

Brain-Behavior Relationships in Young Traumatic Brain Injury Patients: DTI Metrics are Highly Correlated with Postural Control

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Abstract: Traumatic brain injury (TBI) is a major cause of impairment and functional disability in children and adolescents, including deterioration in fine as well as gross motor skills. The aim of this study was to assess deficits in sensory organization and postural ability in a young group of TBI patients versus controls by using quantitative force-platform recordings, and to test whether balance deficits are related to variation in structural properties of the motor and sensory white matter pathways. Twelve patients with TBI and 14 controls (aged 8–20 years) performed the Sensory Organisation Test (SOT) protocol of the EquiTest[®] (Neurocom). All participants were scanned using Diffusion Tensor Imaging (DTI) along with standard anatomical scans. Quantitative comparisons of DTI parameters (fractional anisotropy, axial and radial diffusivity) between TBI patients and controls were performed. Correlations between DTI parameters and SOT balance scores were determined. Findings revealed that the TBI group scored generally lower than the control group on the SOT, indicative of deficits in postural control. In the TBI group, reductions in fractional anisotropy were noted in the cerebellum, posterior thalamic radiation, and corticospinal tract. Degree of white matter deterioration was highly correlated with balance deficits. This study supports the view that DTI is a valuable tool for assessing the integrity of white matter structures and for selectively predicting functional motor deficits in TBI patients. *Hum Brain Mapp* 31:992–1002, 2010. © 2009 Wiley-Liss, Inc.

Key words: traumatic brain injury; DTI; balance; children; neuroplasticity

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INTRODUCTION

Traumatic brain injury (TBI) is the leading cause of acquired disability in children and adolescents (Kraus and McArthur, 1996; Sosinet al., 1996), often due to traffic accidents, and resulting in significant deficits in cognition. Moreover, motor performance is impaired for years following the insult, often including balance deficits that interfere with successful performance on daily tasks. Although children and adolescents with TBI often regain some of their lost postural control after therapy, complaints remain prevalent years after injury (Rossi and Sullivan, 1996). The extensive diffuse nature of axonal injury is often regarded as the primary cause of balance deficits in TBI.

Diffuse axonal injury (DAI) results from the rotational acceleration/deceleration forces occurring at the time of injury (Adams et al., 1980; Gentry, 1994) and is characterized by microscopic lesions scattered throughout the white matter (WM), occurring particularly in the corpus callosum, upper brain stem, and internal capsule (Levin et al., 1997). Whereas conventional MRI is quite insensitive to axonal injury in TBI, diffusion tensor imaging (DTI) has proven to be more appropriate for assessment of diffuse WM damage (Levin, 2003). More specifically, it determines the magnitude and directionality of water diffusion along WM tracts as characterized by the diffusion tensor and its derived diffusion parameters, such as fractional anisotropy (FA), mean diffusivity (MD), and diffusion eigenvalues (Ge et al., 2005; Le Bihan et al., 2001).

A number of recent DTI studies in TBI adults have demonstrated changes in diffusion anisotropy, particularly in the corpus callosum, internal capsule, and centrum semiovale, sometimes with significant correlations to clinical and behavioral parameters (e.g. Kraus et al., 2007; Kennedy et al., 2009; Salmond et al., 2006; Sidaros et al., 2008). On the contrary, DTI applications on TBI children are still very limited but potentially promising. Recent DTI studies in TBI children have provided evidence for associations between FA and performance on neurocognitive and behavioral measures. To the best of our knowledge, DTI studies in TBI children have not yet tested whether deficits in postural control are related to variation in structural properties of WM pathways.

This study determined deficits in sensory organization and postural ability in TBI children versus controls by using quantitative force-platform recordings. DTI was used to assess the structural integrity of principal motor and sensory tracts/regions. It was hypothesized that the degree of microstructural WM damage in principal sensorimotor structures, as assessed by FA, would predict balance performance in TBI patients.

MATERIALS AND METHODS

Participants

Twenty-six children and adolescents participated in the study, including 12 subjects with TBI (mean age 14 years

8 months, *SE* 1 year 1 month, range 8–20 years of age, seven boys and five girls) and 14 control subjects (mean age 12 years 10 months, *SE* 8 months, range 9–17 years of age; seven boys and seven girls). The TBI patients were classified as ‘moderate-to-severe’ based on several factors: the Glasgow Coma Scale score after resuscitation (a subgroup of five children had a GCS of 8 or below), the anatomical features of the injury based on inspection by an expert neuroradiologist (see later), and the injury mechanism (traffic accidents and falls), or combinations thereof. The demographic and clinical characteristics of the TBI group are shown in Table I. All TBI patients were assessed at least 6 months post-injury, when neurological recovery was stabilized. The interval between injury and scanning (age of injury) was on average 3 years, 6 months (*SE* 9 months). Their age at injury was on average 10 years, 6 months (*SE* 3 years, 2 months). Participants were excluded if they had pre-existing developmental or intellectual disabilities, a progressive disease, or were taking medication.

