ORIGINAL ARTICLE

Use of Diffusion Tensor Imaging to Examine Subacute White Matter Injury Progression in Moderate to Severe Traumatic Brain Injury

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ABSTRACT. Greenberg G, Mikulis DJ, Ng K, DeSouza D, Green RE. Use of diffusion tensor imaging to examine subacute white matter injury progression in moderate to severe traumatic brain injury. Arch Phys Med Rehabil 2008;89(12 Suppl 2):S45-50.

Objective: To demonstrate subacute progression of white matter (WM) injury (4.5mo–2.5y postinjury) in patients with traumatic brain injury using diffusion-tensor imaging.

Design: Prospective, repeated-measures, within-subjects design.

Setting: Inpatient neurorehabilitation program and teaching hospital MRI department.

Participants: Brain-injured adults ($N=13$) with a mean Glasgow Coma Scale score of 7.67 ± 4.16.

Interventions: Not applicable.

Main Outcome Measures: Fractional anisotropy (FA) values were measured at 4.5 and 29 months postinjury in right and left frontal and temporal deep WM tracts and the anterior and posterior corpus callosum.

Results: FA significantly decreased in frontal and temporal tracts: right frontal ($.38\pm.06$ to $.30\pm.06$; $P<.005$), left frontal ($.37\pm.06$ to $.32\pm.06$; $P<.05$), right temporal ($.28\pm.05$ to $.22\pm.018$; $P<.005$), and left temporal ($.28\pm.05$ to $.24\pm.02$; $P<.05$). No significant changes were in the corpus callosum.

Conclusions: Preliminary results demonstrate progression of WM damage as evidenced by interval changes in diffusion anisotropy. Future research should examine the relationship between decreased FA and long-term clinical outcome.

Key Words: Brain injuries; Follow-up studies; Magnetic resonance imaging; Rehabilitation.

TRAUMATIC BRAIN INJURY refers to an injury caused by externally inflicted trauma to the brain and can result in significant cognitive, motor, and psychosocial impairments.[1-4] A large proportion of patients with moderate and severe TBI are young adults[5]; consequently, these patients often face decades of disability, with associated emotional, social, and financial difficulties.[6] This chronic period of disability has received only limited scientific attention, particularly with respect to neuroimaging research. Clinically, it is generally assumed that ongoing disability is attributable to the residual deficits from the original injury; however, recent findings suggest that some degree of neurological deterioration may occur after the initial acute injuries have resolved.[7-12] Chronic disability could be caused by a combination of acute injury and chronic progressive damage.

Recovery from TBI has been widely studied with the general finding that recovery is asymptotic. Maximal behavioral recovery occurs during the early months postinjury followed by a plateau at approximately 6 to 18 months post-TBI,[13,14] with plateau variations largely attributable to differences in outcome measures[15] and other methodologic differences across studies.[16,17] Recent findings have suggested, however, that behavioral recovery curves may be characterized— for some patients in some areas of functioning— by a more parabolic shape, with a decline in cognitive status after initial recovery.[8,10,12] There is neurophysiologic evidence of this long-term decline from neuropathologic investigations in animals[7,9] and neuroimaging studies in humans; the latter studies have employed both volumetric MRI measurements[11,15,18] as well as visual inspection of lesions by experts.[11]

Much of the neurophysiologic evidence to date is equivocal, however. Many of the observed changes over time may be attributable to the resolution of early acute effects of the primary injury. In most studies, the baseline (comparator) scan was undertaken early post-TBI, when acute changes were resolving (eg, reduction of inflammatory cells, edema, and hyperemia; involution of hematoma). In some studies, both the first and the second scan were conducted during the acute phase[19-22]; in others, the second scan was conducted in the chronic phase,[23,24] but the first was carried out during the acute phase. Therefore, with the exception of the study in this issue

List of Abbreviations

CT	computed tomography
DAI	diffuse axonal injury
DTI	diffusion-tensor imaging
FA	fractional anisotropy
FLAIR	fluid-attenuated inversion recovery
MRI	magnetic resonance imaging
NS	not significant
PTA	posttraumatic amnesia
ROI	region of interest
SPGR	spoiled gradient recalled
TBI	traumatic brain injury
WM	white matter

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by Ng et al,[11] it is unclear whether the interval change in these studies was attributable to atrophy or rather to the full, neuroradiologic manifestations of the original injury.

