

## ORIGINAL ARTICLE

# Use of Diffusion-Tensor Imaging in Traumatic Spinal Cord Injury to Identify Concomitant Traumatic Brain Injury

Corie W. Wei, MD, Januthy Tharmakulasingam, BSc, Adrian Crawley, PhD, David M. Kideckel, MSc, David J. Mikulis, MD, Cheryl L. Bradbury, PsyD, CPsych, Robin E. Green, PhD, CPsych

**ABSTRACT.** Wei CW, Tharmakulasingam J, Crawley A, Kideckel DM, Mikulis DJ, Bradbury C, Green RE. Use of diffusion tensor imaging in traumatic spinal cord injury to identify concomitant traumatic brain injury. *Arch Phys Med Rehabil* 2008;89(12 Suppl 2):S85-91.

**Objective:** To characterize and differentiate cerebral white matter (WM) changes related selectively to traumatic brain injury (TBI) or spinal cord injury (SCI) in patients with SCIs in order to improve diagnostic accuracy of TBI in people with SCI.

**Design:** Diffusion-tensor imaging (DTI)-derived fractional anisotropy (FA) data in WM tracts were compared between a healthy control and 2 patient groups. Between-subject comparisons of FA were performed using region of interest (ROI) analysis and tract-based spatial statistics.

**Setting:** A large, urban inpatient SCI program.

**Participants:** Three groups: SCI and concomitant TBI (SCI with TBI, n=7); SCI without TBI (SCI only, n=15); and healthy control subjects (n=12).

**Interventions:** Not applicable.

**Main Outcome Measure:** FA was used as a measure of cerebral WM integrity.

**Results:** ROI analyses showed reduced FA in the genu and splenium of the corpus callosum and forceps minor in patients with SCI with TBI compared with both healthy controls and patients with SCI only. ROI analyses did not show evidence of FA differences in patients with SCI only compared with controls. Tract-based spatial statistics did not demonstrate between-group differences in FA.

**Conclusions:** DTI is a sensitive tool to detect TBI-related WM damage in patients with SCI who have suffered concomitant TBI. No WM abnormalities on DTI could be attributed to SCI alone, although this finding should be further explored in future studies. Therefore, DTI may be a valuable tool to identify TBI in the SCI population. Further research to produce normative FA values is needed to allow identification of TBI in individual patients with SCI.

**Key Words:** Brain injuries; Diffusion magnetic resonance imaging; Rehabilitation; Spinal cord injuries.

© 2008 by the American Congress of Rehabilitation Medicine

**T**HE PRESENCE OF TRAUMATIC brain injury in patients with SCI is a well documented phenomenon. This association is not surprising, given the striking similarities between the TBI and SCI populations in demographic profile as well as in injury circumstances.<sup>1</sup> The incidence of both TBI and SCI is higher in male subjects, with over 50% of the affected population being between the ages of 15 and 30 years.<sup>2,3</sup> In addition, both types of injuries typically result from high-velocity impact such as motor vehicle collisions (50% in both cases), falls (21% in both cases), and sporting accidents.<sup>2</sup> However, the precise frequency of comorbidity of TBI with SCI has not been clearly established. In most studies using 1 or 2 indicators of neurotrauma to diagnose TBI (eg, loss of consciousness, PTA, and/or neuropsychological deficits), the prevalence of TBI in traumatic SCI was estimated to be 40% to 60%.<sup>4-11</sup> However, when structural MRI was combined with neuropsychological testing to evaluate the presence of neurotrauma, 74% of patients of SCI were found to have concomitant brain injury in 1 study.<sup>12</sup> Given the high frequency of the comorbidity, the ability to diagnose or rule out concomitant TBI is a major issue in the treatment and rehabilitation of patients with SCI.

A major goal of neuroradiologic investigations in brain trauma is to identify the presence of DAI, a key mechanism of neural damage after TBI.<sup>13</sup> DAI results from unequal rotational or acceleration/deceleration forces that cause multifocal lesions in WM because of a shear-strain deformation.<sup>14-16</sup> DAI sites of predilection include subcortical WM, corpus callosum, fornix,

## List of Abbreviations

ALIC	anterior limb of the internal capsule
ANOVA	analysis of variance
DAI	diffuse axonal injury
DTI	diffusion-tensor imaging
FA	fractional anisotropy
FMRIB	functional magnetic resonance imaging of the brain
gCC	genu of the corpus callosum
GCS	Glasgow Coma Scale
MRI	magnetic resonance imaging
PLIC	posterior limb of the internal capsule
PTA	posttraumatic amnesia
ROI	region of interest
sCC	splenium of the corpus callosum
SCI	spinal cord injury
TBI	traumatic brain injury
TBSS	tract-based spatial statistics
WM	white matter

From Departments of Medical Imaging (Wei) and Cell and Systems Biology (Tharmakulasingam), University of Toronto; Institute of Medical Science, University of Toronto, University Health Network (Kideckel); Department of Medical Imaging, Toronto Western Hospital, University of Toronto (Crawley, Mikulis); Toronto Rehabilitation Institute (Bradbury, Green); Graduate Department of Rehabilitation Sciences, University of Toronto (Bradbury, Green), Toronto, ON, Canada.

Supported by the Canadian Institutes of Health Research, the Physicians' Services Incorporated, and the Ontario Mental Health Foundation (grant nos. MOP-67072, 05-50, 2005-ABI-392).

