Differences in Regional Brain Volumes Two Months and One Year after Mild Traumatic Brain Injury

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Abstract

Conventional structural imaging is often normal after mild traumatic brain injury (mTBI). There is a need for structural neuroimaging biomarkers that facilitate detection of milder injuries, allow recovery trajectory monitoring, and identify those at risk for poor functional outcome and disability. We present a novel approach to quantifying volumes of candidate brain regions at risk for injury. Compared to controls, patients with mTBI had significantly smaller volumes in several regions including the caudate, putamen, and thalamus when assessed 2 months after injury. These differences persisted but were reduced in magnitude 1 year after injury, suggesting the possibility of normalization over time in the affected regions. More pronounced differences, however, were found in the amygdala and hippocampus, suggesting the possibility of regionally specific responses to injury.

Key words: mild traumatic brain injury; MRI; subcortical structures; volume

Introduction

TRAUMATIC BRAIN INJURY (TBI) is a significant public health problem worldwide. Epidemiological studies vary, but it is estimated that there are about 200 persons with TBI hospitalized each year per 100,000 population in Europe and North America. While computed tomography (CT) is the current imaging modality of choice, in particular regarding identification of skull fractures, hemorrhages, contusions, and edema, magnetic resonance (MR) is superior in detecting cerebral and subcortical atrophy. It is thus suited for tracking structural volume changes in white/gray matter, long-term outcome prediction, and monitoring of disease/recovery progression in follow-up studies.¹

Although several studies have documented changes in brain structure and volume associated with moderate and severe TBI,² there have been very few studies addressing whether mild brain injury is associated with change in brain volume and if such changes are stable over time. This is of increasing interest given escalating concerns over potential long-term effects of even a single mild TBI.

Zhou and associates³ reported on 28 persons imaged approximately 1 month after a mild TBI, 19 of whom were studied a second time 1 year after injury. They found significant reductions in brain volume in the mTBI group, and using a voxel-based morphometry

approach, noted changes in white matter volume in the cingulate, and gray matter atrophy in the right precuneus.³ Toth and colleagues⁴ compared 14 patients with mTBI and negative CT findings with 14 matched volunteers. Both groups were imaged 3 days and 1 month after injury. Their analysis revealed a significant decrease in cortical volumes and increase in ventricular volumes at 1 month after injury in the mTBI group.⁴

Ling and coworkers⁵ studied 50 patients with mTBI and 50 healthy controls at two time points (14 days and 4 months) after injury.⁵ They reported increased fractional anisotropy in the bilateral superior frontal cortex during the semi-acute phase with no significant differences between groups in neuropsychological testing and gray matter atrophy at either time point.

Differences in methods, as well as injury-to-imaging time intervals, may underlie the heterogeneous findings with respect to brain regions affected by mTBI. For example, one proposed approach for volumetric brain analysis involves the use of probabilistic atlases. A method that relies on Markov random fields to model local spatial relationships between neighboring structures in the context of a brain atlas was described.⁶ Other proposed approaches are based on learned statistical models of shape and intensity variation.⁷ Comparison of methods for segmentation of subcortical brain structures, including approaches based on both atlases and statistical shape models, indicates that a multi-atlas

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approach exhibits the highest overall accuracy⁸ but can be prohibitively computationally intensive for many clinical applications.

Our group has developed an approach for quantification of subcortical brain structure volume based on a shape-constrained deformable brain model.^{9–11} This approach enables rapid, simultaneous segmentation of multiple structures that can be represented with the same shape topology across different patients. The current version of the model includes subcortical regions that can be modeled as closed surface meshes and provides their explicit shape representations.⁹ Regions were chosen both for their feasibility to be modeled in this fashion, and for their functional role in frontal-subcortical circuits of interest in neuropsychiatric disorders including TBI.

In the present study, we applied this model to a sample of adults with mTBI and healthy comparison subjects. We hypothesized that persons with mTBI would show subtle decreases in regional volume evident 2 months or 1 year after mTBI.

