J Head Trauma Rehabil
Vol. 27, No. 3, pp. 188–198

Diffusion Tensor Imaging Findings Are Not Strongly Associated With Postconcussional Disorder 2 Months Following Mild Traumatic Brain Injury

Rael T. Lange, PhD; Grant L. Iverson, PhD; Jeffrey R. Brubacher, MD; Burkhard Mädler, PhD; Manraj K. Heran, MD

Objective: To examine the relation between diffusion tensor imaging (DTI) of the corpus callosum and postconcussion symptom reporting following mild traumatic brain injury (MTBI). **Participants:** Sixty patients with MTBI and 34 patients with orthopedic/soft-tissue injuries (Trauma Controls) prospectively enrolled from consecutive admissions to a level 1 trauma center. **Procedure:** Diffusion tensor imaging of the corpus callosum was undertaken using a Phillips 3T scanner at 6 to 8 weeks postinjury. Participants also completed a postconcussion symptom checklist. The MTBI group was divided into 2 subgroups based on the International Classification of Diseases, Tenth Revision symptom criteria for postconcussion disorder (PCD): PCD Present ($n = 21$), PCD Absent ($n = 39$). **Main Outcome Measures:** Measures of fractional anisotropy and mean diffusivity for the genu, body, and splenium of the corpus callosum. Participants also completed the British Columbia Post-Concussion Symptom Inventory. **Results:** The MTBI group reported more postconcussion symptoms than the trauma controls. There were no significant differences between MTBI and trauma control groups on all DTI measures. In the MTBI sample, there were no significant differences on all DTI measures between those who did and did not meet the *International Classification of Diseases, Tenth Revision* research criteria for postconcussion disorder. **Conclusions:** These data do not support an association between white matter integrity in the corpus callosum and self-reported postconcussion syndrome 6 to 8 weeks post-MTBI. **Keywords:** *corpus callosum*, *diffusion tensor imaging*, *mild traumatic brain injury*, *postconcussion symptoms*

THE POSTCONCUSSION syndrome is poorly understood and remains controversial.[1] It is generally assumed that postconcussion symptoms are a direct consequence of an injury to the head, brain, or both. However, postconcussion symptoms can be mimicked by a number of preexisting or comorbid conditions. Healthy adults report very similar symptoms,[2] as do various nontraumatic brain injury clinical groups, such as outpatients seen for psychological treatment,[3] outpatients with minor medical problems,[4] personal injury litigants,[4] and individuals with posttraumatic stress disorder,[5] orthopedic injuries,[6,7] chronic pain,[8] and whiplash.[9] Complicating matters further, the perception and reporting of symptoms after mild traumatic brain injury (MTBI) can be influenced by a diverse range of psychological and social-psychological factors that may cause, maintain, or worsen the myriad of symptoms following MTBI. Such factors include, but are not limited to, premorbid personality characteristics,[10] different methods used to illicit symptoms,[11] presence of depression,[12,13] and the contributory role of various sociopsychological factors such as the nocebo effect,[14] "expectation as etiology,"[15] diagnosis threat,[16] and "good old days" bias.[15,17]

Author Affiliations: *Defense and Veterans Brain Injury Center, Walter Reed Army Medical Center, Washington, DC (Dr Lange); University of British Columbia (Drs Lange, Iverson, Brubacher, Mädler, and Heran), Vancouver General Hospital (Drs Brubacher and Heran), and Centre for Clinical Epidemiology and Evaluation (Dr Brubacher), Vancouver, BC, Canada.*

Portions of these data were presented at the International Neuropsychological Society annual conference, February 2009, Atlanta, Georgia.

This study was supported, in part, by a research grant from the Alcohol Beverage Medical Research Foundation and the Canadian Institutes of Health Research (MOP-89374).

The authors thank Jan Buchanen, Liz Holland, Lisa Casagrande Hoshino, and Angela Aquino for assistance with patient recruitment and testing; and the staff at the University of British Columbia MRI center for the provision of neuroimaging services.

The authors declare no conflicts of interest.