No commercial party having a direct financial interest in the results of the research supporting this article has or will confer a benefit on the authors or on any organization with which the authors are associated.

Reprint requests to Robin E. Green, PhD, CPsych, Toronto Rehabilitation Institute, The University Centre, 550 University Ave, Toronto, ON, M5G 2A2, Canada, e-mail: [green.robin@torontorehab.on.ca](mailto:green.robin@torontorehab.on.ca).

0003-9993/08/8912S-00442\$34.00/0

doi:10.1016/j.apmr.2008.07.005

internal capsule, and infratentorial WM.<sup>17-20</sup> Although conventional MRI techniques can readily visualize posttraumatic focal structural lesions, they are unable to detect microscopic WM damage in DAI. Consequently, the diagnosis of TBI is missed in some patients, particularly those with milder brain injuries.<sup>21</sup>

Recently, DTI has proven fruitful in detecting the loss of axonal organization in TBI.<sup>22-25</sup> DTI is a novel MRI technique that can provide information about the microscopic tissue architecture. The diffusion tensor represents a model of water diffusion in biologic tissues<sup>26</sup> and describes the magnitude, direction, and orientation of the diffusion distribution. FA is an index used to characterize the local coherence of fibers<sup>27</sup> and is one of the most widely used metrics in diffusion anisotropy.<sup>28</sup> FA is a convenient measure because it is scaled from 0 (complete isotropic diffusion) to 1 (complete anisotropic diffusion). In WM, water diffusion is less restricted in the direction parallel to the fiber orientation, whereas it is highly restricted in the direction perpendicular to the fibers.<sup>26</sup> FA is highest in major WM tracts (maximum possible value, 1) while it approaches 0 in cerebrospinal fluid. For example, normative WM tracts with coherently oriented fibers typically exhibit higher FA values, whereas reduced FA usually occurs in WM disease states (although this is not always the case). Reduced FA values have been identified in DAI sites<sup>20,22,23,25,29-37</sup> and are more sensitive than conventional MRI to axonal injury in a mouse model of TBI.<sup>38</sup> Early detection of DAI using diffusion-weighted MRI can not only direct acute neurologic intervention<sup>39</sup> and long-term rehabilitation but also improve outcome prediction in adult TBI.<sup>40</sup>

Before DTI can be reliably used to assess for TBI in patients with SCI, however, several questions need to be addressed. First, does SCI without any comorbidity cause alterations in the human brain? If so, is this injury distinguishable from that caused by TBI? SCI-related brain injury must be documented so the effects of SCI alone are not confounded with the effects of brain injury. A false diagnosis of TBI could have serious clinical, ethical, and financial consequences. If injury caused by SCI can be identified and factored out when using DTI to diagnose TBI, we can greatly improve the diagnostic specificity and reduce the likelihood of a false-positive diagnosis of TBI in patients with SCI. Second, even if SCI does cause alterations to the brain, are there areas of the brain that show reduced FA secondary to TBI, but are nonetheless unaffected by the effects of traumatic SCI?

In this study, we attempted to localize WM alterations in the brain caused by traumatic SCI alone using DTI-derived FA values as a marker of axonal integrity. We also attempted to identify those regions of the brain that would reliably discriminate patients with traumatic SCI plus TBI from patients with traumatic SCI only. We therefore included 3 study groups: (1) patients with SCI and no evidence of TBI (SCI only) based on structural 3 Tesla MRI and collateral neurologic findings, (2) patients with SCI and definitive structural MRI evidence of TBI (SCI with TBI), and (3) healthy controls. We examined the data with 2 approaches. We first investigated between-group FA differences in a priori ROIs, including the ALIC and PLIC, forceps minor, and gCC and sCC. These regions were selected because previous studies have shown that DTI abnormalities in the corpus callosum and forceps are particularly sensitive markers for TBI.<sup>29,33</sup> Moreover, WM tracts in the internal capsule, which conduct sensory afferents, may be a region most sensitive to traumatic SCI. In addition, we explored a novel group analysis technique, TBSS, which allows whole-brain, voxel-wise FA comparisons between groups.<sup>41-44</sup> To date, the application of TBSS has not been used to study TBI or SCI.

We conducted 3 between-group analyses of FA: SCI only versus controls, SCI with TBI versus controls, and SCI only versus SCI with TBI. We hypothesized that (1) compared with both patients with SCI only and normal controls, the SCI with TBI group would show multiple areas of FA reductions in predilection sites of DAI; and (2) in WM fiber tracts containing afferent pathways, both SCI only and SCI with TBI would have reduced FA compared with controls because of loss of afferent projections.

## METHODS

### Subjects

The study protocol was approved by the research ethics board at the local institution at which the study was conducted, and the procedures of the study were in accordance with the standards of the research ethics board.