Methods

Participants

A sample of 44 patients with mTBI were imaged with MR (T1-weighted) approximately 2 months after injury and again approximately 1 year after injury. Twenty-nine healthy control subjects without a history of mTBI were recruited from the community and were also imaged twice with a similar interval. The participants with mTBI included consecutive persons with mTBI seen in the emergency department of the Dartmouth-Hitchcock Medical Center, a level 1 trauma center. Mild TBI was diagnosed using American Congress of Rehabilitation Medicine Criteria (ACRM). Glasgow Coma Scale (GCS) scores and absence, presence, and duration of loss of consciousness (LOC) were established when possible from participant/family interview, or available medical records.

Standard protocol approvals, registrations, and patient consents

The protocol was approved by the Institutional Review Board at Dartmouth, and all participants gave written informed consent.

Imaging methods

Scans were acquired on a research-dedicated 3T Philips Achieva magnet. This 3.0T system has the high performance Quasar Dual gradient set with strengths up to 80 mT/m and slew rates up to 200T/m/sec and an anatomical landmark-based longitudinal repositioning system (SameScan/SmartScan). A Philips 8-channel SENSE Head Coil was used.

An MPAGE (Magnetization Prepared Rapid Gradient Echo) T1-weighted sequence was used in each session with the following parameters: 140 contiguous 1.2 mm sagittal slices; TR: 6.8 ms; TE: 3.3 ms; TI: 852.9 ms; TFE prepulse delay: shortest; flip angle: 8 degrees; NEX: 1; BW/Pixel: 241; FOV: 256 mm, matrix 256, 1.0×1.0 mm in-plane resolution. This series balances scan time, signal-to-noise ratio, high gray/white tissue contrast, and high spatial resolution (scan duration: 8:55 min). The sequence also provides optimal tissue contrast on the boundary of key subcortical regions known to be implicated in mTBI. That allows for accurate delineation of brain structures on consecutive slices and provides the basis for generation of accurate ground truth data needed for training of fully automatic segmentation techniques.

Shape-constrained deformable brain model

Shape-constrained deformable surface models^{9,12,13} combine the strengths of both deformable and active shape models by encoding *a priori* shape information while external forces guide the

deformation and adapt the model to a target structure. The geometry of the shape-constrained deformable brain model is represented with a triangular mesh that consists of vertices and triangles, as illustrated in Figure 1. During model creation, various properties describing the local image appearance and shape

FIG. 1. The shape-constrained deformable brain model: (A) shaded surface, and (B) triangular mesh. The brain model consists of a number of subcortical structures that geometrically can be modeled as three-dimensional meshes. Color image is available online at www.liebertpub.com/neu

FIG. 2. The fully automatic segmentation of an arbitrary volume is an iterative process that includes a number of image processing steps. It starts with approximate shape detection followed by an iterative parametric adaptation. Finally, when the model is close to the anatomical structures in the volume, a deformable adaptation is applied. Color image is available online at www.liebertpub.com/neu

variation are extracted and learned from a set of training volumes and their corresponding ground truth data. The ground truth data represent highly accurate segmentations of the structures included in the model from a set of high resolution anatomical MRI volumes acquired with the sequence outlined above. The adaptation of the model to a new volume is rapid, fully automatic, and involves a number of image processing steps illustrated in Figure 2. Detailed methods of this approach and its quantitative accuracy evaluation have been described previously.^{9–11}

Statistical analyses

Distributions for demographic data were examined for outliers and distributional characteristics. mTBI and healthy control groups were compared using *t* tests for continuous variables and chi-square tests for categorical variables with respect to basic demographic information. The shape-constrained deformable brain model was applied to both groups at each time point. Volumetric measures from the amygdala, brainstem, caudate, cerebellum, corpus callosum, hippocampus, putamen, and thalamus in the mTBI and healthy control groups at each time point were examined for significant group differences using multivariate analysis of covariance (MANCOVA), with age and relative intracranial volume included as covariates.¹⁴ MANCOVA with repeated measurements was performed between the two imaging time points within each group. The statistical computations and *post hoc* analysis were performed using STATA 11.