General motor performance was assessed using the Movement Assessment Battery for Children (M-ABC), including measures of manual dexterity, ball skills, and static and dynamic balance (Henderson and Sugden, 1992; Smits-Engelsman, 1998). The TBI group scored on average worse than the control group on the total score of the M-ABC, $t(24) = 4.00$, $p < 0.001$ (Mean TBI = 15.32, Mean Control = 5.64), balance subscore, $t(24) = 4.70$, $p < 0.001$ (Mean TBI = 7.55, Mean Control = 2.46), and manual dexterity subscore, $t(24) = 3.87$, $p < 0.001$ (Mean TBI = 5.63, Mean Control = 1.54), confirming the former’s lower mean motor performance levels.

Sensory Organisation Test

Posturography was used to determine sensory organization (which sensory stimuli a subject primarily relies on) and muscle coordination (how well postural adjustments are realized). The EquiTest System (NeuroCom International, Clackamas, Oregon) provided objective assessment of balance control and postural stability under dynamic test conditions, designed to reflect the challenges of daily life. As part of the EquiTest System, the Sensory Organisation Test (SOT) protocol systematically disrupted the sensory selection processes (i.e. somatosensory, visual inputs, or both) while measuring a subject’s ability to maintain equilibrium. Six sensory conditions evaluated the relative contributions of vision, vestibular, and somatosensory input in balance function (see Fig. 1). In condition 1, all three sensory systems were operational while the participant stood on a fixed platform with eyes open, and a baseline measure of stability was obtained. Condition 2 was the same as condition 1, except that the eyes were closed. Condition 3 was similar to condition 1 but the visual surround moved to track the participant’s sway, which provided inaccurate orientation cues. In condition 4, the subject stood with the eyes open and the visual surround fixed but the platform moved in response to his/her sway

TABLE I. Summary of demographic and injury characteristics for the TBI group

TBI patient #; Age/gender/handedness	GCS	Acute scan within 24 h after injury Lesion location/pathology	MRI scan at examination Lesion location/pathology
TBI 1; 15,7/F/RH	8	(R) FL subdural hematoma	(R) FL, splenium corpus callosum shearing injuries
TBI 2; 9,9/F/RH	5	(R) TL/PL subdural hematoma and (R) cerebellar contusion	(R) TL/PL Subdural hematoma and (R) cerebellar contusion
TBI 3; 13,1/M/LH		Lesion and location not specified in available records	Hemosiderin deposits (R) thalamus and (R) posterior limb of the internal capsule, shearing injuries corpus callosum
TBI 4; 16,6/M/RH	7	Enlarged (R) lateral ventricle, (R) hematoma occipital horn lateral ventricle, hyperdensity (L) thalamus, (LH) shearing injuries	Enlarged (R) lateral ventricle, (RH) atrophy, hemosiderin deposits (splenium corpus callosum, (R) corona radiata), asymmetry cerebral peduncles, (L) contusion pons
TBI 5; 14,1/F/RH	3	(R) FL/PL/OL contusion; contusion basal ganglia (thalamus, (R) nucleus caudatus)	Atrophy (R) FL/TL, nucleus caudatus, lentiformis, thalamus, internal capsule, atrophy (R) amygdala, hippocampus, cerebellum; asymmetry lemniscus, cerebral peduncles, pons; shearing injuries corpus callosum
TBI 6; 16,8/M/RH	8	(L) TL contusion, (L) FL punctiform contusion, (R) contusion mesencephalon, (L) FL hemorrhagic injuries and (L) thalamus	Enlarged ventricles, (L) FL hemosiderin deposits
TBI 7; 19,1/M/RH		Lesion and location not specified in available records	Shearing injury splenium corpus callosum
TBI 8; 20,4/M/RH		(R) FL hematoma, enlarged ventricles	Atrophy RH, (R) contusion superior frontal gyrus, atrophy (R) nucleus caudatus, (R) nucleus lentiformis, injured corpus callosum
TBI 9; 17,2/M/RH		Contusions (L) FL, TL, (R) PL, subdural hematoma	Contusion (L) PL inferior, (L) LH hemosiderin deposits, (R) TL contusion, atrophy (L) lateral TL, atrophy (L) FL
TBI 10; 11,5/F/RH		(R) FL subdural hematoma, hemorrhagic injuries thalamus, fornix, corpus callosum	(R) FL subdural hematoma
TBI 11; 18,7/F/RH		Enlarged ventricles, atrophy PL, FL, RH WM, atrophy (L) hippocampus, shearing injuries	Enlarged ventricles, atrophy LH, (L) PL inferior contusion, injuries superior frontal sulcus, contusion RH, orbitofrontal contusion, (R) nucleus lentiformis contusion, asymmetry cerebral peduncles, atrophy (R) cerebellum
TBI 12; 8,9/M/RH		Hemorrhagic injuries RH/LH, FL/TL contusion, (L) FL subdural hematoma	(L) FL contusion and subdural hematoma, (R) TL contusion and subdural hematoma

Anatomy codes: WM, white matter; GM, grey matter; RH, right hemisphere; LH, left hemisphere; FL, frontal lobe; TL, temporal lobe; PL, parietal lobe; OL, occipital lobe; R, right; L, left. Other codes: TBI, traumatic brain injury; GCS, Glasgow Coma Scale score; MRI, magnetic resonance imaging; RH, right-handed; LH, left-handed; M, male; F, female.

