Diffusion Tensor Imaging Atlas-Based Analyses in Major Depression After Mild Traumatic Brain Injury

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Abstract

There are currently no known early neuroanatomical markers predictive of the development of major depression or depressive symptoms after mild traumatic brain injury (mTBI). The authors conducted a 1-year longitudinal pilot study to determine whether diffusion tensor imaging (DTI) measures collected within 1 month of mTBI could predict incident depression. Of the 14 subjects who met study inclusion criteria, 4 (28.6%) developed major depression over the follow-up period. Compared with the nondepressed group, those who developed depression had white-matter abnormalities in the fronto-temporal regions measured by DTI. These preliminary results highlight the need for additional studies, including studies using a larger sample and appropriate controls.

Major depression is common after a traumatic brain injury (TBI), with an overall prevalence of approximately 30%.[1] After mild traumatic brain injury (mTBI), which accounts for about 80% of all TBIs (Centers for Disease Control and Prevention [CDC], National Center for Injury Prevention and Control: Report to Congress on Mild Traumatic Brain Injury in the United States: Steps to Prevent a Serious Public Health Problem. Atlanta, GA, 2003) major depression develops in approximately 15%–18% of patients.[2,3] Despite the known association between major depression and mTBI, no neuroanatomical markers have been identified that are predictive of the development of major depression. This is not merely an academic question, because early identification of biomarkers associated with depression could facilitate early diagnosis and treatment, significantly reducing morbidity in patients with mTBI.

The pathophysiology of mTBI is complex, and it includes a combination of both diffuse axonal damage and secondary metabolic injury.[4,5] In many patients where clinical deficits are exhibited, neuronal changes after mTBI are subtle and cannot be identified by routine MRI or CT scans. However, diffusion tensor imaging (DTI), which is known to be sensitive to the microscopic anatomical status of axonal structures, may have the potential to detect diffuse microstructural injury that is associated with mTBI and invisible to conventional MRI pulse sequences.[6,7] DTI measures the microscopic random translational motion of water molecules.[8] Because freedom of motion is restricted by interactions with other molecules, the structure of axons, and integrity of neuronal membranes, DTI measures can be used as markers of tissue organization at a microscopic level. Therefore, DTI represents a promising approach to quantifying microscopic brain damage by measuring both water diffusion (mean diffusivity [MD]) and the degree of diffusion directionality, or anisotropy (fractional anisotropy [FA]).[9] To-date, no studies have employed DTI methods during the acute/subacute mTBI period in an effort to define the neuropathology of brain changes associated with major depression that develop during the first year after TBI. However, one recently published cross-sectional study of blast-associated concussion compared DTI measures in servicemen with and without major depression in the chronic-injury period[10] and found a correlation between microstructural abnormalities in the left superior longitudinal fasciculus and depression severity.

In an effort to determine whether DTI measures collected in the acute and subacute mTBI period could provide predictive anatomical correlates of major depression, we conducted a longitudinal pilot study in mTBI patients during the first 12-months after injury. The goal of the present study was to test the hypothesis that injury to cortical and subcortical regions (e.g., frontal cortex, temporal cortex, basal ganglia, and associated white matter) increases the risk for depression in the first year after mTBI. We hypothesized that among mTBI patients, those with increased directional diffusion, measured by FA and increased MD in the white-matter regions of the frontotemporal-basal ganglia circuit would be more likely to develop depression within 1 year after injury. The frontotemporal basal ganglia regions were chosen because they have previously been found to be associated with depression in patients with moderate-to-severe TBI.[1,11,12]

METHOD

Subjects

Subjects with recent closed head injury were recruited from Johns Hopkins Hospital, Johns Hopkins Bayview Medical Center, and from the local community via advertisements, to participate in an IRB-approved longitudinal study of mTBI and depression. After providing informed consent, subjects were assessed with structured and semistructured interviews and underwent a DTI scan once, within 1 month of injury. Subsequent visits took place at 3, 6, and 12 months after mTBI, and involved reassessment of baseline clinical outcome measures, but the MR scans were not repeated. To be included in the study, subjects needed to have sustained a closed head injury with a Glasgow Coma Scale score of 13 within 1 month of study participation, and meet the American Congress Rehabilitation Medicine

(ACRM) criteria for mild TBI. All subjects were between the ages of 18 and 65, and had no history of previous major depression/other psychiatric disorders or previous brain injury.

