

REPORT

Acute mild traumatic brain injury is not associated with white matter change on diffusion tensor imaging

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This study was designed to (i) evaluate the influence of age on diffusion tensor imaging measures of white matter assessed using tract-based spatial statistics; (ii) determine if mild traumatic brain injury is associated with microstructural changes in white matter, in the acute phase following injury, in a large homogenous sample that was carefully screened for pre-injury medical, psychiatric, or neurological problems; and (iii) examine if injury severity is related to white matter changes. Participants were 75 patients with acute mild traumatic brain injury (age = 37.2 ± 12.0 years, 45 males and 30 females) and 40 controls (age = 40.6 ± 12.2 yrs, 20 males and 20 females). Age effects were analysed by comparing control subgroups aged 31–40, 41–50, and 51–60 years against a group of 18–30-year-old control subjects. Widespread statistically significant areas of abnormal diffusion tensor measures were observed in older groups. Patients and controls were compared using age and gender as covariates and in age- and gender-matched subgroups. Subgroups of patients with more severe injuries were compared to age- and gender-matched controls. No significant differences were detected in patient-control or severity analyses (all P -value > 0.01). In this large, carefully screened sample, acute mild traumatic brain injury was not associated with diffusion tensor imaging abnormalities detectable with tract-based spatial statistics.

Keywords: concussion; traumatic brain injury; magnetic resonance imaging; diffusion tensor imaging; statistical analysis

Abbreviations: DTI = diffusion tensor imaging; TBI = traumatic brain injury; TBSS = tract-based spatial statistics

Introduction

In mild traumatic brain injury (TBI) research, white matter integrity assessment by diffusion tensor imaging (DTI) has been the centre

of attention for the last decade (Hulkower *et al.*, 2013). Many studies have reported white matter changes in patients with a history of mild TBI, recently or remotely, although heterogeneous and inconsistent conclusions have been drawn. This heterogeneity

Table 1 A brief summary of previous DTI studies that focus on the acute phase of mild TBI

Reference	Time frame*	Magnet	Patients (gender; age)	Control (gender; age)	Analysis	Findings
Arfanakis et al., 2002	< 24 h	1.5 T	5 (3 M, 2 F; 35.6 ± 14.8)	10 (5 M, 5 F; 28.9 ± 7.6)	ROI	Decreased FA
Bazarian et al., 2007	< 72 h	3 T	6 (4 M, 2 F; mean 21.7, range 18–31 years)	6 (4 M, 2 F; mean 21.7, range 18–31 years)	WBA, ROI	WBA: Decreased trace ROI: Increased FA
Chu et al., 2010	Range 1–6 days	3 T	10 (4 M, 6 F; 15.7 ± 1.18)	10 (4 M, 6 F; 15.7 ± 1.83)	WBA, ROI	Increased FA, Decreased RD
Henry et al., 2011	81.9 ± 46.7 h	3 T	16 (16M; 22.1 ± 1.7)	8 (8 M; 22.8 ± 1.5)	WBA	Increased FA and AD, Decreased MD
Lipton et al., 2009	Range 2–14 days	3 T	20 (9 M, 11 F; 33.4 ± 8.3)	20 (9 M, 11 F; 34.2 ± 9.3)	WBA	Decreased FA, Increased MD
Mayer et al., 2010	12 ± 5.7 days	3 T	21 (8 M, 13 F; 27.45 ± 7.39)	21 (8 M, 13 F; 26.81 ± 6.68)	ROI	Increased FA, Increased RD
Messé et al., 2012	Range 8–21 days	3 T	53 (35 M, 18 F; 35.5 ± 11.0)	40 (28M, 12 F; 36.3 ± 12.5)	TBSS	Decreased FA, Increased MD and RD
Miles et al., 2008	Range 1–10 days	1.5 T	17 (11 M, 6 F; mean 33.44, range 18–58 years)	29 (15 M, 14 F; mean 35, range 18–61 years)	ROI	Decreased FA, Increased MD
Toth et al., 2013	< 72 h	3 T	14 (9 M, 5 F; 34.9 ± 18.4)	14 (9 M, 5 F; 35.8 ± 18.5)	TBSS, volumetric ROI (fornix)	Decreased FA, Increased MD
Yallampalli et al., 2013	Range 1–16 days	3 T	11 (5 M, 6 F; 15.09 ± 1.14)	11 (5 M, 6 F; 15.82 ± 1.78)	ROI (fornix)	Decreased FA, Increased nADC