such that the ankle joints did not bend in response to the sway, providing inaccurate proprioceptive input to the brain. Condition 5 was identical to condition 4 except that the eyes were now closed, such that only the vestibular system was fully operational. Condition 6 was the same as condition 4 except that the visual surround moved in response to the participant's sway, and thus both vision and proprioception were compromised, leaving only the vestibular system as a reliable source. The test protocol consisted of three repetitions of each condition. An equilibrium score was calculated for these 6 sensory conditions. The subject's sway was calculated from the maximum anterior and posterior center of gravity displacements, occurring over the 20-s trial period. Maximum displacement without losing balance was assumed to be within a range of 12.5° (6.25° anterior, 6.25°

posterior). The equilibrium scores were then expressed as percentages, 0 indicating sway exceeding the limits of stability and 100 indicating perfect stability. The test series involved 18 trials overall. A composite equilibrium score, describing a person's overall level of performance during all the SOT trials was also calculated, with higher scores being indicative of better balance performance. This task typically lasted 15 min.

MRI Data Acquisition

MR examination took place without sedation on a 3T scanner (Intera, Philips, Best, the Netherlands) with an eight channel phased-array head coil. A DTI SE-EPI (diffusion weighted single shot spin-echo echoplanar imaging),

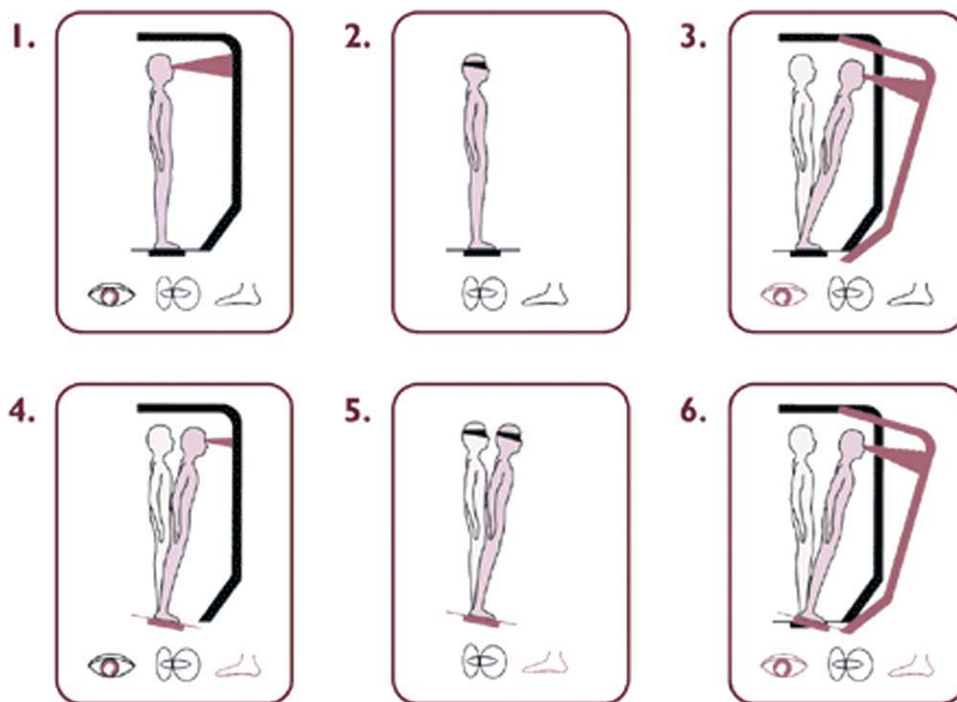


Figure 1.

Schematic representation of the six conditions of the Sensory Organisation Test of the EquiTest System. Reproduced with permission from NeuroCom International, Clackamas, Oregon. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

with a data acquisition matrix = 112×112 ; field of view (FOV) = $220 \times 220 \text{ mm}^2$; TR = 7916 ms, TE = 68 ms, parallel imaging factor 2.5, 68 contiguous sagittal slices (slice thickness = 2.2 mm; voxel size = $2 \times 2 \times 2.2 \text{ mm}^3$) covering the entire brain and the brainstem, was acquired. A pair of diffusion gradients was applied along 45 non-collinear directions with a b-value of 800 s/mm^2 . Additionally, one set of images with no diffusion weighting ($b = 0 \text{ s/mm}^2$) was acquired.

A T1-weighted coronal 3D-TFE (182 contiguous coronal slices covering the whole brain and brainstem; FOV = 250 mm; TE = 4.6 ms; TR = 9.7 ms; slice thickness = 1.2 mm; matrix size = 256×256 ; voxel size = $0.98 \times 0.98 \times 1.2 \text{ mm}^3$; scan duration = 4:21 min) was consequently acquired for anatomical detail. These structural MRI scans were investigated by an expert neuro-radiologist to indicate location and type of pathology (e.g., gliosis, shearing, and haemorrhage) (see Table I).

DTI Processing

The DTI data were analyzed and processed in Explor-eDTI (Leemans et al., 2009), using the following multi-step procedure: (a) Subject motion and eddy-current induced geometrical distortions were corrected (Leemans and Jones, 2009), (b) the diffusion tensors and subsequently the

FA, axial ($\lambda_{||}$) and radial (λ_{\perp}) diffusivity were calculated using a non-linear regression procedure (Mori et al., 2008), (c) the DTI data were coregistered to MNI space for analyzing potential group differences (Leemans et al., 2005; Van Hecke et al., 2007, 2008), (d) a standard deterministic streamline tractography approach was used, as described in Basser et al. (2000), to reconstruct the WM fiber pathways of interest, (e) the probabilistic cytoarchitectonic atlas, developed by Eickhoff et al. (2005), and a digitized version of the original Talairach atlas (Lancaster et al., 2000, 2007), both mapped in MNI space as provided by the FSL toolbox, were used to perform the correlation analysis (Smith et al., 2004).