Clinical Outcome Measures

The Structured Clinical Interview for DSM-IV (SCID-IV) was administered at each visit to establish Axis I psychiatric diagnoses. Per DSM-IV criteria, depressive disorders after TBI were categorized as, 'Mood Disorder Due to General Medical Condition' (MDD GMC), with subtypes of 1) major depressive-like episode (if the full criteria for a major depressive episode were met); or 2) depressive features (prominent depressed mood but full criteria for a major depressive episode were not met). Only those with MDD GMC were included in the analyses. The Hamilton Rating Scale for Depression (Ham-D-17) was used to assess the severity of depression at all follow-up visits.

Neuroimaging Evaluation

Brain MRIs were performed on a research-dedicated Philips 3.0 Tesla scanner. DTI data acquisition was performed by single-shot echo-planar imaging, with 32 diffusion-weighting orientations and 5 b0 images. The b-value was 700 s/mm^2. Parallel imaging with SENSE factor 2.5 was used. More than 60 gapless axial sections with 2.2-mm thickness were acquired to cover the entire brain. The field of view was 212×212 mm, and the image matrix was 96×96, which was zero-filled to 256×256 mm.

Images were processed by someone who was blind to Case/Controls status. All data processing was performed with DTI Studio.[13] The raw diffusion-weighted images (DWIs) were first co-registered to one of the least DWIs and corrected for eddy current and subject motion with a 12-mode affine transformation of Automated Image Registration (AIR). The warping was applied to all raw DWIs. The six elements of the diffusion tensor were calculated for each voxel with multivariate linear fitting.[13] After diagonalization, three eigenvalues and eigenvectors were obtained. For the anisotropy map, FA was used.[9] Before the normalization procedure, the skull was stripped, using the b0 images and a skull-strip tool in ROI Editor software. (Li X, Jiang H, and Mori S: Johns Hopkins University; www.MriStudio.org).

For image analysis, automated parcellation based on large-deformation diffeomorphic metric mapping (LDDMM)[14] was used, as previously described,[15] in which the entire brain was parcellated into 130 structures, as defined in an atlas template called "Eve" atlas.[16] The LDDMM-based transformation was performed by DiffeoMap, using dual-contrast LDDMM (described by Ceritoglu et al., 2009).[17] After LDDMM, the transformation matrix was applied to the parcellation map defined in the Eve atlas, warping it to the shape of the patient images and thereby dividing the brain into 130 structures. For the parcellated structures that contain the cortical area, the cortex and the associated peripheral white matter were further segmented by using FA threshold at 0.25. After this segmentation, the total number of defined structures became 176; then the FA and MD of each parcellated area were quantified, using ROI Editor (Li X, Jiang H, and Mori S: Johns Hopkins University; www.MriStudio.org).

Statistical Analyses

The clinical and DTI data for subjects who developed major depression at any time during the 3–12 month post-injury period were compared with those who had not developed major depression during the same period by Fisher's exact test for categorical variables and Student's *t*-test for continuous variables. Student's *t*-tests were used to examine differences in mean FA and MD of the atlas-based brain regions by Ever/Never major depression diagnosis over the 1-year follow-up. Statistical significance was a priori defined as p<0.05. Linear mixed-effects models with subject-specific intercepts were used to examine the relationship between the atlas-based brain region FA and MD and change in the Ham-D-17 scores over the follow-up. This approach permitted assessment of the effects of key fixed factors, such as baseline DTI, on average rate of change in Ham-D-17 scores, while accounting for individual trajectories and within-subject repeated measures with respect to time.[18] For linear mixed models, FA was transformed by multiplying by 10^2 and MD by 10^4 in order to examine the clinical utility of the relationships.

RESULTS

Approximately 150 mTBI subjects were screened. Of these, only 21 subjects met study inclusion criteria and were enrolled; 4 of the 21 subjects who consented did not return for any follow-up visit. There were no differences between those who had a follow-up visit and those who did not with regard to age, education, gender, living situation, marital status, or severity of body injury. Three others were excluded from the analyses because of a second, severe motor vehicle accident during the study period (N=1), a previous severe TBI (N=1), and a pre-TBI history of bipolar disorder and AIDS (N=1). The most common cause of injury in both groups was motor vehicle accident (N=5). Other causes included falls (N=2), sports (N=3), assault (N=2), and other causes (N=2; wooden board fell on head; ran into door).