Results

Participant characteristic data

There were 44 participants with mTBI and 29 healthy controls who were studied. Table 1 shows that the mTBI and healthy con-

trols groups did not differ significantly with respect to age, sex, scan interval, or relative intracranial volume. The patients with mTBI were studied initially at a mean of 60 days after injury, and then again 444 days after injury. On the whole, this mTBI cohort sustained injuries that were quite mild. Thirty one were judged to have had LOC, but the mean duration of LOC was 2 min, and the maximum was 7.5 min. A subset of 13 patients was thought to have had a disturbance of consciousness without clear LOC. GCS scores were available for 34 of the patients, and the mean score was 14.7. Eight of the patients had abnormal day of injury brain CT scans. The majority were small hemorrhages in frontal and temporal regions. The remainder had normal brain CT scans.

Statistical analyses

Table 2 presents group volumes for the structures included in the shape-constrained deformable brain model. The MANCOVA yielded a significant overall group difference at two months after injury (Wilks' lambda=0.6515, *df*=1, *F*=2.35, *p*=0.0139), with the patients having smaller overall volumes than the controls. Further *post hoc* analysis of the MANCOVA results indicated that the patients had significantly smaller volumes for the caudate and putamen bilaterally, as well as the right thalamus, while the left thalamus showed a trend for being smaller in the patient group. A summary of these findings is illustrated in Figure 3. The MANCOVA also showed significant differences between the mTBI and control groups at the 1-year follow-up (Wilks' lambda=0.5636, *df*=1, *F*=3.39, *p*=0.0007). Patients continued to have smaller caudates, putamen, thalami, and amygdala bilaterally, as well as a trend for smaller hippocampi bilaterally. Results are shown in Figure 4.

TABLE 1. CHARACTERISTICS OF THE TWO GROUPS

Measure	Mild TBI	Control	
Age	31.0 ± 13.9	29.4 ± 11.7	Two-tailed <i>t</i> = 0.50, <i>p</i> = 0.62 χ^2 = 0.065, <i>p</i> = 0.80
Sex	26M + 18F	18M + 11F	
Scan-scan interval	322–490 days (384.3 ± 38.9)	336–437 days (383.9 ± 30.0)	Two-tailed <i>t</i> = 0.05, <i>p</i> = 0.96
Relative Intracranial Volume at Scan 1	224.79 ± 26.19	223.79 ± 22.91	Two-tailed <i>t</i> = 0.50, <i>p</i> = 0.33

TABLE 2. COMPARISON OF GROUP VOLUMES AT 2 MONTHS AND 1 YEAR AFTER INJURY

Measure	Two months after injury					One year after injury				
	Controls		mTBI		p	Controls		mTBI		p
	Mean	Std. error	Mean	Std. error		Mean	Std. error	Mean	Std. error	
RPutamen	4.951	0.093	4.756	0.112	0.0016*	4.887	0.128	4.799	0.085	0.0002*
RThalamus	7.103	0.108	6.842	0.099	0.0049*	7.025	0.090	6.844	0.110	0.0060*
RHippocampus	4.150	0.058	3.988	0.091	0.3090	4.094	0.065	3.884	0.060	0.0819 [†]
RAmygdala	1.857	0.043	1.803	0.036	0.2387	1.858	0.035	1.787	0.027	0.0303*
RCaudate	4.970	0.093	4.725	0.091	0.0010*	4.939	0.079	4.768	0.084	0.0006*
LPutamen	4.963	0.110	4.820	0.126	0.0025*	5.077	0.082	4.862	0.080	0.0000*
LThalamus	7.270	0.091	7.016	0.148	0.0671 [†]	7.179	0.100	6.954	0.097	0.0148*
LHippocampus	4.057	0.059	3.975	0.068	0.5036	4.039	0.049	3.891	0.081	0.0872 [†]
LAmygdala	1.897	0.032	1.887	0.031	0.7198	1.921	0.027	1.830	0.029	0.0009*
LCaudate	4.844	0.095	4.618	0.102	0.0027*	4.804	0.082	4.631	0.084	0.0013*
Corpus Callosum	6.217	0.172	5.897	0.173	0.2888	6.303	0.185	6.083	0.156	0.4784
Brainstem	28.157	0.261	28.762	0.325	0.5756	28.289	0.245	28.700	0.350	0.7361
Cerebellum	143.359	0.698	145.611	0.863	0.4682	143.772	0.842	144.628	0.725	0.4999