Corresponding Author: *Rael T. Lange, PhD, Defense and Veterans Brain Injury Center, Walter Reed Army Medical Center, Bldg No. 1, Room B207, 6900 Georgia Ave NW, Washington, DC 20307 (rlange@dvbic.org).*

DOI: 10.1097/HTR.0b013e318217f0ad

Despite the assumed association between MTBI and postconcussion symptoms, there is little neuroradiological evidence suggesting a direct causal link. Researchers examining the relation between postconcussion symptom reporting and abnormalities identified on computed tomography (CT) or magnetic resonance imaging (MRI) following MTBI have found a relatively weak association between structural brain abnormality and symptom reporting within the first few days,[18,19] 3 months,[20] (also A. G. Taylor et al, unpublished data) 4 to 6 months,[20] or 6 to 12 months (A. G. Taylor et al, unpublished data) postinjury. The most common neuroradiological investigation performed following MTBI is a CT scan. However, CT scans are not sensitive to traumatic axonal injury that can be associated with MTBI,[21] with fewer than 20% of patients having day-of-injury abnormalities visible on CT.[22] Thus, relying on CT likely underestimates the actual number of patients with intracranial abnormalities following MTBI. Although conventional MRI is more sensitive than CT for some intracranial abnormalities,[22] it infrequently reveals macroscopic structural abnormalities following MTBI[23] and the prevalence of abnormal MRI scans following MTBI is relatively low (ie, 10%–57%).[20]

Given the limitations of conventional CT/MRI for evaluating MTBI, many researchers have attempted to use alternative neuroradiological techniques to examine abnormalities in patients following MTBI. One of these techniques is diffusion tensor imaging (DTI). Diffusion tensor imaging is purported to allow examination of the integrity of white matter in the brain at a microstructural level (as opposed to a macrostructural level used by structural MRI scans). Compared to structural MRI techniques, DTI has demonstrated superiority for detecting white matter changes in the brain following traumatic brain injury[24,25] and is becoming increasingly important in the evaluation of MTBI.[26] Diffusion tensor imaging has been found useful for differentiating between MTBI and healthy control participants within the early (ie, 2 weeks to 3 months[27–29]) and late (ie, 2 or more years[26,30,31]) stages of the recovery trajectory. The majority of studies have found lower fractional anisotropy (FA) and higher mean diffusivity (MD) in large white matter structures such as the centrum semiovale,[26,32] internal capsule,[26,32] and the corpus callosum;[32,33] particularly in the splenium[26,28] and genu.[28,29] However, some studies have found higher FA and lower "trace" or radial diffusivity in the corpus callosum in the first few days and weeks post injury.[34–36]

Given the possibility of diffuse microstructural changes resulting from MTBI in some patients, DTI holds great promise as a tool for better understanding the neurobiological underpinnings of the postconcussion syndrome. To date, a small number of studies have examined the relation between DTI and symptom reporting. Researchers have reported that patients with persistent postconcussion symptoms 3 to 6 years following MTBI had lower FA, higher MD in the corpus callosum, internal capsule,[26,32,37] centrum semiovale, deep cerebellar white matter,[32] anterior corona radiata, uncinate fasciculus, and cingulum bundle,[37] or both compared with healthy controls. Bazarian and colleagues[35] examined 6 patients following MTBI who were tested within 72 hours and again at 1-month postinjury. Higher FA and lower "trace" values (ie, sum of the 3 eigenvalues) were found in MTBI patients compared with matched controls, with the vast majority of the MTBI group (5 of 6 subjects) having whole brain trace values lower than matched controls. Low trace values were associated with greater postconcussion symptoms at 72 hours and 1-month postinjury. Similarly, Wilde and colleagues[36] found higher FA and lower apparent diffusion coefficient and radial diffusivity in the corpus callosum, that were correlated with severity of postconcussion symptom reporting, in 10 adolescents within the first 6 days following MTBI.

The purpose of this study is to examine the relation between postconcussion symptom reporting and white matter integrity of the corpus callosum using DTI at 6 to 8 weeks following MTBI. There are 2 hypotheses. First, patients who have sustained an MTBI will report a greater number of postconcussion symptoms, and have lower FA and higher MD in the corpus callosum, compared with patients who have sustained orthopedic, soft tissue injuries (ie, trauma controls), or both. Second, in the MTBI group, patients who report symptoms consistent with *International Classification of Diseases, Tenth Revision* (*ICD-10*) criteria for postconcussion disorder will have lower FA and higher MD in the corpus callosum compared with those patients who do not meet criteria for the syndrome.

METHOD

Participants

Participants were 94 patients (60 MTBI and 34 trauma control [TC]) prospectively recruited from the emergency department of Vancouver General Hospital (level 1 trauma center). Patients were identified for potential inclusion in the study via daily reviews of consecutive emergency department admissions. Patients were initially targeted for recruitment and consent if they presented to the emergency department after sustaining a traumatic brain injury (ie, TBI group), or they had sustained a soft-tissue, or orthopedic injury (ie, trauma control group).