ROIs Definition

Preserving balance requires multisensory integration to drive motor commands (Nashner and Peters, 1990). An automated observer-independent approach was used here to define several WM pathways that are mainly concerned with sensory afferent input on one hand—such as the medial lemniscus, the posterior thalamic radiation, the middle cerebellar peduncle, and the pons—and motor functions on the other hand, including the corticospinal tract, the superior cerebellar peduncle, the cerebral peduncle, and the anterior limb of the internal capsule.

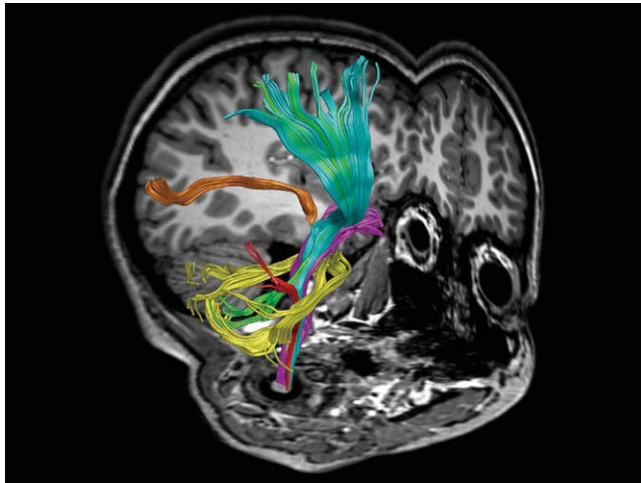


Figure 2.

Sensory and motor tracts used in the study. Tracts were reconstructed and displayed on a 3D T1-image for a typical control subject: Corticospinal tract (cyan), inferior cerebellar peduncle (red), middle cerebellar peduncle (yellow), medial lemniscus (magenta), posterior thalamic radiation (orange), and superior cerebellar peduncle (green). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Pathways carrying both input and output fibers, such as the inferior cerebellar peduncle, the posterior limb of the internal capsule, the brainstem, and the cerebellum, were also analyzed for diffusion parameters. Tracts and regions were reconstructed and presented on a 3D T1-image for a single representative subject and fractional anisotropy maps of the white-matter atlas of Mori et al. (2005) in Figures 2 and 3, respectively.

Statistical Analysis

Analysis of the SOT equilibrium scores was assessed by a 2×6 (Group \times Sensory condition) ANOVA with repeated measures on the last factor. For the composite score of the SOT, two-sample *t*-tests compared the TBI group with the age- and gender-matched control group. These behavioural parameters were also used to assess relationships between measures of WM integrity and balance using partial Pearson correlations (with the effect of age removed) within the TBI group.

The primary analyses carried out on the dependent measures extracted from the DTI data (FA, axial and radial diffusivity) were two-sample *t*-tests with group membership (TBI and control) as the between subjects comparison. Data were confirmed to have a normal distribution using the Shapiro-Wilks Normality Test. Bonferroni corrections for multiple comparisons were made (hence $p < 0.004$ was considered significant following correction for the between-group comparisons regarding the DTI parameters and $p < 0.007$ for the correlation analyses).

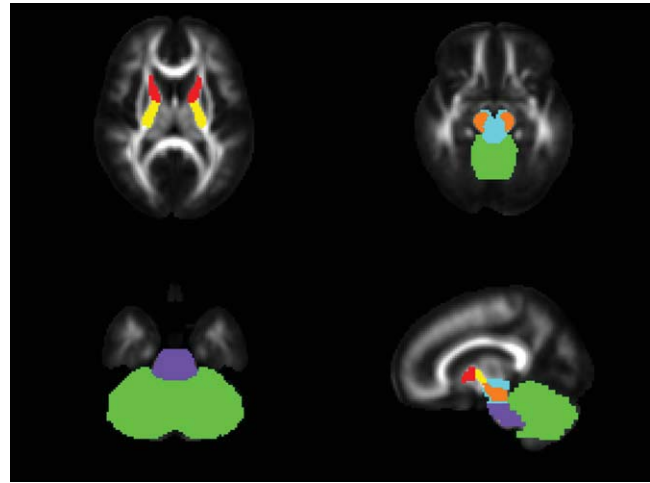


Figure 3.

