, including age and time between injury and MR imaging as covariates, as these two factors were different between the two patient visits.

Table 3

Cross-sectional Comparison of Data in Patients with MTBI at 1-year Follow-up and Control Subjects in Regions That Showed Longitudinal Volume Changes in Patients over 1 Year

Region and Location	Control Subjects	Patients with MTBI	Corrected <i>P</i> Value*
Anterior cingulate WM			
Left rostral	2.37 ± 0.43	1.90 ± 0.42	.004
Right rostral	1.86 ± 0.43	1.46 ± 0.36	.010
Left caudal	2.62 ± 0.45	2.14 ± 0.37	.021
Cingulate gyrus isthmus WM—left	3.16 ± 0.54	2.76 ± 0.27	.024
Frontal GM			
Right inferior	2.93 ± 0.58	2.56 ± 0.63	.23
Right medial orbital olfactory	1.15 ± 0.36	0.92 ± 0.20	.06
Cuneal and occipital GM—right precuneus	5.71 ± 0.70	4.92 ± 0.44	.004

Note.—Data are mean brain volumes in cubic millimeters ± standard deviation. Values were obtained by normalizing each mean regional volume from Freesurfer with individual intracranial volume and multiplying the result by a factor of 1000.

* Calculated with two-sample *t* test with Bonferroni multiple-region corrections.

subgroups at initial or follow-up examination ($P > .2$, one-sample *t* test).

There were no statistically significant differences in GM or WM volume (symmetrical percentage of atrophy rate, calculated by using the QDEC toolbox in Freesurfer) between baseline and 1-year follow-up imaging studies in control subjects (Fig 2). After normalization to supratentorial brain volume,

there were no significant regional brain volume differences between patients with MTBI at the time of their initial visit and the control group in any of the structures studied, either.

Group analyses based on the VBM method between patients with MTBI at 1-year follow-up and control subjects (threshold-free cluster enhancement; corrected $P < .05$) showed a pattern of

regional atrophy similar to the results obtained by using Freesurfer (atrophy in the anterior cingulate and cingulate gyrus isthmus regions, in the right precuneus and cuneus, and in scattered frontal areas) (Fig 3). Also consistent with the Freesurfer results, group analyses based on the VBM method between patients with MTBI at the time of their initial visit and control subjects showed no differences between the two groups with a relatively loose threshold of uncorrected $P < .01$.

Regarding neurocognitive and clinical assessment, patients with MTBI demonstrated significantly higher scores on scales of depression and anxiety and the PCSS, both at the initial visit and at the 1-year follow-up visit, compared with control subjects ($P < .01$) (Fig 4, A). There were no significant longitudinal differences in patients in terms of anxiety and PCS measures. A two-way Friedman nonparametric ANOVA with post-hoc comparison that included age and time to MR imaging after injury as covariates showed significantly increased depression scores for patients at 1-year follow-up compared with the initial visit ($P = .001$) (Fig 4, B). There were no differences in performance on neurocognitive tests between patients with MTBI and control subjects. At 1-year follow-up, patients with MTBI showed improvement in performance ($P < .05$) on two specific neurocognitive tests (the Digit Span test and the Rey-Osterrieth Complex Figure Test, tests of working memory and attention) compared with initial assessment. Left rAC volume loss in patients correlated positively with change in CVLT score over time ($r = 0.65$, $P = .005$) (Fig 5, A), and loss of right rAC volume correlated positively with change in PASAT trial 2 score over time ($r = 0.60$, $P = .01$) (Fig 5, B). At 1-year follow-up, patients showed a negative correlation between left cingulate gyrus isthmus WM volume and anxiety score on the Beck Anxiety Inventory (Spearman rank correlation $r = -0.68$, $P = .007$) (Fig 6, A). In addition, there was a negative correlation between left cingulate gyrus isthmus WM volume and PCS ($r = -0.65$, $P = .01$) (Fig 6, B).