The overall multivariate analysis of covariance was significant at 2 months after injury ($p=0.0139$) and 1 year after injury ($p=0.007$). Significant *post hoc* comparisons ($p<0.05$) are signified by *, trends ($p<0.1$) signified by [†]. mTBI, mild traumatic brain injury.

MANCOVA with repeated measures indicates no significant volumetric changes in the control group over time (Wilks' lambda = 0.9003, $df=1$, $F=0.37$, $p=0.9711$). In contrast, the mTBI group showed significant overall group difference (Wilks' lambda = 0.6752, $df=1$, $F=2.66$, $p=0.0042$), and reduced group volumes over time for the amygdala, hippocampus, brainstem, and cerebellum. Significant *post hoc* comparisons ($p<0.05$) were detected in the left caudate ($p=0.0322$), right putamen ($p=0.0448$), and left amygdala ($p=0.0284$). *Post hoc* trends ($p<0.1$) were detected in the left putamen ($p=0.0652$). Results are illustrated in Figure 5; all group volumes are provided in Table 2.

Discussion

Our results are consistent with the hypothesis that mTBI is associated with small but detectable and statistically significant re-

ductions in volume in key subcortical structures 2 months after injury. These differences persist at 1 year but are less marked in the caudate and putamen and increased in the hippocampus and amygdala. This suggests the possibility of normalization over time in basal ganglia structures, whereas mesial temporal structures may follow a different and perhaps less favorable trajectory.

Further, from a technological and methodological perspective, these results suggest that the shape-constrained deformable brain model has the necessary sensitivity to detect volumetric changes in affected persons, and the potential to enhance our understanding of underlying disease mechanisms and their related clinical manifestation. The ability to have rapid and highly accurate evaluation of volume and shape of a large number of brain structures would allow for the development of novel imaging biomarkers that are needed in the diagnosis and monitoring of TBI. It would allow for tracking of

FIG. 3. The overall multivariate analysis of covariance was significant at 2 months after injury ($p=0.0139$). Significant *post hoc* comparisons ($p<0.05$) signified by *, and trends ($p<0.1$) signified by [†], were detected in the caudate, putamen, and thalamus ($p=0.0027^*$; 0.0010^* ; 0.0025^* ; 0.0016^* ; $0.0671^{\dagger}$; 0.0049^*). mTBI, mild traumatic brain injury.

FIG. 4. The overall multivariate analysis of covariance was significant at 1 year after injury ($p=0.0007$). Significant *post hoc* comparisons ($p<0.05$) signified by *, and trends ($p<0.1$) signified by [†], were detected in the caudate, putamen, thalamus, amygdala, and hippocampus at 1 year ($p=0.0013^*$; 0.0006^* ; 0.0001^* ; 0.0002^* ; 0.0148^* ; 0.0060^* ; 0.0009^* ; 0.0303^* ; $0.0872^{\dagger}$; $0.0819^{\dagger}$). mTBI, mild traumatic brain injury.

FIG. 5. The overall multivariate analysis of covariance with repeated measures indicates significant volumetric changes in the mild traumatic brain injury (mTBI) group over time ($p=0.0042$). Significant *post hoc* comparisons ($p<0.05$) were detected in the left caudate ($p=0.0322$), right putamen ($p=0.0448$), and left amygdala ($p=0.0284$). *Post hoc* trends ($p<0.1$) were detected in the left putamen ($p=0.0652$).

measurements over time and their correlation with various functional modalities. The data, however, reflect group level change, and more work is needed to establish volumetric norms and validate this model before applying it to persons in a clinical context.