Example sensory and motor regions of interest masks depicted on fractional anisotropy maps of the white-matter atlas of Mori et al. (2005): Anterior limb of the internal capsule (red), posterior limb of the internal capsule (yellow), cerebellum (green), brainstem (blue), pons (violet), cerebral peduncle (orange). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

RESULTS

Group Differences in Postural Control

Group \times Sensory condition ANOVAs with repeated measures on the last factor were conducted on the SOT. The control group scored higher than the group with TBI for all posturography SOT conditions, $F(1,22) = 5.00$, $p < 0.05$. Moreover, a significant main effect of sensory condition was found, $F(5,110) = 138.1$, $p < 0.001$. Post hoc (Tukey) testing exhibited significant differences between

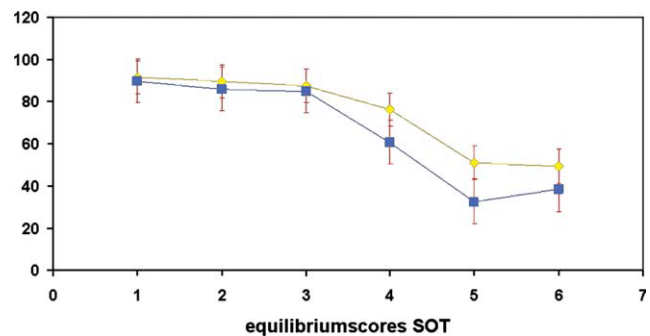


Figure 4.

Graph depicting the significant interaction effect between sensory condition and group. The TBI group performed significantly worse than the controls on condition 5 (eyes closed, sway referenced surface). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE II. Diffusion parameters, mean, and standard error for each ROI for both groups

ROI	Fractional anisotropy					Axial diffusivity [$\times 10^{-3}$ mm ² /s]					Radial diffusivity [$\times 10^{-3}$ mm ² /s]				
	TBI		Control			TBI		Control			TBI		Control		
	M	SE	M	SE	<i>p</i>	M	SE	M	SE	<i>p</i>	M	SE	M	SE	<i>p</i>
Middle cerebellar peduncle	0.406	0.023	0.403	0.012	0.895	1.316	0.026	1.231	0.014	0.006	0.608	0.021	0.588	0.009	0.359
Inferior cerebellar peduncle	0.386	0.026	0.403	0.017	0.579	1.244	0.037	1.270	0.024	0.542	0.634	0.023	0.640	0.011	0.823
Superior cerebellar peduncle	0.349	0.029	0.438	0.017	0.011	2.142	0.170	1.649	0.040	0.006	1.189	0.127	0.781	0.030	0.003
Cerebral peduncle	0.492	0.026	0.597	0.012	0.001	1.461	0.043	1.503	0.031	0.423	0.594	0.042	0.507	0.008	0.039
Anterior limb of the internal capsule	0.372	0.028	0.469	0.013	0.003	1.384	0.127	1.131	0.012	0.042	0.816	0.135	0.519	0.010	0.026
Posterior limb of the internal capsule	0.517	0.020	0.606	0.006	<0.001	1.325	0.026	1.359	0.016	0.269	0.534	0.022	0.468	0.004	0.004
Cerebellum	0.172	0.004	0.206	0.003	<0.001	1.146	0.034	0.995	0.007	<0.001	0.830	0.031	0.681	0.004	<0.001
Brainstem	0.341	0.016	0.390	0.006	0.005	1.391	0.038	1.331	0.011	0.126	0.710	0.030	0.643	0.007	0.028
Pons	0.370	0.025	0.426	0.010	0.035	1.369	0.036	1.365	0.018	0.902	0.677	0.029	0.624	0.012	0.087
Corticospinal tract	0.252	0.009	0.306	0.004	<0.001	1.250	0.027	1.108	0.012	<0.001	0.751	0.021	0.635	0.008	<0.001
Medial lemniscus	0.454	0.034	0.546	0.012	0.012	1.343	0.047	1.383	0.034	0.486	0.621	0.046	0.542	0.009	0.084
Posterior thalamic radiation	0.430	0.023	0.526	0.012	0.001	1.475	0.042	1.420	0.021	0.235	0.685	0.022	0.578	0.018	0.001

Results of the two-sample-*t*-tests, bold values indicate that results remained significant following Bonferroni correction ($p < 0.004$).

condition 1 and 4 on one hand and condition 5 and 6 on the other hand ($p < 0.05$). Finally, the interaction between group and sensory condition was also significant, $F(5,110) = 3.66$, $p < 0.01$ (see Fig. 4). Post hoc (Tukey) testing showed that the TBI group performed significantly worse than the controls on condition 5 (eyes closed, sway referenced surface). The mean composite SOT score (average across all six conditions) also differed significantly between the TBI patients ($M = 58.8$; range, 32.0–80.0) and the controls ($M = 69.4$; range, 58.2–75.7), $t(22) = -2.20$, $p < 0.001$. The lower scores of the subjects with TBI indicate poorer balance (larger anterior/posterior body sway) than the control subjects.

Group Differences in DTI Parameters

A distinct pattern of significant differences between both groups was observed throughout the brain. Table II lists the diffusion parameters for the different fiber tracts studied in the TBI and control group.

Fractional Anisotropy

Significant main effects of group were observed for several regions of interests (ROIs). As can be seen in Table II, TBI patients showed reduced fractional anisotropy along the corticospinal tract [$t(24) = -5.54$, $p < 0.001$], cerebral peduncle [$t(24) = -3.82$, $p < 0.001$], anterior [$t(24) = -3.25$, $p < 0.01$] and posterior limb of the internal capsule

[$t(24) = -4.58$, $p < 0.001$], cerebellum [$t(24) = -7.29$, $p < 0.001$], and posterior thalamic radiation [$t(24) = -3.82$, $p < 0.001$].