We also tested for correlations between regional volume loss and clinical injury metrics (eg, injury site, duration of loss of consciousness, time between injury and MR imaging). We found only a mild correlation between WM loss in the left rAC and the time between injury and the initial MR imaging examination ($r = 0.58$, $P = .01$), and no significant correlations were found between volumetric findings and injury metrics after Bonferroni multiple comparison adjustment ($P > .05$).

Discussion

Study results (37,44,45) show that 10%–20% of patients with MTBI continue to experience neurologic and psychologic symptoms more than 1 year after trauma. We used automated techniques to objectively measure longitudinal changes in global and regional brain volume over a 1-year period in a well-defined cohort of patients with MTBI. Our observations demonstrate that after a single concussive episode, there is measurable atrophy 1 year after injury. This atrophy is revealed as global changes according to the BSI as well as specifically affecting the anterior cingulate WM bilaterally and the left cingulate gyrus isthmus WM. These changes are greater than those we would normally expect to see after 1 year in a control population. Volume loss is known to occur after moderate and

Figure 1

Figure 1: Coregistered data (from 28 patients with MTBI) projected onto right cerebral hemisphere template show areas of significant volume loss (Bonferroni-corrected $P < .05$) at 1-year follow-up according to both the one-sample t test for within-group longitudinal comparison (patients at 1-year follow-up compared with patients at initial visit) and the two-sample t test for across-group comparison (patients at 1-year follow-up compared with control subjects) based on Freesurfer regional volumetry. *A*, and, *B*, show medial and lateral views, respectively.

Figure 2

Figure 2: Coregistered data (from 22 control subjects) projected onto right cerebral hemisphere template show minor areas of volume loss in the occipital lobe (Bonferroni-corrected $P < .05$); atrophy was significant in no region after false-discovery-rate correction. *A*, and, *B*, show medial and lateral views, respectively.

Figure 3

Figure 3: Areas of significant difference (threshold-free cluster enhancement; Bonferroni-corrected $P < .05$) using VBM (shown here overlaid on two-dimensional axial view of standard Montreal Neurological Institute 2-mm template on which across-group brain normalization morphometry was performed) highlight differences between patients with MTBI at 1-year follow-up and control subjects that confirm a pattern of differences in regional volume similar to that observed by using Freesurfer (ie, in the anterior cingulum, cingulate gyrus isthmus, right precuneus and cuneus, and scattered frontal areas).

Figure 4

Figure 4: A, Bar graph shows that patients with MTBI showed significantly ($P < .01$) elevated scores on clinical symptom scales of depression, anxiety, and PCS compared with control subjects at both initial and 1-year follow-up visits. Higher scores on clinical symptom scales = more severe symptoms; error bars = standard errors of the mean. Average scores were also higher at 1-year follow-up than at the initial visit in patients with MTBI. B, Bar graph created after ANOVA with Friedman test after accounting for six confounding factors (age, sex, injury site, mechanism of injury, loss of consciousness duration, and time between injury and initial imaging) shows significantly elevated depression scores with least-square estimates in patients at follow-up compared with the initial visit ($P = .001$).

severe head injury. In addition, previous studies (14,46,47) in patients with severe TBI have found the anterior corona radiata and cingulum bundle to be particularly susceptible to traumatic injury. Our observations complement these findings and indicate that the cingulum and precuneus may be specifically vulnerable to long-term structural changes. To the best of our knowledge, ours is the first study to examine regional brain volume changes over time in MTBI. A very small number of patients (four of 28) underwent the initial MR imaging examination within a week of the injury, and therefore brain swelling relating to the original injury is not believed to be a major factor. Moreover, our cross-sectional data (comparing patients with MTBI at 1-year follow-up with control subjects) also point to volume loss over time rather than initial brain swelling.