Twenty-two patients (15 men, 7 women; mean age, 34.3y; range, 19-53y) with traumatic SCI were recruited from a large urban SCI program within a rehabilitation hospital, to which they were referred for subacute rehabilitation between 2006 and 2008. The demographic and clinical information of the participants in this study is summarized in table 1. All patients underwent an MRI scan of the brain in the subacute period after their traumatic SCI. Each patient was assigned to 1 of 2 groups, SCI with TBI or SCI only, based on MRI findings and collateral information examinations (ie, GCS, PTA, loss of consciousness, neuropsychological assessment). For the SCI-only group, all patients had negative MRIs of the brain. Fifteen patients were assigned to the SCI-only group (13 men, 2 women; mean age, 35.7y; range, 20-54y). All collateral information available at the time of writing is included in table 1, with the exception of invalid information, which was excluded. This included 2 GCS scores, invalid because of alcohol at the time of assessment, and 1 PTA score, invalid because of medications during the period of PTA. Seven patients were assigned to the SCI plus TBI group (5 men, 2 women; mean age, 31.6y; range, 20-50y). All 7 patients had positive MRI findings consistent with previous brain trauma. For this group, only collateral information with positive findings is reported in table 1 (eg, depressed GCS, presence of PTA).

The healthy control group included 12 healthy volunteers (7 men, 5 women; mean age, 34.6y; range, 21-51y) who had had no known history or MRI evidence of central nervous system disease.

Exclusion criteria for all participants included any history of TBI and any history of neurologic or psychotic illness, and prior structural abnormality of the brain. All participants were proficient in English.

The patient groups were well matched on the key parameters. There were no significant differences or differences approaching significance between the 2 patient groups on age, years, or number of days between injury and MRI. There were no differences between either of the patient groups and the healthy control group on age. However, both patient groups differed significantly from the control group on years of education: the SCI-only group differed from controls at the  $P < .000$  level of significance; the SCI with TBI group differed at the  $P < .001$  level of significance.

### Magnetic Resonance Imaging Data Acquisition

All patients and controls were scanned using a GE 3 Tesla MRI scanner<sup>a</sup> equipped with an 8-channel head-coil (MRI devices). Subjects underwent the routine MRI protocol (including T<sub>1</sub>-weighted spin-echo, T<sub>2</sub>-weighted spin-echo, T<sub>2</sub>\*-weighted

Table 1: Demographic and Injury Data of Participants Included in the Study

Participants	Sex	Age at SCI	Injury Type	SCI Level/ Completeness	Structural MRI Findings	Days Between Injury and MRI	Additional Neurologic Evidence TBI+/-	Years of Education
<b>SCI only</b>								
1	M	28	Sports	C5/Inc	Negative	123	Neg CT	12
2	F	44	Sports	T11/Com	Negative	59	No PTA, LOC; GCS=15	10
3	M	54	Fall	C6/Com	Negative	64	No PTA; neg NP	15
4	M	44	Fall	C6/Inc	Negative	73	No PTA; neg NP	10
5	M	53	MVC	T11/Com	Negative	61	No PTA; GCS=15	19
6	M	42	Fall	T12/Com	Negative	91	No PTA, no LOC	12
7	M	21	Fall	C5/Inc	Negative	66	Neg NP	12
8	F	41	Fall	T12/Inc	Negative	59	No PTA, LOC; neg NP	16
9	M	20	MVC	C7/Inc	Negative	86	No LOC	12
10	M	31	Fall	T12/Inc	Negative	54	No LOC	12
11	M	24	MVC	C8/C5/Inc	Negative	186	No LOC, GCS=15	12
12	M	38	Fall	L1/Inc	Negative	157	No PTA, LOC	9
13	M	22	Sports	C1/Inc	Negative	102	No LOC, GCS=15	14
14	M	39	MVC	T5/Inc	Negative	74	No LOC	14
15	M	34	MVC	C4/Com	Negative	147	GCS=15	13
Mean ± SD	2F/13M	35.7±11.1	5 MVC: 10 other			93.5±41.3		12.8±2.5
<b>SCI with TBI</b>								
1	F	26	MVC	T11/Inc	Positive	273	GCS=11, LOS	14
2	F	20	MVC	T3/Com	Positive	134	PTA	12
3	M	50	Fall	C4/Inc	Positive	82	NA	9
4	M	39	Fall	L4/Inc	Positive	59	None	16
5	M	40	Blow/Fall	C4/Inc	Positive	64	PTA, LOC	9
6	M	19	MVC	C4/Com	Positive	185	PTA, LOC, GCS=3	12
7	M	22	MVC	T7/Com	Positive	101	PTA, LOC	12
Mean ± SD	2F/5M	31.6±12.0	4 MVC: 3 other			128.3±77.5		12.0±2.5
<b>Controls</b>								
Mean ± SD	5F/7M	34.6±10.2						18.1±3.1

NOTE. For SCI only, all collateral information reported except that which is invalid, as noted in text. For SCI with TBI group, only positive findings reported. The SCI only group includes patients with SCI and no evidence of TBI based on structural MRI and collateral neurologic findings. The SCI with TBI group includes patients with SCI and definitive structural MRI evidence of TBI. Abbreviations: C, cervical; Com, complete; CT, computed tomography; F, female; Inc, incomplete; LOS, loss of consciousness; L, lumbar; M, male; MVC, motor vehicle collision; NA, not applicable; Neg, negative; NP, neuropsychological assessment; T, thoracic.

gradient-echo, and fluid-attenuated inversion recovery) as well as the DTI protocol. Three sets of DTI data for each subject were acquired using a diffusion-weighted spin-echo single-shot echo-planar imaging sequence with diffusion encoding in 15 noncollinear directions. The total DTI acquisition time was approximately 9 minutes and 30 seconds. The sequence parameters were as follows: repetition time, 10,000ms; echo time, 84ms; matrix, 128 × 128; field of view, 240mm<sup>2</sup>; 5-mm thickness; 0-mm gap; *b* factor, 1000s/mm<sup>2</sup>.