*Time from injury to imaging. Reported as mean time ± SD, maximum time or time range. ADC = apparent diffusion coefficient; F = female; FA = fractional anisotropy; M = male; MD = mean diffusivity (= apparent diffusion coefficient); ROI = region of interest; WBA = whole brain analysis.

can partly be explained by methodological differences and limitations, such as small sample sizes, failure to control for pre-injury health factors, major differences in time from injury to imaging, diverse patient characteristics, and differing DTI analysis techniques. A brief summary of previous DTI studies that focus on the acute phase of mild TBI are presented in Table 1.

The current study had three objectives: (i) to evaluate the influence of age on DTI measures and axonal integrity assessed by tract-based spatial statistics (TBSS); (ii) to determine if mild TBI is associated with microstructural changes in white matter in the acute phase following injury, in a large homogenous sample that was carefully screened for pre-injury medical, psychiatric, or neurological problems; and finally (iii) to examine if mild TBI severity is related to white matter changes. Through rigorous inclusion and exclusion criteria, the goal was to reduce or eliminate numerous confounding variables to study a relatively 'pure' sample of civilian patients with acute mild TBIs.

Materials and methods

This work is part of the Tampere Traumatic Head and Brain Injury Study. Subjects were enrolled from the emergency department of the Tampere University Hospital between August 2010 and July 2012; all met mild TBI criteria of the World Health Organization's Collaborating Centre for Neurotrauma Task Force (Holm et al., 2005). The enrolment protocol included three inclusion criteria and nine exclusion criteria, as described in our previous publication (Luoto et al., 2013), that resulted in a small percentage of patients with head trauma being enrolled (the majority of eligible adults were excluded due to comorbidities). Ethics approval was obtained from the Ethical Committee of Pirkanmaa Hospital District, Finland. All patients and controls provided written informed consent according to the Declaration of Helsinki.

Subjects

Of the 75 patients with mild TBI, 45 were male and 30 were female. The mean age was 37.2 ± 12.0 years. Of the 40 control subjects, 20 were male and 20 were female. The mean age for the control subjects was 40.6 ± 12.2 years. The mean time interval between injury and acute clinical assessment was 48.1 ± 45.4 h. The clinical characteristics of the mild TBI sample are presented in Table 2. For mild TBI severity analyses, mild TBI subgroups were formed based on clinical markers as follows: (i) loss of consciousness > 5 min, $n = 7$; (ii) post-traumatic amnesia > 3 h, $n = 25$; (iii) acute traumatic lesion on CT and/or MRI (complicated mild TBI), $n = 15$; (iv) Glasgow Coma Scale = 14, $n = 6$; and (v) a group of patients with a combination of any of the previous criteria (definite mild TBI), $n = 29$.

Control subjects were patients evaluated in the emergency department of Tampere University Hospital who suffered ankle injuries. The same study criteria used with the mild TBI sample were applied in the enrolment of the controls when applicable. Control subjects were enrolled in an age and gender stratified manner, with five males and five females in the following age groups: (i) 18–30 years, (ii) 31–40 years, (iii) 41–50 years; and (iv) 51–60 years. All 40 control subjects underwent a head MRI with the same sequences as the mild TBI sample. With controls, all MRI findings were interpreted as normal.

Table 2 Characteristics of classic clinical mild TBI severity markers

	Presence, n (%)		Duration			
	Yes	No	Mean	Median	SD	IQR
Loss of consciousness (min)	28 (37.3)	47 (62.7)	0.9	0	2.2	0–1.0
Post-traumatic amnesia (h)	69 (92.0)	6 (8.0)	2.66	1.5	3.4	0.1–4.5
Retrograde amnesia (h)	17 (22.7)	58 (77.3)	0.4	0	1.7	0
Disorientation	53 (70.7)	22 (29.3)				
Focal neurological deficit	17 (22.7)	58 (77.3)				
GCS, 15 points	69 (92.0)	6 (8.0)				
GCS, 14 points	6 (8.0)	69 (92.0)				
Acute traumatic lesion on CT*	7 (9.3)	68 (90.7)				
Acute traumatic lesion on MRI	15 (20.0)	60 (80.0)				
Diffuse axonal injury	7 (9.3)					
Diffuse axonal injury and subdural haemorrhage	1 (1.3)					
Subdural haemorrhage	1 (1.3)					
Subdural effusion	1 (1.3)					
Subarachnoid haemorrhage	1 (1.3)					
Contusion and subdural haemorrhage	2 (2.7)					
Contusion	2 (2.7)					

*All traumatic lesions were also visible on MRI.