Previous human neuroimaging studies that have examined the question of progression of atrophy have employed conventional MRI techniques such as proton, T2-weighted, and SPGR imaging. To date, there are no studies that have used DTI. However, this technique is highly sensitive to the neuropathology of TBI, more so than conventional imaging,[19,25-27] and therefore represents a valuable tool for examining this question.

DTI is a relatively recent development in MRI technology. It is an ideal tool for investigating progression of atrophy in TBI because of its sensitivity to abnormalities in the microstructure of WM (eg, Naganawa et al[21]), which is extensively disrupted after TBI,[28,29] and because correlations have been observed between DTI and TBI outcome.[23,30] DAI lesions are frequently microscopic and often underestimated by conventional MRI and typically invisible on CT[19,22,31] compared with DTI. In 1 study, Huisman et al[19] found that approximately 16% of DAI lesions were identifiable exclusively by DTI compared with conventional MRI (T2/FLAIR and T2-weighted gradient echo sequences).

In general, DTI works by incorporating pulsed magnetic field gradients into a standard MRI sequence that characterizes the local diffusivity of water.[31] In healthy WM, there is greater diffusion along the long axis of axonal bundles than along the radial axis because of hindrance from the myelin sheath.[22,32] Two key measures associated with water diffusion are diffusivity, the magnitude of diffusion; and anisotropy, the directionality of water diffusion.[32] DTI data can be used to generate images of FA,[22] an index comparing the preferred direction of water diffusion with its orthogonal component. Accordingly, a decreased FA value has been shown to be largely the result of selected increases in diffusion along the radial axis of axonal bundles. FA is sensitive to changes in WM integrity[33,34] and provides pertinent information regarding the degree of WM damage including factors such as myelin sheath thickness and axonal membrane integrity.[22,35] Given that WM damage is a predominant feature of TBI, it is not surprising that a number of studies have demonstrated decreases in FA values in severe TBI.[21,22,24,27,32]

The aim of the current study was to determine whether there is evidence of increasing WM injury after moderate and severe TBI using DTI-derived FA values. This is based on previous findings from our group that showed robust progression of atrophy, often adjacent to the site of original lesions. Thus, based on the findings by Ng et al,[11] we predicted significant declines in FA values in the selected ROIs, which were selected for the high probability of damage from the initial injury. Six preselected ROIs were examined. These include frontal and temporal deep WM tracts, and the anterior and posterior regions of the corpus callosum. These regions were selected because previous studies have identified them as particularly susceptible to WM injury after TBI.[21,22,25,27,32,36-39] Thirteen patients underwent neuroimaging at 2 time points: the first was undertaken at 4.5 months postinjury, after resolution of acute injury; and the second was completed at 2.5 years postinjury. ROI maps were generated at both time points, and the change in FA values was compared within subjects for each ROI.

METHODS

Participants

The study protocol was approved by the research ethics board at the Toronto Rehabilitation Institute, and the procedures of the study were in accordance with the standards of the research ethics board.

Thirteen adult patients (10 men, 3 women) with TBI were enrolled in the study. As indicated in table 1, this group was in the severely impaired range, had a high school education, was of average estimated premorbid intelligence, and had the expected high male to female ratio. All patients had been admitted to the Inpatient Neurorehabilitation Program of the Toronto Rehabilitation Institute, a large, urban inpatient hospital, between 2004 and 2007. They were recruited from a larger, ongoing prospective study of cognitive and motor recovery from TBI.

Patients were eligible for the larger study if they met the following criteria: (1) acute care diagnosis of TBI, (2) PTA 1 hour or more and/or Glasgow Coma Scale of 12 or less either at the emergency department or the scene of accident and/or positive acute care CT or MRI findings, (3) age between 18 and 80 years, (4) able to follow simple commands in English, and (5) competency to provide informed consent for study or availability of legal decision-maker. Exclusion criteria were (1) orthopedic injury affecting both upper extremities and/or both lower extremities, (2) diseases primarily or frequently affecting the central nervous system, (3) history of psychotic disorder, (4) not emerged from PTA by 6 weeks postinjury, (5) TBI secondary to other brain injury (eg, a fall because of stroke), and (6) metal implants precluding MRI.