**Evaluation of Conventional Magnetic Resonance Imaging**

The conventional MRI images were qualitatively evaluated for all subjects by an experienced neuroradiologist blinded to the DTI findings and clinical ratings. This evaluation included classification of all visible lesions based on their signal characteristics. The presence or absence of DAI consistent with previous TBI was used to confirm assignment of patients with SCI to either the SCI-only or the SCI with TBI group. Healthy control subjects with incidental signal abnormalities on MRI were excluded from the study.

**Diffusion-Tensor Imaging Data Processing and Tract-Based Spatial Statistics**

Three sets of diffusion-weighted images were initially registered to the first reference image (*b*=0) in the first dataset

using the automatic image registration toolkit in DTI Studio, version 2.40.<sup>b</sup> Affine transformations and the trilinear interpolation method were used. Data were then visually inspected,<sup>b</sup> and if necessary, poor quality slices and gradient orientations were discarded to prevent biased and inaccurate estimates of FA. A mean set of DTI images was generated from the 3 DTI datasets and was then brain-extracted using a brain extraction tool,<sup>41</sup> and FA maps were generated using the FMRIB diffusion toolbox,<sup>45</sup> both of which are part of the FMRIB software library suite ([www.fmrib.ox.ac.uk/fsl](http://www.fmrib.ox.ac.uk/fsl)).<sup>42</sup>

Voxel-wise analysis of FA data was completed using TBSS, version 1.1 in FSL, version 4.0.<sup>b</sup> TBSS is described in detail elsewhere.<sup>43</sup> TBSS conducted 3 between-group analyses and tested whether FA was reduced across the whole brain in SCI with TBI compared with SCI only, SCI with TBI compared with healthy controls, and SCI only compared with healthy controls. An omnibus F test was used for this purpose. In brief, TBSS analyses involved a 4-step procedure, whereby all subjects' FA images were nonlinearly aligned<sup>46</sup> to the 1×1×1mm MNI152 standard-space template in FSL. The mean of all aligned FA images was then created and thinned to produce a mean FA skeleton, which represents the tract centers common to the 3 groups of subjects. The skeleton was then thresholded to FA 0.20 or higher to include major WM tracts but to exclude WM tracts with great intersubject variability. Each subject's

aligned FA image was then projected onto the skeleton, and voxel-wise statistics across subjects were carried out on the skeleton-space FA data.

Group comparison of FA was performed using nonparametric inferential statistics (Monte-Carlo permutations) with threshold-free cluster enhancement.<sup>47</sup> Threshold-free cluster enhancement is an improvement over existing cluster-level inference methods, which required the user to specify an arbitrary cluster-forming threshold. The threshold-free cluster enhancement approach enhances areas of signal without having to rely on threshold-based clustering.

### Region of Interest Analysis

ROI analyses were carried out using the same FA maps already generated for each subject from TBSS. Our study focused on ROIs in the following WM tracts: ALIC, PLIC, forceps minor, gCC, and sCC. ROIs of specific WM structures were taken from the ICBM-DTI-81 WM labels atlas included in FSL.<sup>48</sup> The atlas was originally created by hand-segmentation of a standard-space average of diffusion MRI tensor maps from 81 subjects (42 men, 39 women; mean age, 39y). All subjects' FA maps were nonlinearly warped onto the ICBM mean FA template using IRTK software available as part of the FMRIB software library package ([www.fmrib.ox.ac.uk/fsl](http://www.fmrib.ox.ac.uk/fsl)).<sup>43,b</sup> The ROI masks were applied to each subject's FA map, and the average FA value in each ROI was computed. An example of the various ROI masks available in the ICBM-DTI-81 WM labels atlas is represented in figure 1.

### Statistical Analysis

All data were analyzed using SPSS 16.0.<sup>c</sup> Mean FA values for each group for each ROI were examined in a 1-way ANOVA. For those ANOVAs that showed statistical significance, 1-tailed, independent-samples *t* tests were implemented for comparison across groups. For each comparison, equality of variance was assessed using the Levene test. The threshold for statistical significance was set to *P* less than .05.

## RESULTS

### Region of Interest Analysis

**One-way analysis of variance.** The group mean FA value for each of the ROI is presented in table 2. Of the 5 ROIs analyzed in this study, 4 illustrated significant differences on 1-way ANOVAs: the ALIC ( $F_{2,31}=4.537$ ;  $P<.05$ ), forceps minor ( $F_{2,31}=3.784$ ;  $P<.05$ ), gCC ( $F_{2,31}=3.494$ ;  $P<.05$ ), and sCC ( $F_{2,31}=5.186$ ;  $P<.05$ ). Thus, planned comparisons were performed for these ROIs.

In the PLIC, results of the 1-way ANOVA were not significant ( $F_{2,31}=0.664$ ;  $P=.522$ ). Therefore, planned comparisons were not carried out.