Axial and Radial Diffusivity

Investigating the changes in the underlying eigenvalues revealed that the TBI group showed significantly increased axial diffusivity ($\lambda_{||}$) in the cerebellum [$t(24) = 4.68$, $p < 0.001$], and corticospinal tract [$t(24) = 5.07$, $p < 0.001$], relative to controls (Table II). Likewise, radial diffusivity (λ_{\perp}) increased in the superior cerebellar peduncle [$t(24) = 3.35$, $p < 0.01$], posterior limb of the internal capsule [$t(24) = 3.21$, $p < 0.01$], cerebellum [$t(24) = 5.10$, $p < 0.001$], corticospinal tract [$t(24) = 5.56$, $p < 0.001$], and posterior thalamic radiation [$t(24) = 3.75$, $p < 0.001$]. Hence, a decrease of FA was mediated by the combined effects of $\lambda_{||}$ and λ_{\perp} increase.

Relationship Between WM Integrity and Postural Control

To examine the relationship between WM integrity and postural control, correlations were determined for the entire group of TBI subjects in specific tracts (Table III). Significant correlations were obtained between the equilibrium score of condition 1 (eyes open, fixed surface and visual surround) and FA in the superior cerebellar peduncle ($r = 0.83$, $p < 0.01$), the anterior limb of the

TABLE III. Results of the correlation analyses between FA and equilibrium scores

ROI	Fractional anisotropy						
	EqC1	EqC2	EqC3	EqC4	EqC5	EqC6	Comp
Middle cerebellar peduncle	0.51 <i>p</i> = 0.113	0.45 <i>p</i> = 0.163	0.78 <i>p</i> = 0.005	0.19 <i>p</i> = 0.584	0.33 <i>p</i> = 0.316	0.41 <i>p</i> = 0.205	0.43 <i>p</i> = 0.192
Inferior cerebellar peduncle	0.30 <i>p</i> = 0.369	0.39 <i>p</i> = 0.236	0.24 <i>p</i> = 0.469	0.24 <i>p</i> = 0.485	0.11 <i>p</i> = 0.757	0.21 <i>p</i> = 0.545	0.22 <i>p</i> = 0.506
Superior cerebellar peduncle	0.83 <i>p</i> = 0.002	0.48 <i>p</i> = 0.139	0.65 <i>p</i> = 0.030	0.27 <i>p</i> = 0.416	0.61 <i>p</i> = 0.046	0.35 <i>p</i> = 0.287	0.51 <i>p</i> = 0.113
Cerebral peduncle	0.69 <i>p</i> = 0.018	0.32 <i>p</i> = 0.337	0.73 <i>p</i> = 0.011	0.29 <i>p</i> = 0.394	0.61 <i>p</i> = 0.045	0.37 <i>p</i> = 0.266	0.51 <i>p</i> = 0.107
Anterior limb of the internal capsule	0.78 <i>p</i> = 0.004	0.65 <i>p</i> = 0.029	0.64 <i>p</i> = 0.033	0.40 <i>p</i> = 0.220	0.44 <i>p</i> = 0.179	0.43 <i>p</i> = 0.184	0.52 <i>p</i> = 0.099
Posterior limb of the internal capsule	0.71 <i>p</i> = 0.015	0.52 <i>p</i> = 0.100	0.64 <i>p</i> = 0.036	0.41 <i>p</i> = 0.213	0.61 <i>p</i> = 0.049	0.42 <i>p</i> = 0.199	0.56 <i>p</i> = 0.074
Cerebellum	0.82 <i>p</i> = 0.002	0.59 <i>p</i> = 0.055	0.67 <i>p</i> = 0.023	0.28 <i>p</i> = 0.400	0.58 <i>p</i> = 0.063	0.35 <i>p</i> = 0.288	0.51 <i>p</i> = 0.112
Brainstem	0.57 <i>p</i> = 0.065	0.51 <i>p</i> = 0.112	0.73 <i>p</i> = 0.011	0.19 <i>p</i> = 0.585	0.47 <i>p</i> = 0.145	0.43 <i>p</i> = 0.191	0.47 <i>p</i> = 0.144
Pons	0.53 <i>p</i> = 0.094	0.53 <i>p</i> = 0.095	0.75 <i>p</i> = 0.008	0.26 <i>p</i> = 0.441	0.45 <i>p</i> = 0.170	0.53 <i>p</i> = 0.097	0.52 <i>p</i> = 0.099
Corticospinal tract	0.60 <i>p</i> = 0.053	0.63 <i>p</i> = 0.039	0.63 <i>p</i> = 0.039	0.56 <i>p</i> = 0.071	0.66 <i>p</i> = 0.027	0.68 <i>p</i> = 0.021	0.72 <i>p</i> = 0.013
Medial lemniscus	0.83 <i>p</i> = 0.002	0.47 <i>p</i> = 0.142	0.71 <i>p</i> = 0.014	0.22 <i>p</i> = 0.514	0.55 <i>p</i> = 0.079	0.41 <i>p</i> = 0.216	0.50 <i>p</i> = 0.116
Posterior thalamic radiation	0.67 <i>p</i> = 0.023	0.70 <i>p</i> = 0.018	0.56 <i>p</i> = 0.076	0.66 <i>p</i> = 0.027	0.65 <i>p</i> = 0.029	0.63 <i>p</i> = 0.038	0.71 <i>p</i> = 0.013

Bold values indicate scores remaining significant following Bonferroni correction ($p < 0.007$). Cursive values are significant at $p < 0.05$, but did not survive correction for multiple comparisons.

internal capsule ($r = 0.78$, $p < 0.01$), the cerebellum ($r = 0.82$, $p < 0.01$), and the medial lemniscus ($r = 0.83$, $p < 0.01$), with higher FA being related to higher scores on the SOT. Moreover, the equilibrium score of condition 3 (eyes open, fixed surface, sway referenced visual surround) was significantly related to mean FA in the fibers passing through the middle cerebellar peduncle ($r = 0.78$, $p < 0.01$; see Fig. 5). Hence, higher balance levels were associated with a higher WM anisotropy. Correlations that were significant at $p < 0.05$, but did not survive correction for multiple comparisons, are reported for descriptive purposes only in Table III.