GCS = Glasgow Coma Scale; IQR = interquartile range.

Clinical assessment

A broad clinical assessment of the patients in the final sample was performed by T.L. The patients were interviewed regarding past health including diagnosed medical conditions, medication use, head injury history, alcohol consumption according to the Alcohol Use Disorders Identification Test (Saunders *et al.*, 1993), and drug and narcotics abuse history. The presence and duration of retrograde amnesia and post-traumatic amnesia were assessed using the Rivermead Post-Traumatic Amnesia Protocol (King *et al.*, 1997) together with the Galveston Orientation and Amnesia Test (GOAT) (Levin *et al.*, 1979). All patients scored ≥ 80 points on the GOAT (normal 76–100). Persistent post-traumatic amnesia was screened using the revised Westmead Post-Traumatic Amnesia Scale (Shores *et al.*, 1986) and all the patients scored a flawless 12 points at the time of assessment. Glasgow Coma Scale (Teasdale and Jennett, 1976) scores were collected from ambulance forms (if applicable) and the emergency department records (the lowest scores were recorded). The clinical assessment included a complete neurological examination. Participants were determined to have met ICD-10 diagnostic criteria for post-concussional syndrome if they endorsed symptoms on the Sports Concussion Assessment Tool (SCAT2) (McCrorry *et al.*, 2009) 22-item symptom scale in at least three of the ICD-10 symptom categories. The time duration criterion was not applied to the acute analyses. The SCAT2 was added later in the study, so only a subset of patients were administered the test ($n = 51$ at emergency department, and $n = 50$ at 1 month due to a patient dropping out of the follow-up evaluation).

Neuroimaging

In the emergency department, a non-contrast head CT was performed with a 64-row CT scanner (GE, Lightspeed VCT) for all consecutive patients with head injury. Head MRI was done with a 3 T MRI scanner (Siemens Trio). The MRI protocol included sagittal T_1 -weighted 3D inversion recovery prepared gradient echo, axial T_2 turbo spin echo,

conventional axial and high resolution sagittal FLAIR, axial T_2^* , axial susceptibility weighted, and diffusion weighted imaging series. Head MRIs were done within 14 days after injury (mean 5.8 ± 2.5 days). All head MRIs were analysed and systematically coded by two neuroradiologists.

The DTI data were collected by a single-shot, spin echo-based and diffusion-weighted echo planar imaging sequence. The parameters for the DTI sequence were repetition time 5144 ms, echo time 92 ms, field of view 230 mm, matrix 128×128 , three averages, slice/gap 3.0/0.9 mm, and voxel dimension of $1.8 \times 1.8 \times 3.0$ mm. Two b-factors were used, 0 and 1000 s/mm^2 with 20 diffusion gradient orientations. A 12-channel head matrix coil was used. Finally, the signal to noise ratio value was well above the limit of acceptance for diffusion imaging, following the group's previous work (Hakulinen *et al.*, 2012).

Tract-based spatial statistics

Whole brain voxel-wise statistical analysis was carried out using TBSS (Smith *et al.*, 2006), a part of FSL, version 5.0.1 (Smith *et al.*, 2004). A threshold for fractional anisotropy values for the creation of the skeleton was chosen at ≥ 0.3 to exclude peripheral areas from the skeleton and to reduce bias in the results. Effects of age and gender were controlled by adding them as covariates of no interest (nuisance variables) to general linear model setup in non-matched group analysis. No covariates were used in the analyses with matched groups.

Statistical analysis

Non-parametric, permutation-based tests were carried out by Randomize (included in FSL) (Nichols and Holmes, 2002) with 5000 permutations and threshold-free cluster enhancement. To reduce experiment-wise type 1 errors associated with multiple comparisons, the threshold for statistical significance was set at $P \leq 0.01$, adjusted for multiple comparisons. Two-sided, two-sample Wilcoxon-Mann-Whitney tests were used for each age- and gender-matched analysis to test the groups' ages for significant differences.