One potential mechanism that could contribute to the observed findings is initial brain edema with subsequent normalization after injury, rather than true volume loss over time; however, a number of factors suggest that the

results point to true volume loss and that initial brain edema is not a major factor. As mentioned earlier, only a very small number of patients in this cohort (four of 28) underwent the initial MR imaging examination within a week of injury. On average, the first imaging study was performed approximately 1 month after injury, at which point edema is largely resolved. In addition, looking at our subgroup analysis, we did not find significant differences in change in volume between patients imaged within the 1st week of injury and those imaged later. Volume loss over the 1st year was nevertheless present in both subgroups. Moreover, our cross-sectional data (comparing patients with MTBI at 1-year follow-up with control subjects) showed differences between groups only at 1 year, favoring true volume loss over time rather than initial brain swelling followed by normalization. In either case, these particular brain regions appear to be affected after MTBI with regard to changes in volume over time.

The anterior part of the cingulum plays a critical role in several complex

neural systems, including both affective and cognitive domains: mood, selective attention, working memory, and executive function (48,49), which are all frequently abnormal in the postconcussive state (50,51). Specifically, the caudal anterior portion of the cingulum is activated in response to error and interference (52,53), and the rAC is involved with error processing and feedback (54). Furthermore, decreased rAC volume has been associated with depression and depressive symptoms in populations without trauma (46), as well as in patients after TBI (46,55). The rAC is actively implicated in cognitive control domains (56) such as selective attention processing and working memory (48,49). These are cognitive domains that have previously been found to be dysfunctional in PCS (57,58). Consistent with the functional role of the rAC, we found that rAC WM volume changes in patients with MTBI correlated significantly with scores on the CVLT, a test of verbal memory, learning, and encoding, as well as with scores on the PASAT, a test of attention.

Supplementary to the anterior cingulate findings, we also found atrophy of the left cingulate gyrus isthmus and in the right precuneal GM in patients with MTBI. More posterior regions, including the posterior cingulate and retrosplenial regions, have been reported to be vulnerable to injury after moderate-to-severe TBI (14,47). The precuneal region is important because of its large number of reciprocal connections with frontal systems and its involvement in executive function, working memory, and conscious information processing (59). The cingulate gyrus isthmus and the precuneus region are of considerable interest given their vulnerability to traumatic injury (20,60).

Findings of volume loss were bilateral in the rAC; however, other areas, including the left caudal anterior cingulum, the left cingulate gyrus isthmus, and the right precuneal GM, showed unilateral volume loss. It is not clear why these findings lateralized. The patients had variable laterality in terms of the site of their external injuries, with three patients having left-sided injuries, nine patients having right-sided injuries, and 16 patients having nonlateralized

injuries (eg, injuries to the front, back, or crown); therefore, this is not believed to relate to side of impact. Potentially, hemispheric dominance may play a role in defining the areas injured. All of the regions that demonstrated atrophy over time are paramedian structures, leading us to speculate that these specific paramedian regions are somehow more susceptible to injury. Two frontal regions (inferior and medial orbital olfactory) demonstrated statistical differences longitudinally but were not statistically different from those in control subjects. Inferior frontal regions are known to be at risk for contusional injury after moderate and severe head trauma (60). Our findings in this area suggest that such frontal regions may also be at risk for injury, and further investigation with a larger subject cohort would be needed to confirm this result.

Studies of patients with moderate and severe TBI have reported longitudinal WM volume decline in several areas, including the corona radiata and cingulum, believed to be secondary to Wallerian degeneration after diffuse axonal injury. Animal and cadaveric studies have shown axonal pathologic features 24 hours after TBI, although we know that damaged axons continue to undergo changes, including axonal swelling, axoplasmic transport, and disconnection, in the ensuing months and years after injury (61,62). Levine et al (47) studied a hospitalized patient cohort with a range of TBI severities by using a cross-sectional study design and incorporating manual tracing and manual landmark identification of several brain regions. They also showed brain volume reduction in the cingulum, though more prominently in the posterior part of the cingulum. This difference may be due to differences in the patient cohorts studied: The current study includes only patients with MTBI, while the study of Levine and colleagues included patients with a range of injury severities. The average time to the initial MR imaging examination in our patients was 23 days. It is not certain whether the observed WM volume changes in our study are a result of primary axonal injury after MTBI or ongoing secondary injury affecting the WM.