To be eligible for the current study, participants needed additionally to have completed the 4.5-month MRI, to have reached the long-term follow-up stage, and to have not developed further neurological complications (eg, subsequent brain injury, hydrocephalus). There were 18 eligible patients. Four patients were unreachable by telephone or mail; 1 had compromised MRI acquisition data. Thus, 13 patients participated in the current study, representing a retention rate of 72%. (Note that this sample of patients, minus 1, was also tested in the study by Ng[11]). As shown in table 1, those participating were highly similar to those lost to follow-up, with the possible exception of estimated premorbid intelligence quotient, for which the mean was more than 4 points higher in the latter group. This was attributable to 1 patient with 21 years of education, however.

Design and Procedures

Baseline MRI was performed at a mean ± SD of 4.5±.40 months postinjury. Follow-up MRI was conducted at a mean ± SD of 29.3±4.0 months postinjury.

Magnetic Resonance Imaging Acquisition

All patients were scanned on a GE 1.5-Tesla HD MRI system[a] using a series of conventional sequences. These included sagittal T1, axial gradient-recalled echo, axial FLAIR, axial proton density/T2, and axial 3D fast spoiled gradient-echo. DTI parameters were echo time 1 equals minimum, repetition time equals 8300, field of view equals 30 cm, frequency equals 128, phase equals 128, number of excitations equals 1, 30 contiguous sections, 5-mm section thickness, and diffusion gradients set in 25 directions.

Diffusion-Tensor Imaging Processing and Region of Interest Measurements

All images were processed on a GE Advantage Workstation 4.2_06[a] using the Functool software 3.1.22.[a] Corrections were made to remove echo-planar imaging distortions from the raw images. For each patient, 6 preselected ROIs were examined including the anterior corpus callosum (including genu), posterior corpus callosum (including splenium), deep frontal WM of anterior frontal lobes (deep frontal WM), and deep temporal

Table 1: Demographic and Injury Data of Participants Included in the Study as Well as Those Lost to Follow-Up

	Sex	Age	Injury	Glasgow Coma Scale (Lowest)	Estimated PTA (wk)	SES	Acute Length of Stay	Years of Education	Estimated Premorbid Intelligence Quotient
Participants (N=13)									
1	Female	24	MVC (ped)	3	>2	4	24	8	NA
2	Male	58	MVC	13	>0.5	4	33	12	NA
3	Male	41	MVC	13	>0.5	3	35	9	78
4	Female	52	MVC (ped)	13	0.5	3	—	12	113
5	Male	21	MVC	8	3	4	17	9	NA
6	Male	22	Fall	4	2	2	29	9	85
7	Male	42	Fall (bike)	5	1	4	24	17	119
8	Male	20	MVC	5	>1	2	17	13	80
9	Male	32	Fall	13	>1	2	37	16	83
10	Male	42	MVC	3	>3	4	45	11	99
11	Male	19	MVC	—	1.2	4	14	9	103
12	Male	31	MVC	6	4–6	2	53	16	97
13	Female	44	Fall (bike)	6	NA	2	24	16	120
Mean:(totals)	(10 males/3 females)	34.46	(9 MVC, 4 fall)	7.67		3.08	29.33	12.07	97.70
Lost to follow-up (n=5)									
1	Male	49	Sport, fall	13	1	1	38	21	123
2	Male	36	MVC, Fall	11	2	4	21	9	81
3	Male	41	MVC	6	1	2	37	15	108
4	Male	20	Fall	3	>1.5	2	49	12	108
5	Female	43	MVC	3	NA			13	108
Mean:(totals)	(4 males/1 female)	37.8	(3 MVC, 2 fall)	7.2		2.25	36.25	14.0	105.6

Abbreviations: GCS, Glasgow Coma Scale; IQ, intelligence quotient; LOS, length of stay; MVC, motor vehicle collision; NA, not applicable; ped, pedestrian; SES, socioeconomic status, as measured by the Hollingshead[48] classification: 1 (major business/professional); 2 (medium business/minor professional, technical); 3 (skilled craftsperson, clerical, sales worker); 4 (machine operator, semiskilled worker); 5 (unskilled laborer, menial service worker).

WM bilaterally. An ROI in the range of 32 to 34mm^2 was manually copied and pasted to each region using the reference voxel grid generated by the software ensuring symmetry. ROI mapping was carried out as follows: for the anterior corpus callosum, the genu of the corpus callosum was centered in the axial plane; for the posterior corpus callosum, the splenium of the corpus callosum was centered in the axial plane; for deep frontal WM, a slice contained the corpus callosum and the ROI was centered in WM diagonal to the tip of anterior horn of the lateral ventricle; for deep temporal WM, the slice contained the temporal horns, and the ROI was centered anterior to the cap of the temporal horn (fig 1).