Results

Effect of age on diffusion measures

In the control subjects, comparison of fractional anisotropy values among the four age groups yielded significantly ($P \leq 0.01$) lower fractional anisotropy values in age groups 41–50 years and 51–60 years in comparison with control subjects aged between 18 and 30 years. The areas with fractional anisotropy deviations extended widely across the whole cerebral white matter (Fig. 1A). Statistically significant ($P \leq 0.01$) differences in apparent diffusion coefficient values were obtained only in the oldest of the age groups, 51–60 years. Apparent diffusion coefficient values were elevated in the anterior parts of the right cerebral hemisphere (Fig. 1B).

Axial diffusivity was found to decrease with age. In the second oldest age group, 41–50 years, lower axial diffusivity values extended from the brainstem to the posterior part of the cerebrum. Similar areas of lower axial diffusivity were found in the oldest age group (Fig. 1C). Radial diffusivity values were increased in the two oldest age groups in a widespread manner (Fig. 1D). See [Supplementary Table 1](#) for quantitative information for the age effect analyses.

Group comparison between controls and patients

The age- and gender-covared TBSS analysis between the patients with mild TBI and controls did not reveal statistically significant

differences in fractional anisotropy, apparent diffusion coefficient, axial diffusivity or radial diffusivity. For the age- and gender-matched analyses, 40 patients with mild TBI were carefully matched on age and gender to the 40 control subjects. No statistically significant differences in fractional anisotropy, apparent diffusion coefficient, axial diffusivity, or radial diffusivity were found.

The association between mild traumatic brain injury severity and diffusion measures

Subgroup analyses were conducted based on injury severity characteristics. For patients with a loss of consciousness for >5 min ($n = 7$) compared with matched control subjects, no statistically significant differences were found in fractional anisotropy, apparent diffusion coefficient, axial diffusivity or radial diffusivity. A subgroup of 25 patients with post-traumatic amnesia >3 h was compared with 25 matched control subjects. There were no statistically significant differences in fractional anisotropy, apparent diffusion coefficient, axial diffusivity or radial diffusivity. A subgroup of 15 patients with complicated mild TBIs (i.e. all had a trauma-related structural abnormality on CT and/or MRI) was compared to 15 matched control subjects. There were no statistically significant differences in fractional anisotropy, apparent diffusion coefficient, axial diffusivity or radial diffusivity. Six patients with Glasgow Coma Scale = 14 were compared to six matched control subjects. There were no statistically significant differences in fractional anisotropy, apparent diffusion coefficient, axial