Similar results were obtained using both axial and radial diffusivity indices: increased diffusivity (e.g., in the cerebellum, middle cerebellar peduncle, medial lemniscus, anterior limb of the internal capsule) was associated with lower performance on the SOT. However, we used FA as a damage marker without consideration of other DTI parameters, because FA has been suggested to be the most important DTI marker in patients with brain injury (Assaf and Pasternak, 2008; Mori and van Zijl, 2002).

DISCUSSION

In this study, we determined relations between brain WM structure and postural function in a young TBI group.

First, we used DTI to assess WM differences between a TBI and matched control group in structures related to postural control. Second, the functional relevance of these microstructural abnormalities was underscored by statistically significant correlations between balance deficits and FA scores in the TBI group. To the best of our knowledge, this is the first time that such strong relationships between brain WM structure and postural control have been established.

Group Differences in Postural Control

Our behavioural results provide evidence of compromised sensorimotor processing as shown by disturbed postural control in TBI when compared with control subjects, especially in conditions where visual and vestibular inputs must be relied upon to produce stability. Balance deficits in TBI children have also been reported in studies using primarily clinical tests for field use (e.g. Gagnon et al., 1998, 2001, 2004; Geurts et al., 1996, 1999). For example, children with mild TBI showed balance deficits at 12 weeks post injury on the balance subtest of the Bruininks-Oseretsky Test of Motor Proficiency, the Postural Stress Test, and on the eyes-closed conditions in the Pediatric Clinical Test of Sensory Interaction for Balance (Gagnon et al., 2004). Moreover, our results also paralleled those

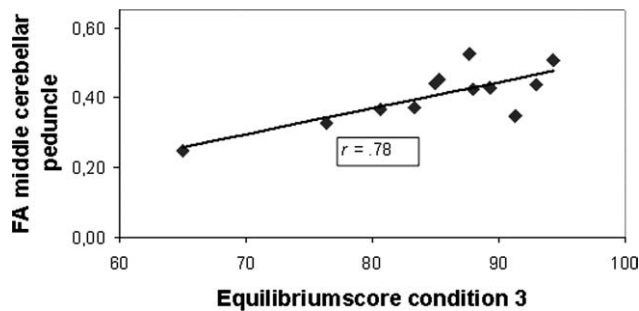


Figure 5.

Scatter plot indicating the relationship between FA and equilibrium scores of the SOT within the TBI group.

revealed with the SOT in mild TBI adults, showing increased postural instability as measured by the SOT composite score (Guskiewicz et al., 1997, 2001; Kaufman et al., 2006; Riemann and Guskiewicz, 2000). However, these findings cannot be compared directly with the results of this study due to the variation in patient populations (such as different age groups, severity and chronicity).

Group Differences in Diffusion Tensor Imaging

We found that mean FA in several fiber systems was lower in a young group suffering from moderate-to-severe TBI when compared with a typically developing group that was matched on demographic variables. These findings extend previous adult DTI studies showing long-term WM disruption following TBI (Benson et al., 2007; Kraus et al., 2007; Mathias et al., 2004; Salmond et al., 2006), as well as case reports suggesting decreased FA in children with TBI (Ewing-Cobbs et al., 2006). However, in contrast to previous DTI studies, which used a priori ROI analyses, making them vulnerable to intra- and inter-subject variability, we applied an automated observer-independent approach for assessing groupwise microstructural differences in several WM pathways/regions of the brain, as discussed next.

Firstly, we demonstrated significantly lower FA in the internal capsule of our TBI patients compared with controls. This region is a site with a predilection to shearing injuries (DAIs) (Gentry et al., 1988). More specifically, we found FA to be decreased in several motor tracts and regions, including the corticospinal tract and the cerebral peduncle. Recent studies using predefined ROIs for analysis of diffusion characteristics along WM tracts also demonstrated FA reduction in these two regions (Kraus et al., 2007; Sidaros et al., 2008). Because our field of view was not confined to these ROIs, we discovered WM disintegration at different levels of the motor system, including the cerebellum, i.e. a decrease in anisotropy and increase in diffusivity. The pattern of WM cerebellar impairment corresponds well with previous studies. MRI findings in children confirm that the cerebellum is often affected even

when the initial injury does not involve the cerebellum (Spanos et al., 2007; Soto-Ares et al., 2001). The indirect damage can be obtained via several mechanisms, such as mechanical forces, metabolic changes, and presynaptic hyperexcitability (Potts et al., 2009). This is further supported by studies using animal models of indirect and direct TBI trauma (Igarashi et al., 2007; Park et al., 2006, 2007). Following either direct or indirect cerebellar injury, several pathophysiologic mechanisms mediating TBI-induced cerebellar damage can be identified. These include Purkinje cell injury or loss due to excitotoxic injury, activation of an inflammatory response, and traumatic axonal injury. Moreover, functional (compensatory) changes in the cerebellum have been reported in our previous fMRI study (Caeyenberghs et al., 2009), suggesting that brain injury may lead to cerebellar disorganization. This study complements previous work, emphasizing the vulnerability of the cerebellum to TBI.