RESULTS

Paired, 1-tailed *t* tests were used to compare the initial and follow-up scans. A Bonferroni-Holm adjustment was applied to the 6 comparisons, giving an initial Bonferroni significance level of P equal to .008 (all 6 comparisons) and a final Bonferroni-Holm adjusted significance of P equal to .013. This revealed no significant differences in the corpus callosum ($t_{12}=1.00$, NS [anterior corpus callosum]; $t_{12}=-.02$, NS [posterior corpus callosum]). Findings from the frontal and temporal lobes, presented in figure 2, were significant. For the frontal lobes, mean FA values at time 1 and time 2 for the right

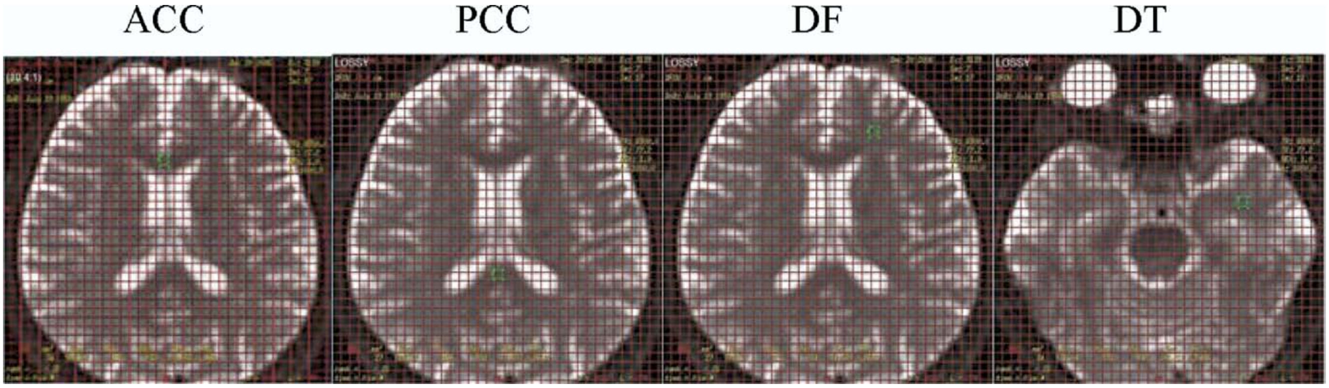

Fig 1. T2-weighted images with overlying grid from Functool software, showing the ROI selection. Abbreviations: ACC, anterior corpus callosum; DF, deep frontal white matter; DT, deep temporal white matter; PCC, posterior corpus callosum.

hemisphere were, respectively, .38±.06 and .30±.06, with a significantly smaller FA at time point 2 (t_{12}=3.21, P<.005). For the left hemisphere, means ± SDs were .37±.06 and .32±.06 across the 2 time points, and were significantly different (t_{12}=2.67, P<.013). For deep temporal lobe WM, mean FA values ± SDs at time 1 and time 2 for the right hemisphere were .28±.05 and .22±.02, respectively (t_{12}=3.62, P<.005). For the left hemisphere, the means ± SDs were .28±.05 and .24±.02 (t_{12}=2.68, P<.013).

DISCUSSION

Because of its unique sensitivity to DAI,[19,27,40,41] we employed DTI to examine fiber tract changes during subacute and chronic TBI.

Analysis of ROIs at follow-up DTI (≈29mo months postinjury) showed that FA had significantly decreased in the frontal and temporal lobes bilaterally. These abnormalities are concordant with a small number of previous reports[7,9,11,15,18] and are likely to reflect demyelination, edema, and persistent axonal injury as described in a mouse model.[42] Progression of injury was not observed in the corpus callosum, either anteriorly or posteriorly, although previous studies that investigated injured subjects at a single point of time after TBI, such as Nakayama et al,[38] have shown decrease in callosal FA compared with healthy subjects. MacDonald et al[42] suggest that DTI signals at the contusion site are affected by pericontusional wallerian degeneration secondary to cell loss, as depicted in their mouse model. According to their study, this is a result of axonal injury at acute time points and primarily demyelination and edema at subacute time points. The underlying cause of the decreased FA may represent apoptosis, and indeed, several studies have shown that neurons are affected by apoptotic pathways after TBI.[43] The neuronal apoptosis was described in both postmortem and *in vivo* studies,[44-46] and Cernak et al[47] have demonstrated diffusion signal changes in areas of apoptosis in their rat model.