Of the 14 subjects who were followed, 4 (28.6%) met criteria for Mood Disorder Due to General Medical Condition' (MDD-GMC), major depressive-like episode subtype for at least one follow-up visit within 1 year after the TBI. Demographic data for these subjects and the 10 subjects who did not develop major depression are provided in Table 1.

The image quality for one individual was poor and could not be processed, leaving 13 persons with DTI for subsequent analyses. To test the primary study hypotheses, FA values from the depressed (Case) and the non-depressed (Control) groups were compared in several brain regions included in the fronto-temporal basal ganglia circuit (Table 2). The only statistically significant difference was observed in the left superior temporal gyrus (p=0.03). Despite the lack of significance, the effect sizes of many regions were quite large (>0.8). Mean values for MD values in the same regions were also compared between the depressed and nondepressed groups, but no statistically significant associations or trends toward significance were found.

The relationship between DTI measures in atlas-based brain regions and Ham-D-17 score trajectories were also examined with linear mixed models (Table 3). As mentioned above, DTI scan were only performed once, within the first month of mTBI, whereas psychiatric

evaluations and Ham-D scores were determined at the 3rd, 6th, and 12th month after mTBI. Although there was no association between FA or MD in any region and Ham-D-17 score at baseline, lower baseline FA scores (indicating decreased white-matter integrity) in the superior temporal gyrus (p=0.042) and the middle temporal gyrus (p=0.016) were predictive of higher Ham-D-17 scores over time. Similarly, higher MD scores (indicating more microstructural abnormalities) in the right superior longitudinal fasciculus (p=0.045), inferior frontal white matter (p=0.004), and superior (p=0.02) temporal white matter were predictive of increasing Ham-D-17 scores. However, higher MD in the left side of the superior longitudinal fasciculus (p=0.05) was associated with lower Ham-D-17 scores.

DISCUSSION

To our knowledge, this is the first study to examine whether brain white-matter changes, quantified using DTI, in the acute mTBI period could be used as predictive markers for the subsequent development of major depression in the year after brain injury. Results from this pilot study suggest that microstructural abnormalities in the fronto-temporal white-matter regions in the early mTBI period are associated with the development of major depression and more depressive symptoms, as measured with the Ham-D-17, in the first year post-TBI. These results are supported by other studies that have found gray- and white-matter abnormalities in the temporal lobe in primary major depression. Takahashi et al.,[19] using MRI imaging, delineated the superior temporal gyrus subregions and compared subjects with current primary major depression and remitted depression and noted that both current and remitted depressed subjects had significant volume reduction of the left planum temporale and bilateral caudal superior temporal gyrus as compared with controls. Abe et al.[20] also compared subjects with primary major depression and normal-controls and reported increased median diffusivity in the depressed patients in several regions, including bilateral parahippocampal gyri, hippocampus, pons, cerebellum, left frontal and temporal lobes, and right frontal lobe, implicating the role of the fronto-limbic circuit in the neuropathology of depression. An MRI volumetric study by Morys et al.[21] also found that the only difference between patients with primary major depression and healthy-controls was the increased volume of the left temporal horn of the lateral ventricle.

The only previous study to examine DTI neurocorrelates of mTBI depression is a study of military veterans by Mathews et al.[10] They compared 11 MDD and 11 non-MDD Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) servicemen recruited from outpatient clinics with a self-reported history of blast-related concussion about 2 years after injury. They found lower FA values in the left superior longitudinal fasciculus (SLF), which is a large, white-matter tract that connects the DLPFC with the temporal, parietal, and occipital lobes. Our study results reveal a positive relationship between increased white-matter diffusivity in the right SLF and increased Ham-D-17 scores, and a negative relationship between left SLF integrity and depressive symptoms; that is, reduced diffusivity in the left SLF is associated with increased Ham-D-17 scores. Inconsistencies such as these can be best resolved by studying a larger sample than in the current study.