Participants were included if they were (*a*) aged between 19 and 55 years, (*b*) were injured as a result of a traumatic injury (eg, fall, motor vehicle accident, assault, etc), and (*c*) had a blood alcohol level obtained at

the time of injury.* General exclusion criteria included the following (*a*) lack of proficiency in conversational English; (*b*) educated in a language other than English after the age of 10 years; (*c*) history of a significant neurological disorder (eg, stroke or multiple sclerosis), TBI, learning disability, or psychiatric illness requiring hospitalization; (*d*) presence of any contraindications to MRI; (*e*) history of significant drug abuse other than alcohol; (*f*) presence of upper body injuries restricting the use of hands or arms; or (*g*) difficulties with eyesight.

Participants in the trauma control group were included if (*a*) they sustained a soft-tissue or orthopedic injury below the neck; (*b*) there was no evidence of an altered state of consciousness as indicated by a reduction in Glasgow Coma Scale (GCS) score, or presence of a loss of consciousness (LOC), posttraumatic amnesia (PTA), or posttraumatic confusion; and (*c*) there was no evidence of physical head trauma, whiplash, or cervical strain based on medical chart review (eg, absence of lacerations/contusions to the head, absence of complaints of head, neck, or back pain). In a small number of cases ($n = 3$, 7.8%), participants had undergone a head CT but had no evidence of intracranial abnormality.

Participants in the MTBI group were selected from a larger group of patients who had sustained a mild-severe TBI ($n = 70$). Patients in the larger TBI group were included if they (*a*) presented to the emergency department with a closed head injury, and (*b*) had evidence of brain injury as indicated by at least 1 of the following: (1) witnessed LOC of at least 1-minute duration; (2) PTA of more than 15 minutes, (3) GCS score of less than 15, or (4) presence of intracranial abnormality on day-of-injury CT scan. Patients selected in the final MTBI group all met criteria for MTBI as outlined by the American Congress of Rehabilitation Medicine Special Interest Group[38] and the WHO Working Group.[39]

Participant recruitment

Participants were recruited between June 2007 and December 2009. During this time, 183 151 consecutive patient visits were screened. Of these, approximately 28 416 were trauma admissions. Participant selection was based on a 3-phase screening process. Phase 1 involved a brief review/triage of all patient visits. Patients were initially selected for further follow-up if the person was injured in a traumatic event, between the age of 19 and 55 years, and had a blood alcohol level taken on the day of injury (ie, 583 TBI, 353 TC). Phase 2 involved a review of the medical chart to determine whether there was any documentation that would preclude them from meeting inclusion/exclusion criteria. Those patients who met inclusion/exclusion criteria based on the available medical information were designated for further follow-up (TBI = 453 [77.7%], TC = 292 [82.7%]). Those patients who failed to meet inclusion/exclusion criteria were excluded (TBI = 130 [22.3%], TC = 61 [17.3%]). Phase 3 involved contacting and assessing each patient to determine whether they met final inclusion/exclusion criteria and was willing to consent. Of the 292 patients in the TC group designated for further follow-up, 35 consented (12.0%), 103 declined (35.3%), 92 could not be contacted (31.5%), and 62 were excluded (21.2%). Of the 453 patients in the TBI group designated for further follow-up, 70 consented (15.5%), 120 declined (26.5%), 182 could not be contacted (40.2%), and 81 were excluded (17.9%). Common reasons for exclusion for both groups included the following: limited English, psychiatric or neurological disorders, illicit drug use, equivocal TBI/TC, contraindications to MRI, learning disability, or Attention Deficit Hyperactivity Disorder. Of those patients consented in the TBI group, injury severity classification was as follows: 4 severe, 5 moderate, and 61 mild (45 uncomplicated, 16 complicated). Note that 1 patient each from the MTBI and TC group did not complete MRI scanning and was not included in this study.

Comparison of those patients in the TC group who consented versus those that refused to participate revealed no significant differences for age in years ($P = .246$; consented, $M = 37.6$, SD = 11.8; declined, $M = 35.1$, SD = 10.7), day-of-injury blood alcohol level ($P = .623$; consented, $M = 11.2$, SD = 22.4; declined, $M = 9.2$, SD = 20.1), or gender ($P = .790$; consented = 74.3% men; declined = 76.5% men). For the TBI group, there were no differences between those who consented and those who declined for age in years ($P = .302$; consented, $M = 31.9$, SD = 10.3; declined, $M = 33.7$, SD = 11.1), day-of-injury blood alcohol level ($P = .672$; consented, $M = 23.7$, SD = 28.9; declined, $M = 22.0$, SD = 25.4), GCS scores at the scene of the injury ($P = .739$; consented, $M = 13.5$, SD = 2.5; declined, $M = 13.6$, SD = 2.4), GCS scores in the trauma center ($P = .435$; consented, $M = 13.7$, SD = 2.5; declined, $M = 14.0$, SD = 2.1), gender ($P = .910$; consented = 72.9% men; declined = 73.6% men) or the presence of day-of-injury intracranial abnormality ($P = .117$; consented = 31.4%; declined = 22.0%). There were, however, significant differences between groups for the presence/absence of PTA and LOC. There was a larger portion of those patients who consented that experienced a period of PTA ($P < .05$; consented = 100%; declined = 64.0%) and LOC ($P < .05$; consented = 85.7%; declined = 60.8%) compared with those that declined.