**Planned comparisons.** As predicted, FA values were decreased in the predilection sites for DAI in the SCI with TBI

Table 2: Mean FA in Each ROI for All Groups

ROIs	Control	SCI Only	SCI With TBI
ALIC (bilateral)	0.495±0.124	0.508±0.133	0.474±0.133
PLIC (bilateral)	0.646±0.081	0.655±0.079	0.646±0.085
Forceps minor (bilateral)	0.447±0.108	0.446±0.108	0.400±0.106
gCC	0.582±0.139	0.580±0.148	0.540±0.147
sCC	0.636±0.168	0.634±0.170	0.593±0.171

NOTE: Means ± SDs of FA are presented for each region. The SCI-only group includes patients with SCI and no evidence of TBI based on structural MRI and collateral neurologic findings. The SCI with TBI group includes patients with SCI and definitive structural MRI evidence of TBI. ROIs in the ALIC and PLIC capsule and forceps minor combine bilateral structures.

group: for the forceps minor ROI, FA values were significantly decreased in the SCI with TBI group compared with the control group ( $t_{17}=2.158$ ;  $P<.05$ ) and compared with the SCI-only group ( $t_{20}=2.344$ ;  $P<.05$ ). FA values for the gCC were reduced in the SCI with TBI group in comparison to the healthy controls ( $t_{17}=2.185$ ;  $P<.05$ ) and to the SCI-only group ( $t_{20}=2.334$ ;  $P<.05$ ). In the sCC, too, there was a reduction in FA values in the SCI with TBI group relative to the control group ( $t_{7,439}=2.192$ ;  $P<.05$ ) and relative to the SCI-only group ( $t_{7,499}=2.037$ ;  $P<.05$ ; equal variance not assumed because of significant Levene test). There were no significant differences or differences approaching significance between the healthy controls and the SCI-only group for any of these ROIs.

Our prediction of reduced FA in the internal capsule in the patient groups was not supported. In fact, the SCI-only group showed significantly higher FA values than the SCI with TBI group ( $t_{20}=2.653$ ;  $P<.01$ ), suggesting that the ALIC is more vulnerable to DAI than to loss of afferent projections. The SCI-only group showed a higher mean than that of controls, a difference that did not reach statistical significance ( $t_{25}=-1.673$ ;  $P=.054$ ).

### Tract-Based Spatial Statistics

TBSS did not reveal any cross-subject FA differences even at a liberal *P* value set to .01 uncorrected for multiple voxel comparisons.

## DISCUSSION

Using DTI, we attempted to detect changes in brain WM microstructures associated with SCI using 3 groups of subjects: SCI patients with no evidence of TBI on structural MRI and neurologic examination (SCI only), SCI patients with MRI-proven brain injury (SCI with TBI), and healthy controls. We found that compared with both controls and patients with SCI only, patients with SCI with TBI had multiple WM regions with reduced FA, including the forceps minor, sCC, and gCC.

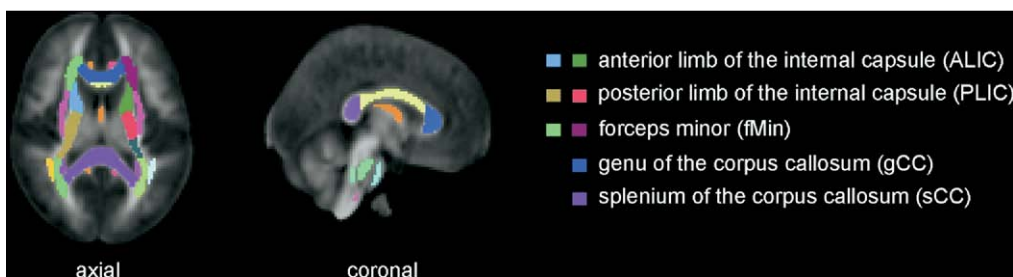


Fig 1. Various ROI masks available in ICBM-DTI-81 WM labels atlas.<sup>48</sup> We applied the following ROIs to each subject's FA map to derive regional mean FA values: ALIC, PLIC, forceps minor, gCC, and sCC.

In addition, patients with SCI with TBI had reduced FA in the ALIC compared with the SCI-only group, while no between-group differences were found in the PLIC. No significant regional FA differences were found between the SCI-only group and healthy controls.

In patients with SCI who have had concomitant brain injury and structural abnormalities on MRI, we expected to find FA reductions in WM tracts prone to DAI. Predilection sites of traumatic axonal injury include subcortical WM, corpus callosum, internal capsule, and infratentorial WM.<sup>17-20</sup> Previous studies have shown that even mild TBI could lead to significant FA reductions in the subcortical WM, including the corpus callosum, minor, and major forceps.<sup>29,33</sup> In our study, patients with SCI with TBI were found to have decreased FA in the gCC, sCC, and forceps minor in the subacute period after the original trauma. However, TBI was not associated with any FA changes in the internal capsule in patients with SCI with TBI compared with controls. This is likely because abnormalities in the internal capsule are markers of more severe TBI, whereas our patients with SCI underwent different severities of brain trauma. Our results confirmed that DTI is a sensitive tool to detect microstructural WM damage associated with DAI in patients with SCI who have had concomitant brain injury. FA changes in the corpus callosum and forceps minor are sensitive markers for TBI in cross-subject comparisons; however, normative data need to be established before FA value can be used to diagnose TBI on an individual basis.