The small sample size, absence of a healthy-control group, and multiple comparisons are the major limitations of the study. The results, therefore, should be considered preliminary and

used for designing a larger study. Similarly, because of the absence of data from a healthy-control group, the white-matter abnormalities noted can also be viewed as the direct results of brain injury from trauma. Tips of the frontotemporal lobes are more vulnerable to injury after trauma, and previous studies have found white-matter abnormalities in this region in mTBI subjects, as compared with normal-controls.[7,22] Rutgers et al.[23] compared 21 mTBI subjects, with a median time of 5.5 months after injury with 11 normal-control subjects and found that mTBI subjects had reduced FA in nine regions, with the most severe in the cerebral white matter, cingulum, and corpus callosum. Cubon et al.[24] found diffuse white-matter tract abnormalities in the left hemisphere, more specifically in the inferior/superior longitudinal and fronto-occipital fasciculi, the retrolenticular part of the internal capsule, posterior thalamic and acoustic radiations in college athletes with sports-related concussion 1 month after injury. However, in a recently published study[25] compared 37 blast-injured servicemen with mild-to-moderate TBI with 15 veterans without history of blast injury or TBI. There were no differences between the two groups on FA or MD on DTI-based tractography and voxel-based analysis. It is important to note that in that study, TBI/blast-injured subjects were, on average, more than 2 years post-injury, in contrast to the present study, in which subjects were studied acutely.

It is possible that the results of our study are chance findings because of multiple comparisons and the small sample size. However, the results of the linear mixed models reveal an association between Ham-D-17 scores and FA/MD values, suggesting that the results are more than a chance finding. Also, a previous cross-sectional study of blast-associated concussion reported an association between the superior longitudinal fasciculus and depression,[10] further suggesting that these findings are not simply due to chance.

In summary, the results of this pilot study suggest that microstructural abnormalities in the fronto-temporal regions in the early mTBI period are predictive of incident major depression in the first year post-TBI in subjects without a previous history of major depression.

CONCLUSION

These results should be considered preliminary and as the first step to designing a larger study with matched healthy-control subjects. Studies such as these have the potential for identifying neuroimaging predictive markers of depression in mTBI, which are much-needed.

Acknowledgments

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TABLE 1

Demographic Comparison of mTBI Depressed and mTBI Nondepressed Patients

Variables	mTBI Depressed (N=4)	mTBI Non-Depressed (N=10)	p
Age, years	37 (9)	35.7 (12)	NS
Sex (Males)	6 (60%)	4 (100%)	NS
Education	14.6 (2.8)	12.2 (1.5)	NS
LOC duration	0.75 (0.5)	0.70 (0.5)	NS
Body injury	25%	20%	NS
Abnormal MRI	25%	40%	NS
LOC	75%	80%	NS
Memory loss	75%	60%	NS
Caucasians	25%	30%	NS
Marital status	50	40%	NS
Employed	100%	50%	NS
Income >$20K	75%	10%	0.04
Positive family history of depression	25%	10%	NS
Ham-D-17 score, baseline	0.5 (1.0)	1.9 (3.2)	NS
Ham-D-17 score, 3 months	3.3 (4.6)	5.4 (6.8)	NS
Ham-D-17 score, 6 months	9.8 (11.4)	4.0 (4.1)	NS
Ham-D-17 score, 12 months	20.5 (3/7)	7.1 (6.7)	0.004

Values are mean (standard deviation), unless otherwise specified.

TABLE 2

Comparison of the Fractional Anisotropy Values Between Depressed and Nondepressed Subjects