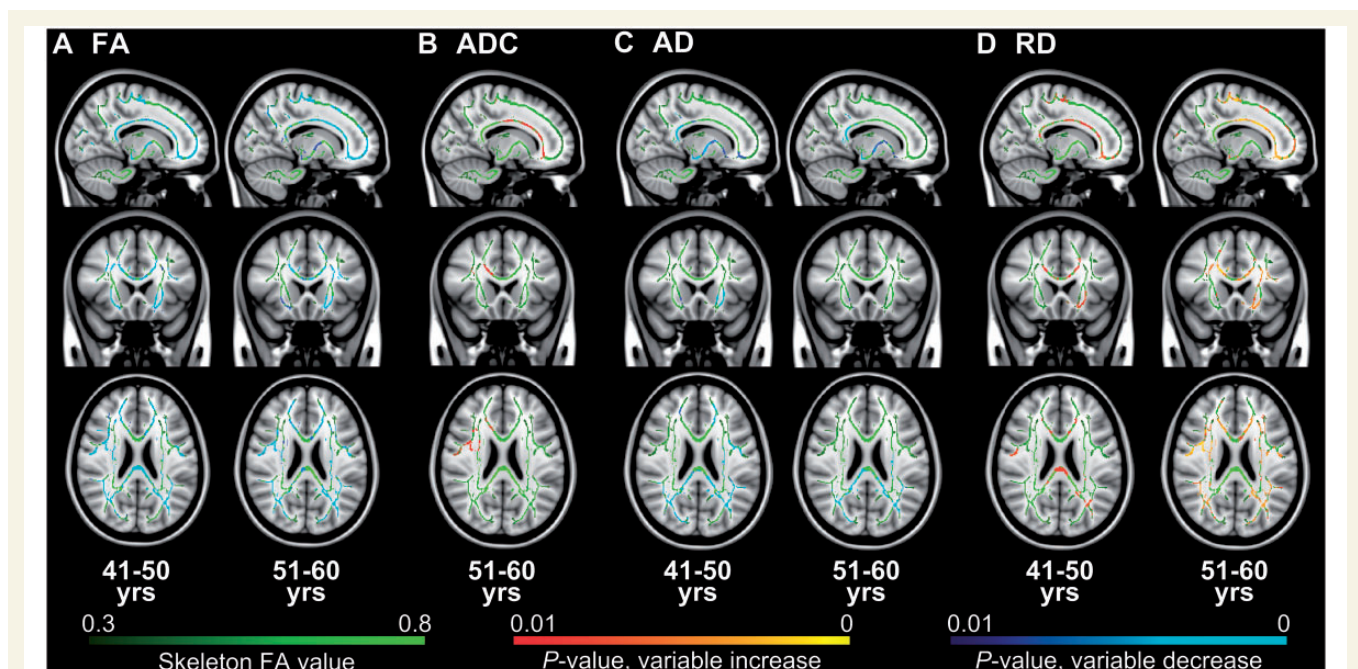


Figure 1 Qualitative results of age effect on DTI measures; the mean fractional anisotropy skeleton is presented in green and laid on top of greyscale MNI152 1 mm T_1 image. Colour coding is used to differentiate whether values on the skeleton increase (red–yellow) or decrease (blue–light blue) in the older age group. The youngest age group (18–30 years) is used as a reference for the other age groups in the analyses. Slice coordinates (MNI152 aligned anatomical) $x = 15$ mm, $y = 20$ mm, $z = 23$ mm. Radiological convention (Left is Right). AD = axial diffusivity; ADC = apparent diffusion coefficient; FA = fractional anisotropy; RD = radial diffusivity.

Table 3 Group sizes, ages and minimum P-values of each Mild TBI analysis

	Mild TBI versus covaried controls	Mild TBI versus matched controls	LOC > 5 min versus matched controls	PTA > 3 h versus matched controls	Complicated Mild TBI versus matched controls	GCS = 14 versus matched controls	Definite mild TBI versus matched controls	Mild TBI and PCS versus mild TBI and no PCS: acute	Mild TBI and PCS versus mild TBI and no PCS: 1 month
Sample sizes	75 versus 40	40 versus 40	7 versus 7	25 versus 25	15 versus 15	6 versus 6	29 versus 29	20 versus 20	12 versus 12
Age, patients	37.2 ± 12.0	40.2 ± 11.6	35.9 ± 10.4	37.4 ± 11.6	35.9 ± 10.2	33.0 ± 10.1	38.0 ± 11.2	34.2 ± 10.6	36.3 ± 10.7
Age, controls	40.6 ± 12.2	40.7 ± 12.1	35.9 ± 10.7	38.0 ± 11.4	36.3 ± 10.0	34.5 ± 10.1	40.0 ± 11.7	34.3 ± 10.5	36.2 ± 10.4
Min. P-values									
Fractional anisotropy	0.131	0.185	0.158	0.166	0.306	0.212	0.162	0.123	0.320
Apparent diffusion coefficient	0.102	0.118	0.059	0.022	0.186	0.157	0.031	0.102	0.247
Axial diffusivity	0.086	0.189	0.039	0.023	0.021	0.268	0.045	0.220	0.324
Radial diffusivity	0.102	0.118	0.079	0.069	0.330	0.158	0.054	0.070	0.297

All of the analyses, except the final column, suggest an increase in fractional anisotropy values and decrease in apparent diffusion coefficient, axial diffusivity and radial diffusivity values when compared with matched subjects. The post-concussional syndrome (PCS) analysis at 1 month suggested a decrease in fractional anisotropy and increase in apparent diffusion coefficient, axial diffusivity, and radial diffusivity values, although clearly non-significant. GCS = Glasgow coma score; LOC = loss of consciousness; PTA = post-traumatic amnesia.

diffusivity, or radial diffusivity. The final subgroup (definite mild TBI) included patients with a combination of any of the previous criteria. This mild TBI group consisted of 29 patients who were compared to 29 matched controls. There were no statistically significant differences in fractional anisotropy, apparent diffusion coefficient, axial diffusivity or radial diffusivity.