Figure 5

Figure 5: A, Graph shows significant Pearson correlation ($r = 0.65$, $P = .005$) between longitudinal changes in left rAC WM volume after 1 year and changes in CVLT memory encoding z score during the same period in patients with MTBI. B, Graph shows additional correlation, which reached statistical significance ($r = 0.60$, $P = .01$), between longitudinal changes in right rAC WM volume after 1 year and changes in PASAT attention z score during the same period. Upper and lower lines = upper and lower 95% confidence intervals of linear fitting of data.

Figure 6

Figure 6: Graphs show the significant Spearman rank correlations found between regional brain volume and clinical symptoms in patients with MTBI. A, Correlation of left cingulate gyrus isthmus WM volume and anxiety score at 1-year follow-up ($r = -0.68$, $P = .007$). B, Correlation of left cingulate gyrus isthmus WM volume and PCS score at 1-year follow-up ($r = -0.65$, $P = .01$).

The volumetric changes in the cingulate gyrus isthmus we observed after MTBI were associated with clinical symptoms, including postconcussive and anxiety symptoms. The cingulum has been implicated as dysfunctional in several psychologic disorders, including schizophrenia (63). Our findings are supported by those of previous studies that demonstrated frontal WM loss associated with anxiety (46) in patients with TBI with varying severities of injury

(46,55,64). We found no such correlations in our control population. The total supratentorial volume measured by using Freesurfer and whole-brain BSI in patients were mildly correlated ($r = 0.54$). Both methods are well known for their reliability in longitudinal analysis. The difference between the two results might come from the different registration algorithms used. For example, the BSI method assumes rigid boundary changes of longitudinal studies of the

same subject, while Freesurfer makes no such assumption but instead involves steps of iterative atlas registration.

Limitations of our study included its relatively small sample size; however, to our knowledge, this is the largest report of longitudinal brain volume changes in an MTBI cohort. Follow-up is difficult in this patient population, which introduces potential selection bias—namely, studying relatively more symptomatic individuals at follow-up. Nevertheless, our findings clearly indicate that at least in a subset of patients after MTBI, there are measurable brain volume changes 1 year after injury that are greater than those expected in the control population. In addition, the population of patients with MTBI is by definition a heterogeneous population, as is reflected in the different injury mechanisms and various brain injury sites in our patient population; however, we adhered strictly to American Congress of Rehabilitation Medicine criteria and included only patients with documented injury from the emergency department.

In conclusion, whole-brain automated volumetric analysis of longitudinal changes in global and regional volume in a well-defined cohort of patients with MTBI demonstrates both global atrophy and atrophy that specifically affects the anterior part of the cingulate WM bilaterally, the left cingulate gyrus isthmus WM, and the precuneal GM after 1 year. Brain atrophy, which is known to occur after moderate and severe head trauma, is not exclusive to the more severe spectrum of injury but can occur after a single concussion. We found that volume changes in the rAC WM correlated with performance on neurocognitive tests. Furthermore, negative correlations between the cingulate gyrus isthmus volume and clinical symptom scales of anxiety and PCS support the idea that there are pathophysiologic origins to persistent symptoms after MTBI. Although we believe these findings to be provocative, we caution the use or application of such a technique on an individual basis. There is also normal, not-insignificant intersubject variability in brain morphology. Future studies in a larger cohort of patients with multiple follow-up times to validate our

results and to further characterize the full trajectory of volumetric changes after MTBI, including the effects of edema, disease progression, and recovery, are needed.

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