The posterior thalamic radiation was also affected in the TBI group, impairing peripheral sensory input to the cortex and reciprocal corticothalamic projections (Kamali et al., 2009). This suggests that WM projections to or from sensory cortex, besides classical pyramidal motor tracts, may play an important role in the pathophysiology of motor disabilities in TBI. Contribution of sensory pathways to motor outcome has also been demonstrated in children with cerebral palsy (Hoon et al., 2002; Thomas et al., 2005).

Although global FA is commonly reported in pediatric TBI studies (Ewing-Cobbs et al., 2008; Wilde et al., 2006), the underlying eigenvalues are also valuable because these may show more specific associations with certain pathological processes (Pierpaoli et al., 2001; Song et al., 2002). Human (Arfanakis et al., 2002; Concha et al., 2006) and animal studies (Boska et al., 2007; Mac Donald et al., 2007) suggest that the second and third eigenvalues (radial diffusivity) assess myelin changes. The first eigenvalue (axial diffusivity) is more related to axonal morphology and degradation. Here, we found increased radial and axial diffusivity in the TBI group for specific ROIs, suggesting damage to both myelin and axons. Kraus et al. (2007) found similar changes in patients with moderate-to-severe TBI, whereas only axial diffusivity was elevated in patients with mild TBI. This suggests a continuum of widespread neural changes in moderate to severe TBI affecting tissue organization, myelin, and axonal integrity. Regardless of the exact proportionate contribution of these pathological processes, the observed DTI pattern reflects the consequences of DAI and secondary insults.

Structural Integrity of the Brain (DTI) and its Relation to Postural Control

Our ultimate goal was to investigate whether damage in motor and sensory WM tracts/regions in the TBI group was associated with impairments in balance, as assessed

by the SOT protocol of the EquiTest. Lower balance levels were associated with a lower WM anisotropy. More specifically, significant correlations were obtained between the SOT equilibrium score of condition 1 and FA in the superior cerebellar peduncle, the anterior limb of the internal capsule, the cerebellum, and the medial lemniscus. Also, the equilibrium score of condition 3 was significantly related to mean FA of the middle cerebellar peduncle. Interestingly, in most of the regions where FA values in TBI patients were significantly lower than controls (e.g. anterior limb of the internal capsule, cerebellum, and medial lemniscus), high correlations with the equilibrium scores were observed (Tables II and III). Even FA values for the cerebellar peduncles, which did not differ significantly between groups, were correlated with equilibrium. This in agreement with a previous study of Hong et al. (2009), showing that the junction and peri-junctional areas between the brainstem and cerebellum are most vulnerable to DAI. Evaluation of the cerebellar peduncles using DTI could be helpful in patients with ataxia following TBI.

Moreover, the importance of the changes in diffusivity in this study is also highlighted by the significant correlations between radial/axial diffusivity and the equilibrium scores. Increases in diffusivity (both axial and radial) were associated with poor scores on condition 1 and 3 of the SOT.

Against our expectations, significant correlations were primarily observed for the less challenging postural control conditions and only for a specific set of WM tracts. However, it is important to note that high correlations were observed across the postural conditions even though these did not survive Bonferroni correction (see Table III). For example, performance on condition 5 was positively related to the mean FA in the posterior thalamic radiation and the superior cerebellar peduncle.

Limitations of this study pertain to the small sample size and the cross sectional design. Despite the clear findings, their replication in a larger sample is mandatory. In addition, further histopathology studies are required to investigate the processes underlying the DTI findings. Such research should also be explored for broader age ranges because the effects of TBI on FA and diffusivity indices may be age-dependent. Finally, longitudinal studies are needed to determine how changes in DTI metrics are related to recovery and objective measures of postural control.

Taking into account these limitations, this study is the first report illustrating associations between microstructure and postural control scores in a young TBI group. Correlations between indices derived from diffusion-weighted imaging during acute scanning and injury severity have previously been noted (Huisman et al., 2004), as well as with neurocognitive measures in chronic TBI patients (Kraus et al., 2007; Salmond et al., 2006). Motor indices, though not investigated in the head injury literature, have previously been reported to be associated with DTI measures in other disorders. For example, DTI metrics are cor-

related with tests of upper-limb function in patients with congenital hemiplegia and chronic stroke patients (Bleyenheuft et al., 2007; Schaechter et al., 2009). Unfortunately, DTI studies that use quantitative measures of kinematics are scarce.

CONCLUSIONS

This is the first report demonstrating a strong relation between reduced FA and balance deficits in a young TBI group using quantitative force-platform recordings. DTI may complement prognosis and may serve as a biomarker for TBI severity and potential functional motor impairment. Such work may clarify the brain structure-function relations that mediate the development of postural control and provide a basis for early prognosis and effective treatment of balance deficits.

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