Our study did not find any WM FA changes attributable to SCI alone. SCI may cause disruption of the ascending sensory tracts to the brain. One may expect that the loss of afferent connections might lead to axonal degeneration in the higher-order neurons and thus result in reduced FA in cerebral WM tracts that conduct the sensory pathways. Major sensory afferents including the dorsal column-medial meniscus and spinothalamic pathways project to the ventral posterolateral nucleus of the thalamus, from which the thalamocortical afferents travel to the primary somatosensory cortex via the posterior limb of the internal capsule.<sup>49</sup> A previous study showed that patients with cervical SCI had reduced gray matter volume bilaterally in the primary somatosensory cortex.<sup>50</sup> However, our study did not demonstrate any between-group FA differences in the PLIC. In the ALIC, neither the SCI-only group nor the SCI with TBI group had decreased FA compared with healthy controls. In fact, the SCI-only group showed increased FA in the ALIC compared with healthy controls (trend only); this difference reached significance compared with the SCI with TBI group. This finding cannot be reasonably explained and needs to be explored in future studies. The absence of SCI-related WM changes in the chosen WM tracts as shown by our study have many causes. First, changes in cerebral WM as a result of spinal afferent denervation may develop in the chronic postinjury period, while our study included patients in the subacute period after SCI (mean time between injury and brain MRI was 93.5d). One mechanism for the cerebral WM changes in SCI is transsynaptic degeneration, a process of neuronal atrophy caused the lack of synaptic input from afferent fibers.<sup>51</sup> Second, we placed our ROIs in the anterior and posterior limbs of the internal capsule, which contain both ascending and descending neuronal tracts. As a result, we were unable to compare FA values selectively in the ascending WM tracts, such as the thalamocortical afferents, which we expected would be most affected by SCI. Future studies should investigate cerebral WM changes in patients with chronic SCI as well as elucidate WM FA changes in afferent-specific ROIs in the internal capsule and near the sensory cortex. We should also

correlate changes in cerebral WM organization with neurologic and function outcome in patients with SCI.

We adopted TBSS as well as the ROI technique to assess between-group FA differences. TBSS is an automated technique that allows voxel-wise statistical testing of FA and has been successfully used to assess changes in neuronal WM integrity associated with various pathologic processes, including Alzheimer disease, epilepsy, and schizophrenia.<sup>52-54</sup> In our study, TBSS did not find any between-group FA differences, which we detected using the ROI technique. One explanation for the negative results in TBSS is that we did not include enough subjects to achieve sufficient power for TBSS analysis, especially in the SCI with TBI group ( $n=7$ ). In addition, the discrepancy between TBSS and ROI results may be explained by the methodology employed in TBSS, which involves creating an FA skeleton by thinning the mean of all FA images and carrying out voxel-wise statistics across subjects on the skeleton-space FA data.<sup>43</sup> As a result, this technique only considers tracts in the center of WM fiber bundles. However, it is known that 1 major mechanism of DAI is a deceleration-acceleration impact that generates enough rotational force to cause axonal shearing.<sup>55</sup> Maximum shearing force occurs in areas with the greatest tissue density difference—that is, at the gray-WM junction. Thus, fiber tracts in the periphery of WM tracts are more likely to be damaged in a closed-head injury and exhibit DAI-related reductions in FA. Using ROIs that incorporated both the inner and outer WM fiber tracts, we were able to detect changes in WM integrity associated with DAI in patients with SCI. These findings support the use of an ROI approach for discriminating patients with SCI with and without concomitant TBI. The current findings do not support the use of TBSS for this purpose. However, the limited power in this study may have contributed to the null findings. Further studies employing TBSS are needed to confirm our results.

### Study Limitations

We present the first study that attempts to characterize and differentiate microstructural WM changes related to either brain injury or traumatic SCI in patients with SCI. We selected ROIs in WM tracts, which would best allow us to differentiate the 3 study groups. As a result, the number of ROIs included in this study was limited. Future studies can achieve a broader search for cerebral WM changes in patients with SCI by incorporating more ROIs or by using an alternative automated voxel-based technique. Another limitation of our study is that we combined bilateral brain structures into 1 ROI in the cross-subject comparisons (eg, forceps minor, ALIC, PLIC). It is possible that both TBI and SCI may cause unilateral changes in cerebral axonal organization. Finally, the sample size in the SCI with TBI group is relatively small ( $n=7$ ). While we are presenting the preliminary data, we hope to continue to expand our data series and improve the power of the statistical analyses.

### CONCLUSIONS

The present study showed that patients with SCI and concomitant brain injury had reduced FA in the corpus callosum and minor forceps, which are susceptible areas to diffuse axonal injury. SCI was not found to be associated with any changes in cerebral axonal organization. Therefore, DTI shows promise as a sensitive tool for the detection of TBI-related WM damage in patients with SCI who have had concomitant TBI. Future research that provides normative FA values in healthy control subjects would improve the use of DTI for the diagnosis of TBI in individual patients.

**Acknowledgments:** We thank Kadeen Johns, BSc, and Areeba Adnan, BSc, for their help with the manuscript preparation. The authors acknowledge the support of Toronto Rehabilitation Institute who receives funding under the Provincial Rehabilitation Research Program from the Ministry of Health and Long-Term Care in Ontario. The views expressed do not necessarily reflect those of the Ministry.