To date, only 1 previous human study examining progression of atrophy in humans (this issue) has examined patients prospectively, within subjects, and solely after the acute period has resolved.[11] Thus, this is the second study to offer strong evidence of atrophy unconfounded by the effects of acute injury.

This is the first study published to date to use DTI to examine the question of progression of WM damage during the subacute period. There are only 2 previous longitudinal studies[21,37] that have employed DTI in TBI; however, neither of them was designed to address the question of progression of injury, and neither conducted all assessments after the acute injury period. In 1 study,[21] a single case design, the subject was scanned 3 times, but within 2 months of injury. In the second study,[37] there was a long-term follow up at 18 months postinjury, but the first scan was done at 6 days postinjury; here, FA improved over time.

CONCLUSIONS

Our results show that interval decline in diffusion anisotropy in frontal and temporal lobes was present in a group of patients

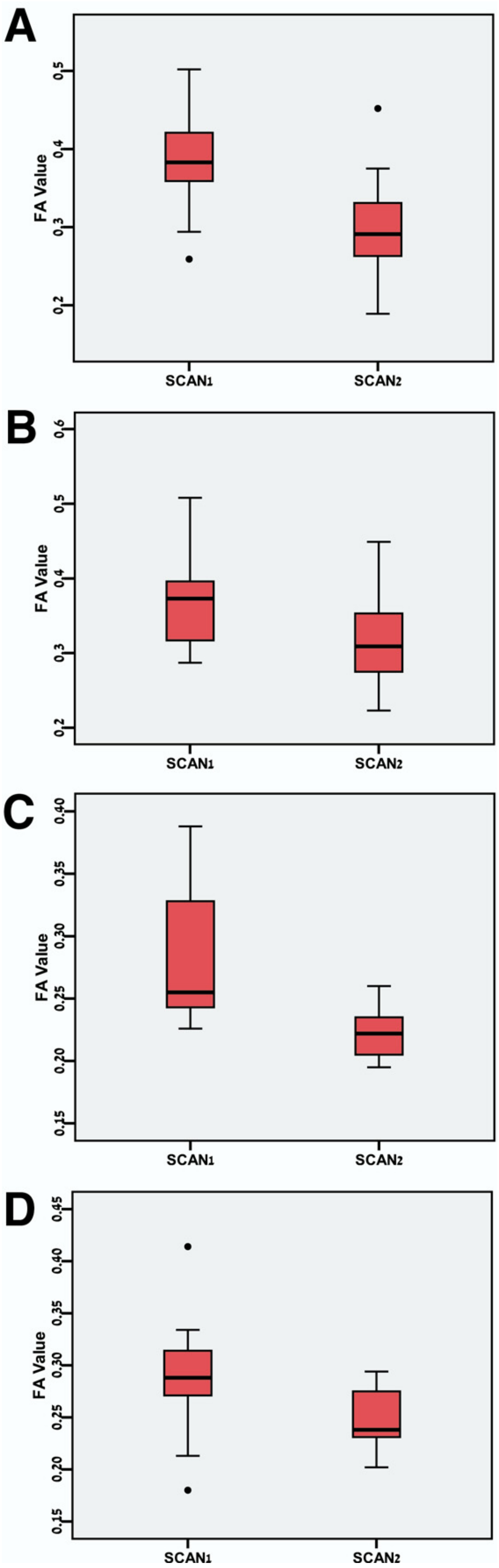

Fig 2. Box plot diagrams showing FA reduction in right and left frontal lobes (A, B) and right and left temporal lobes (C, D), respectively. Mean, first to third quartiles and minimum and maximum scores are indicated. For each pair of box plots, the left box plot contains values from the 4.5 month postinjury scan; the right box plot contains 2.5 year postinjury scan values. FA values, presented on the Y axis, range from .2 to .5 (A, B); .15 to .4 (C), and .15 to .45 (D).

with moderate-severe, subacute TBI. The location of this progression is concordant with increasing frontotemporal atrophy observed in our previous study that also included these patients.[11] It is of interest, however, that the corpus callosum, another frequently affected area, did not show progression of WM damage. Further research is needed on a larger sample to replicate this pattern of findings. It remains to be determined how these measurements correlate with clinical outcome in larger populations.

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