Measures and procedure

Participants completed an MRI brain scan and an evaluation of postconcussion symptoms at 6 to 8 weeks

*This criterion is not specific to the current study but was used as a criterion for a larger study relating to alcohol and outcome from traumatic brain injury.

postinjury (M = 47.0 days, SD = 6.5, range = 31–66). All participants gave written informed consent in accordance with the clinical research ethics board at the University of British Columbia, Vancouver, Canada.

Postconcussion Symptoms

Postconcussion symptom reporting was measured using the British Columbia Postconcussion Symptom Inventory (BC-PSI).[40] Completion of the BC-PSI was undertaken as part of a larger test battery designed to evaluate neurocognitive and neurobehavioral outcome postinjury. The BC-PSI is based on *ICD-10*[41] criteria for postconcussion syndrome and requires the test taker to rate the frequency and intensity of 13 symptoms (ie, headaches, dizziness/light-headedness, nausea or feeling sick, fatigue, sensitivity to noises, irritability, sadness, nervousness/tension, temper problems, poor concentration, memory problems, reading difficulty, and sleep disturbance) as well as the effect of 3 cooccurring life problems on daily living (ie, greater present versus past effects of alcohol consumption, worrying and dwelling on symptoms, and self-perception of brain damage). The 3 life problems are rated on a scale from 1 to 5, where 1 = "not at all" and 5 = "very much." The 13 symptoms are rated on a 6-point Likert-type rating scale that measures the frequency (ie, "how often") and intensity ("how bad") of each symptom in the past 2 weeks. Frequency ratings range from 0 = "not at all" to 5 = "constantly." Intensity ratings range from 0 = "not at all" to 5 = "very severe problem." For each of the 13 symptoms, the 2 ratings are multiplied together (how often × how bad) to create a single score for each item. These product-based scores are then converted to item scores that reflect both the frequency and intensity of symptom endorsement (range = 0–4). Item scores of 1 are interpreted as falling in the mild range. Item scores of 3 are interpreted as falling in the moderate range.

Effort Testing

As part of the larger test battery, participants also completed the Test of Memory Malingering.[42] Participants were not included if they scored below the recommended cutoff score on the Test of Memory Malingering on Trial 2 of the test. No participants were excluded on the basis of this criterion.

DTI Acquisition and Processing

Magnetic resonance imaging scanning was performed using a Philips Achieva 3T scanner (Philips) with Dual Nova Gradients (maximum gradient strength 80 mT/m, maximum slew rate 200 mT/m/s) and an 8-channel phased array head coil in parallel imaging mode. Diffusion tensor imaging was used to examine the integrity of white matter in 3 regions of the corpus callosum; genu, body, and splenium. The regions of interest were operationally defined using Witelson's[43] protocol for segmenting the corpus callosum (ie, genu = areas 1, 2; body = areas 3–6; splenium = area 7). Diffusion tensor imaging data were acquired using an eddy current compensated, single-shot, spin-echo, echo planar imaging sequence with unipolar diffusion weighting along 16 noncollinear directions and a maximum b value of 1000 s/mm^2. Further DTI parameters were as follows: acquisition matrix 96 × 96, 50 slices to cover the entire brain, 2.5 × 2.5 × 2.5 isotropic acquisition resolution, time to echo 75 ms, time to repetition 5600 ms, parallel imaging SENSE-factor = 2.4. Three averages were conducted for improved signal-to-noise performance. Analyzed measures from DTI included the diffusion tensor invariants of mean diffusivity (MD) and fractional anisotropy (FA). The image processing to calculate FA and MD was completed off-line with in-house developed software tools as well as analysis tools provided by Philips Healthcare (PRIDE). Measures of MD and FA were calculated for each of the 3 regions of the corpus callosum. For a subset of 25 participants who had sustained MTBIs, each region of interest was sampled twice by the same rate to evaluate intrarater reliability. The intraclass correlation for each of the 6 regions of interests was as follows: FA Genu (0.946), FA Body (0.947), FA Splenium (0.951), MD Genu (0.992), MD Body (0.983), and MD Splenium (0.982). These intraclass correlation values constitute excellent agreement for intrarater reliability.