#### References

- Povolny M, Kaplan S. Traumatic brain injury occurring with spinal cord injury: significance for rehabilitation. *J Rehabil* 1993; 59:23-8.
- Buchanan L, Nawoczenski D. *Spinal cord injury: concepts and management approaches*. Baltimore: William & Wilkins; 1987.
- Jennet B, Teasdale G. *Management of head injuries*. Philadelphia: FA Davis; 1981.
- Roth E, Davidoff G, Thomas P, et al. A controlled study of neuropsychological deficits in acute spinal cord injury patients. *Paraplegia* 1989;27:480-9.
- Davidoff G, Morris J, Roth E, Bleiberg J. Closed head injury in spinal cord injured patients: retrospective study of loss of consciousness and post-traumatic amnesia. *Arch Phys Med Rehabil* 1985;66:41-3.
- Davidoff G, Morris J, Roth E, Bleiberg J. Cognitive dysfunction and mild closed head injury in traumatic spinal cord injury. *Arch Phys Med Rehabil* 1985;66:489-91.
- Davidoff G, Roth E, Morris J, Bleiberg J, Meyer PR Jr. Assessment of closed head injury in trauma-related spinal cord injury. *Paraplegia* 1986;24:97-104.
- Davidoff G, Thomas P, Johnson M, Berent S, Dijkers M, Doljanac R. Closed head injury in acute traumatic spinal cord injury: incidence and risk factors. *Arch Phys Med Rehabil* 1988;69: 869-72.
- Davidoff GN, Roth EJ, Richards JS. Cognitive deficits in spinal cord injury: epidemiology and outcome. *Arch Phys Med Rehabil* 1992;73:275-84.
- Richards JS, Brown L, Hagglund K, Bua G, Reeder K. Spinal cord injury and concomitant traumatic brain injury: results of a longitudinal investigation. *Am J Phys Med Rehabil* 1988;67:211-6.
- Wilmot CB, Cope DN, Hall KM, Acker M. Occult head injury: its incidence in spinal cord injury. *Arch Phys Med Rehabil* 1985;66: 227-31.
- Tolonen A, Turkka J, Salonen O, Ahoniemi E, Alaranta H. Traumatic brain injury is under-diagnosed in patients with spinal cord injury. *J Rehabil Med* 2007;39:622-6.
- Murray JG, Gean AD, Evans SJ. Imaging of acute head injury. *Semin Ultrasound CT MR* 1996;17:185-205.
- Povlishock JT, Katz DI. Update of neuropathology and neurological recovery after traumatic brain injury. *J Head Trauma Rehabil* 2005;20:76-94.
- Smith DH, Meaney DF, Shull WH. Diffuse axonal injury in head trauma. *J Head Trauma Rehabil* 2003;18:307-16.
- Gennarelli TA, Graham DI. Neuropathology of the head injuries. *Semin Clin Neuropsychiatry* 1998;3:160-75.
- Adams JH, Graham DI, Murray LS, Scott G. Diffuse axonal injury due to nonmissile head injury in humans: an analysis of 45 cases. *Ann Neurol* 1982;12:557-63.
- Gentry LR. Imaging of closed head injury. *Radiology* 1994;191: 1-17.
- Parizel PM, Van Goethem JW, Ozsarlak O, Maes M, Phillips CD. New developments in the neuroradiological diagnosis of cranio-cerebral trauma. *Eur Radiol* 2005;15:569-81.
- Nakayama N, Okumura A, Shinoda J, et al. Evidence for white matter disruption in traumatic brain injury without macroscopic lesions. *J Neurol Neurosurg Psychiatry* 2006;77:850-5.
- Meythaler JM, Peduzzi JD, Eleftheriou E, Novack TA. Current concepts: diffuse axonal injury-associated traumatic brain injury. *Arch Phys Med Rehabil* 2001;82:1461-71.
- Salmond CH, Menon DK, Chatfield DA, et al. Diffusion tensor imaging in chronic head injury survivors: correlations with learning and memory indices. *Neuroimage* 2006;29:117-24.
- Niogi SN, Mukherjee P, Ghajar J, et al. Extent of microstructural white matter injury in postconcussive syndrome correlates with impaired cognitive reaction time: a 3T diffusion tensor imaging study of mild traumatic brain injury. *AJNR Am J Neuroradiol* 2008.
- Huisman TA. Diffusion-weighted imaging: basic concepts and application in cerebral stroke and head trauma. *Eur Radiol* 2003; 13:2283-97.
- Kraus MF, Susmaras T, Caughlin BP, Walker CJ, Sweeney JA, Little DM. White matter integrity and cognition in chronic traumatic brain injury: a diffusion tensor imaging study. *Brain* 2007; 130:2508-19.
- Alexander AL, Lobaugh NJ. Insights into brain connectivity using quantitative MRI measures of white matter. In: Jirsa VK, McIntosh AR, editors. *Handbook on brain connectivity*. Berlin Heidelberg: Springer; 2007. p 221-71.
- Basser PJ, Pierpaoli C. Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. *J Magn Reson B* 1996;111:209-19.
- Mori S, Zhang J. Principles of diffusion tensor imaging and its applications to basic neuroscience research. *Neuron* 2006;51: 527-39.
- Inglese M, Makani S, Johnson G, et al. Diffuse axonal injury in mild traumatic brain injury: a diffusion tensor imaging study. *J Neurosurg* 2005;103:298-303.
- Huisman TA, Schwamm LH, Schaefer PW, et al. Diffusion tensor imaging as potential biomarker of white matter injury in diffuse axonal injury. *AJNR Am J Neuroradiol* 2004;25:370-6.
- Ptak T, Sheridan RL, Rhea JT, et al. Cerebral fractional anisotropy score in trauma patients: a new indicator of white matter injury after trauma. *AJR Am J Roentgenol* 2003;181:1401-7.
- Arfanakis K, Haughton VM, Carew JD, Rogers BP, Dempsey RJ, Meyerand ME. Diffusion tensor MR imaging in diffuse axonal injury. *AJNR Am J Neuroradiol* 2002;23:794-802.
- Rutgers DR, Toulgoat F, Cazejust J, Fillard P, Lasjaunias P, Ducreux D. White matter abnormalities in mild traumatic brain injury: a diffusion tensor imaging study. *AJNR Am J Neuroradiol* 2008;29:514-9.
- Lee ZI, Byun WM, Jang SH, Ahn SH, Moon HK, Chang Y. Diffusion tensor magnetic resonance imaging of microstructural abnormalities in children with brain injury. *Am J Phys Med Rehabil* 2003;82:556-9.
- Wozniak JR, Krach L, Ward E, et al. Neurocognitive and neuro-imaging correlates of pediatric traumatic brain injury: a diffusion tensor imaging (DTI) study. *Arch Clin Neuropsychol* 2007;22: 555-68.
- Chan JH, Tsui EY, Peh WC, et al. Diffuse axonal injury: detection of changes in anisotropy of water diffusion by diffusion-weighted imaging. *Neuroradiology* 2003;45:34-8.
- Huisman TA, Sorensen AG, Hergan K, Gonzalez RG, Schaefer PW. Diffusion-weighted imaging for the evaluation of diffuse axonal injury in closed head injury. *J Comput Assist Tomogr* 2003;27:5-11.
- Mac Donald CL, Dikranian K, Song SK, Bayly PV, Holtzman DM, Brody DL. Detection of traumatic axonal injury with diffusion tensor imaging in a mouse model of traumatic brain injury. *Exp Neurol* 2007;205:116-31.
- Jacka MJ, Zygun D. Survey of management of severe head injury in Canada. *Can J Neurol Sci* 2007;34:307-12.
- Hou DJ, Tong KA, Ashwal S, et al. Diffusion-weighted magnetic resonance imaging improves outcome prediction in adult traumatic brain injury. *J Neurotrauma* 2007;24:1558-69.