Existing work suggests that mTBI is associated with quantifiable atrophy of regional brain parenchyma. Mackenzie and coworkers¹⁵ reported no difference in total brain parenchyma volume between 14 patients with mild-moderate TBI shortly after injury and 10 healthy controls; however, 7 of the patients followed up at least 3 months later had greater decline in parenchymal volume than the comparison subjects ($n=4$). Ross and associates¹⁶ compared regional brain volumes in 16 patients with mTBI and 20 healthy controls. The mTBI group was imaged initially a mean of 2 years after injury and then imaged again 1 year later on average. Results suggested significantly greater volume loss for whole brain, “forebrain,” cerebral white matter, and cerebellum, with a trend for brainstem ($p=0.07$).

Mayer and colleagues¹⁷ compared 15 semi-acute pediatric patients with mTBI (pmTBI) with 15 matched controls with a subset of patients returning for a second visit. Results indicated decreased attention scores and processing speed. Increased anisotropic diffusion in the left superior temporal gyrus and right thalamus were also reported. The cognitive performance partially normalized at 4 months while the increased diffusion persisted in addition to cortical atrophy in bilateral frontal and left-hemisphere cortical areas. The study suggested differential time-course of recovery for neurobehavioral markers, anisotropic diffusion, and atrophy after pmTBI.

Our work extends these studies in a much larger cohort of patients with mTBI, using a novel method of quantifying subcortical volume of structures known to play important roles in the neurobehavioral symptoms often associated with TBI. Our findings are consistent with these previous suggestions that sensitive measures of brain structure do suggest changes associated with mTBI when examined approximately 2 months after injury. Another important practical consideration is that our quantification approach is fully automatic. It does not require any user interaction and can be accomplished in just seconds per volume versus minutes to hours needed by existing leading examples.

The finding that some subcortical structures appeared to normalize with time (caudate, putamen), whereas other regions (hip-

pocampus and amygdala) showed a greater discrepancy relative to controls is of interest. A body of work in animal models of TBI suggests that some brain regions, particularly hippocampus and other mesial temporal structures, may be differentially sensitive to the effects of TBI (see McIntosh¹⁸ and Thompson and associates¹⁹ for reviews).

On the other hand, a recent report of college athletes engaged in contact sports found no significant differences in white matter metrics relative to noncontact sport athletes before the season of play, but did find subtle differences at the end of a single season that were correlated with how hard and how often athletes were hit during the season.²⁰ The absence of preseason differences despite years of exposure to repetitive head impacts suggests the possibility that normalization in some measures of brain structure can occur over time. Further work is needed to replicate these observations, and to characterize whether different brain regions may have different susceptibility to trauma in humans.

This study has several limitations that should be considered. First, because we do not have volumetric measures before brain injury, we cannot conclude that the group volumetric differences are attributable to the injury itself. An alternate possibility would be that these differences pre-dated the injury and perhaps even represent a risk factor for having a mTBI. On the other hand, the fact that the volumes changed over time in the mTBI group is arguably more consistent with the theory that smaller regional volumes were a response to the injury rather than a trait. In addition, there was no statistically significant difference in relative intracranial volume between the two groups at 2 months, which could be another indication that the mTBI did not have pre-morbidly smaller subcortical volumes.

The neurophysiological processes underlying these subtle changes in volume in the mTBI group are not known. The observed differences could be related primarily to changes in gray matter volume, white matter volume, or both. Further, although these are statistically significant between-group differences, we have not established that the initial group differences are functionally significant, nor that normalization of regional volumes is associated with normalization of function. Future work will be needed to replicate these findings and to examine the relationship between the observed volume differences and neurocognitive outcome and recovery.

Despite these limitations, the newly developed shape constrained deformable brain model shows promise as a sensitive measure of structural brain change after mTBI, and the results of this study are consistent with our hypothesis that mTBI is associated with subtle differences in regional brain volumes. The observation that volumes of these regions changed over the study interval in the mTBI group but not in controls is intriguing and suggests that volume change may be a dynamic process after injury.

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Author Disclosure Statement

No competing financial interests exist.

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