Association between diffusion measures and post-concussional symptoms

TBSS was used to compare the post-concussional syndrome subgroups against age-matched patients who did not meet the ICD-10 symptom criteria for post-concussional syndrome at the acute stage ($n = 20$) or at 1 month post-injury ($n = 12$). Acutely, there were no statistically significant differences between post-concussional syndrome subgroups in fractional anisotropy, apparent diffusion coefficient, axial diffusivity or radial diffusivity. Moreover, there were no statistically significant differences in fractional anisotropy, apparent diffusion coefficient, axial diffusivity, or radial diffusivity in those who had, versus those who did not have post-concussional syndrome, at 1 month after injury.

Discussion

There were three objectives in this study: (i) to illustrate the extensive impact of ageing on brain white matter in adults between the ages of 18 and 60; (ii) to determine whether 'pure' acute mild TBI is associated with white matter changes detectable with TBSS; and (iii) to study the effects of mild TBI severity on DTI measures. No significant ($P < 0.01$) mild TBI-related DTI abnormalities were detectable, even with greater injury severity taken into account. Importantly, none of the DTI measures were significantly associated with post-concussional symptoms acutely or at 1 month after injury. Some of the mild TBI severity analyses resulted in nearly statistically significant results (Table 3). The results of this study would have been different if a liberal criterion for significance, with no consideration of multiple comparisons, was applied (i.e. $P < 0.05$). That is, some of the subgroup analyses would have been considered statistically significant. In contrast, statistically significant age-related axonal degradation was observed in the control group. This is in line with previous reports (Stadlbauer *et al.*, 2008; Yoon *et al.*, 2008) and further establishes that age should be considered carefully in white matter analyses.

In the group comparison between the control subjects and the patients with mild TBI, we used two different methods to manage the effects of age on white matter integrity: (i) covariance correction; and (ii) pair-wise age-matching. Previous studies suggest, in contrast with our results, abnormal DTI findings in acute mild TBI (Hulkower *et al.*, 2013) (Table 1). Differences in the methodology and timing of MRI scanning can partly explain the difference between the present results and previous reports. Pathophysiological alterations after mild TBI are time-dependent, thus rendering chronology a crucial factor in the interpretation of DTI findings (Hulkower *et al.*, 2013; Toth *et al.*, 2013). For the acute stage of mild TBI, multiple publications illustrate an increase or decrease in fractional anisotropy values and decrease in apparent diffusion

coefficient values (Hulkower *et al.*, 2013; Toth *et al.*, 2013). From a neurometabolic view, statistical unification of neuroimaging data obtained acutely (e.g. 2 days) and post-acutely (e.g. 1 month) after injury does not seem justifiable. More research is needed to better understand acute versus post-acute changes in DTI measures after mild TBI.

This study was larger and more tightly methodologically controlled than most previous DTI studies of acute mild TBI. The patients were clinically assessed by the same physician using structured instruments and strict clinical enrolment criteria were applied to both patient and control groups. A specific time interval was used in imaging to reduce the possible effect of diverse neurometabolic stages of mild TBI recovery.

The negative main outcome of this study can be partly caused by the statistical group-wise nature of TBSS. The current result does not rule out individualized patterns of focal white matter changes in different anatomical regions. Moreover, some of the non-significant findings in mild TBI severity subgroups may be explained by the lower statistical power of these analyses. For post-concussional syndrome analyses, patient matching was limited to age-matching due to lack of uniformity in gender distributions. Lack of gender-matching is a methodological limitation in the post-concussional syndrome analysis. Indeed, the heterogeneous nature of brain trauma, combined with methodological differences across studies, likely underlies the fact that the anatomical areas showing DTI differences vary considerably across past mild TBI studies. Therefore, TBSS as a supplement to region of interest analysis could be an appropriate alternative for a comprehensive DTI analysis.

In conclusion, in this large homogeneous, premorbidly healthy sample, acute mild TBI was not associated with obvious DTI abnormalities detectable with TBSS. Clear differences in DTI findings were associated with age, even in healthy subjects in their 40s. Therefore, age should always be considered a potential confounder in DTI studies.

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Conflict of interest

Grant Iverson, PhD has been reimbursed by the government, professional scientific bodies, and commercial organizations for discussing or presenting research relating to MTBI and sport-related concussion at meetings, scientific conferences, and symposiums.

He has a clinical practice in forensic neuropsychology involving individuals who have sustained MTBIs. He has received honorariums for serving on research panels that provide scientific peer review of programs. The other authors report no competing or conflicts of interest.

Supplementary material

Supplementary material is available at *Brain* online.

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