41. Smith SM. Fast robust automated brain extraction. *Hum Brain Mapp* 2002;17:143-55.
42. Smith SM, Jenkinson M, Woolrich MW, et al. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage* 2004;(23 Suppl 1):S208-19.
43. Smith SM, Jenkinson M, Johansen-Berg H, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage* 2006;31:1487-505.
44. Smith SM, Johansen-Berg H, Jenkinson M, et al. Acquisition and voxelwise analysis of multi-subject diffusion data with tract-based spatial statistics. *Nat Protoc* 2007;2:499-503.
45. Behrens TE, Woolrich MW, Jenkinson M, et al. Characterization and propagation of uncertainty in diffusion-weighted MR imaging. *Magn Reson Med* 2003;50:1077-88.
46. Rueckert D, Sonoda LI, Hayes C, Hill DL, Leach MO, Hawkes DJ. Nonrigid registration using free-form deformations: application to breast MR images. *IEEE Trans Med Imaging* 1999;18:712-21.
47. Smith SM, Nichols TE. Threshold-free cluster-enhancement: addressing the problem of threshold-dependence in cluster inference. *Proceedings of the 13th Annual Meeting of the Organization for Human Brain Mapping*. Chicago; 2007.
48. Mori S, Wakana S, van Zijl PCM, Nagae-Poetscher LM. *MRI atlas of human white matter*. Amsterdam: Elsevier; 2005.
49. Waxman SG. *Clinical neuroanatomy*. 25th ed. Toronto: McGraw-Hill; 2002.
50. Jurkiewicz MT, Crawley AP, Verrier MC, Fehlings MG, Mikulis DJ. Somatosensory cortical atrophy after spinal cord injury: a voxel-based morphometry study. *Neurology* 2006;66:762-4.
51. Chang CW. Evident transsynaptic degeneration of motor neurons after spinal cord injury: a study of neuromuscular jitter by axonal microstimulation. *Am J Phys Med Rehabil* 1998;77:118-21.
52. Damoiseaux JS, Smith SM, Witter MP, et al. White matter tract integrity in aging and Alzheimer's disease. *Hum Brain Mapp* 2008.
53. Focke NK, Yogarajah M, Bonelli SB, Bartlett PA, Symms MR, Duncan JS. Voxel-based diffusion tensor imaging in patients with mesial temporal lobe epilepsy and hippocampal sclerosis. *Neuroimage* 2008;40:728-37.
54. Douaud G, Smith S, Jenkinson M, et al. Anatomically related grey and white matter abnormalities in adolescent-onset schizophrenia. *Brain* 2007;130:2375-86.
55. Hammoud DA, Wasserman BA. Diffuse axonal injuries: pathophysiology and imaging. *Neuroimaging Clin N Am* 2002;12:205-16.

#### Suppliers

- a. Signa EXCITE; GE HealthCare, PO Box 414, Milwaukee, WI 53201.
- b. FMRIB Centre, Dept of Clinical Neurology, John Radcliffe Hospital, Headington, Oxford, UK OX3 9DU.
- c. SPSS Inc, 233 S Wacker Dr, 11th Fl, Chicago, IL 60606.