	Nondepressed (N=9)	Depressed (N=4)	p	Cohen's d
Superior frontal gyrus, left	0.108 (0.004)	0.105 (0.003)	NS	0.85
Middle frontal gyrus, left	0.102 (0.005)	0.096 (0.004)	0.07	1.33
Inferior frontal gyrus, left	0.108 (0.003)	0.105 (0.004)	0.11	0.84
Superior temporal gyrus, left	0.112 (0.004)	0.106 (0.004)	0.03	1.50
Middle temporal gyrus, left	0.111 (0.005)	0.106 (0.004)	0.05	1.10
Inferior temporal gyrus	0.112 (0.006)	0.110 (0.009)	NS	0.26
Caudate nucleus, left	0.215 (0.030)	0.198 (0.002)	NS	0.80
Putamen, left	0.198 (0.021)	0.204 (0.010)	NS	−0.36
Globus pallidus, left	0.300 (0.027)	0.303 (0.028)	NS	−0.11
Thalamus, left	0.333 (0.018)	0.341 (0.019)	NS	−0.43
Superior frontal WM, left	0.368 (0.012)	0.381 (0.025)	NS	−0.66
Middle frontal WM, left	0.341 (0.014)	0.352 (0.018)	NS	−0.68
Inferior frontal WM, left	0.357 (0.019)	0.365 (0.013)	NS	−0.49
Superior temporal WM, left	0.336 (0.012)	0.337 (0.010)	NS	−0.09
Middle temporal WM, left	0.350 (0.010)	0.356 (0.011)	NS	−0.57
Inferior temporal WM, left	0.326 (0.014)	0.325 (0.011)	NS	0.08
Superior frontal gyrus, right	0.110 (0.004)	0.107 (0.002)	NS	0.95
Middle frontal gyrus, right	0.101 (0.005)	0.097 (0.002)	0.10	1.05
Inferior frontal gyrus, right	0.109 (0.003)	0.105 (0.005)	0.07	0.97
Superior temporal gyrus, left	0.112 (0.004)	0.108 (0.005)	NS	0.88
Middle temporal gyrus, right	0.111 (0.004)	0.105 (0.005)	0.06	1.33
Inferior temporal gyrus, right	0.113 (0.008)	0.108 (0.005)	NS	0.75
Caudate nucleus, right	0.219 (0.034)	0.202 (0.009)	NS	0.68
Putamen, right	0.205 (0.018)	0.199 (0.021)	NS	0.31
Globus pallidus, right	0.348 (0.046)	0.325 (0.029)	NS	0.60
Thalamus, right	0.330 (0.018)	0.346 (0.020)	NS	−0.84
Superior frontal white matter, right	0.365 (0.014)	0.369 (0.024)	NS	−0.20
Middle frontal WM, right	0.343 (0.017)	0.348 (0.014)	NS	−0.32
Inferior frontal WM, right	0.354 (0.016)	0.356 (0.017)	NS	−0.12
Superior temporal WM, right	0.339 (0.014)	0.339 (0.012)	NS	0
Middle temporal WM, right	0.352 (0.013)	0.355 (0.009)	NS	−0.27
Inferior temporal WM, right	0.323 (0.013)	0.321 (0.010)	NS	0.17

Values are mean (standard deviation), unless otherwise specified.

WM: white matter.

TABLE 3

DTI Measures Predict Changes in Ham-D-17 Over 1 Year Among 13 Mild TBI Participants

Regions of Interest	Baseline Association: b (95% CI); p	Longitudinal Association b Time (95% CI); p
FA superior temporal gyrus, left	3.09 (−3.72, 9.91); 0.374	−0.80 (−1.56, −0.03); 0.042
FA middle temporal gyrus, left	−1.05 (−6.35, 4.26); 0.70	−0.80 (−1.45, −0.15); 0.016
MD superior longitudinal fasciculus, right	−0.91 (−4.43, 2.61); 0.61	0.50 (0.12, 0.87); 0.009
MD superior longitudinal fasciculus, left	0.04 (−4.35, 4.43); 0.99	−0.51 (−1.02, −0.01); 0.045
MD superior frontal gyrus, right	−0.32 (−2.77, 2.12); 0.80	0.26 (−0.02, 0.54); 0.066
MD superior frontal WM, right	0.27 (−3.72, 4.26); 0.89	0.40 (−0.03, 0.83); 0.07
MD inferior frontal WM, right	−0.38 (−4.27, 3.51); 0.85	0.66 (0.21, 1.10); 0.004
MD superior temporal WM, right	−0.56 (−4.48, 3.35); 0.78	0.52 (0.10, 0.95); 0.016
MD middle temporal WM, right	−1.73 (−7.54, 4.09); 0.56	0.54 (−0.07, 1.15); 0.08

CI: confidence interval; FA: fractional anisotropy; MD: mean diffusivity; WM: white matter.

b: association between the region of interest and FA or MD at baseline.

b: *Time: baseline FA or MD predicting change over 1 year (4 visits), using linear mixed models.