RESULTS

MTBI versus trauma control

Demographic and injury severity characteristics of the MTBI and trauma control group are presented in Table 1. Group comparisons (ie, analysis of variance or ANOVA [continuous variables] and χ^2 analyses [categorical variables]), revealed no significant differences for education, days tested postinjury, gender, ethnicity, mechanism of injury, day-of-injury alcohol intoxication, or preinjury alcohol use. However, there was a significant difference for age (P = .006, d = .60, medium effect size). The trauma control group was slightly older compared with the MTBI group.

Descriptive statistics, group comparisons, and the Cohen effect sizes[44] for the 6 DTI measures (ANOVA) and BC-PSI total score (Mann-Whitney U test due to nonnormal distribution) by group are presented in Table 2. There were no significant main effects for any of the 6 DTI measures. Further analyses using analysis of covariance revealed no significant group differences for all DTI measures when age was used as a covariate (P = .100). There was, however, a medium effect size

TABLE 1 *Demographic and injury severity characteristics*[a]

	Mild TBI		Trauma Control		
	M	**SD**	***M***	**SD**	***P* (*d*)**
Age, y	30.8	9.9	37.1	11.7	.006 (0.60)
Education, y	14.6	2.5	14.4	2.4	.731 (0.07)
Days tested postinjury	47.0	6.3	47.2	7.0	.881 (0.03)
Lowest valid GCS >30 min postinjury	14.2	0.7	15.0	0.0	<.001 (1.66)
	N	**%**	***n***	**%**	***P***
Gender					
Male	43	71.7	25	73.5	.846
Female	17	28.3	9	26.5	
Ethnicity					
White	48	80.0	26	76.5	.688
Asian/East-Indian/Other	12	20.0	8	23.5	
Mechanism of injury					
MVA	25	41.7	11	32.4	.372
Non-MVA	35	58.3	23	67.6	
Preinjury alcohol[b]					
Low-Moderate	26	43.3	19	55.9	.242
Heavy	34	56.7	15	44.1	
Day-of-injury BAL					
Intoxicated (≥21 mmol/L)	36	60.0	27	79.4	.054
Sober (<21 mmol/L)	24	40.0	7	20.6	
LOC					
Positive	37	61.7	...	...	...
Negative	5	8.3	...	...	
Equivocal[c]	18	30.0	...	...	
GCS category					
15	23	38.3	...	...	...
13–14	37	61.7	...	...	
PTA					
Positive	60	100	...	...	...
Negative	0	0	...	...	
CT scan					
Normal	41	68.3	3	8.8	.018[d]
Abnormal	15	25.0	0	0	
Not ordered	4	6.7	31	91.2	

Abbreviations: BAL, blood alcohol level; CT, computed tomography; GCS, Glasgow coma scale; LOC, loss of consciousness; MVA, motor vehicle accident; PTA, posttraumatic amnesia; TBI, traumatic brain injury.

[a] $N = 94$ (Mild TBI, $n = 60$; Trauma Control, $n = 34$)

[b] Defined based on criteria for heavy drinking established by the National Institute on Alcohol Abuse and Alcoholism: (*a*) Females: 8 or more drinks per week or 4 or more drinks on a single occasion more than 24 times per year; (*b*) Males: 15 or more drinks per week or 5 or more drinks on a single occasion more than 24 times per year.

[c] Defined as a period of LOC that was unable to be confidently confirmed due to discrepant ambulance and hospital records, or the patient reported a period of LOC that was not substantiated by a witness.

[d] The Fisher exact test statistic reported by comparing 2 × 2 of CT Abnormal versus CT Normal/Not Ordered categories.

for MD in the splenium of the corpus callosum ($d = .42$). For this measure, there was a nonsignificant trend ($P = .050$) for higher MD in the MTBI group compared with trauma controls.

For the BC-PSI, the MTBI group reported a significantly greater number of total symptoms compared with the trauma control group (Mann-Whitney U tests, $P = .001$; $d = .64$, medium-large effect size). The majority of the MTBI sample (81.7%) met *ICD-10* Category C symptom criteria for postconcussion disorder based on symptoms endorsed at a mild level or greater, and 35% met *ICD-10* criteria based on symptoms endorsed at a moderate level or greater. One-half of the trauma control group (52.9%) met *ICD-10* criteria for postconcussion disorder (PCD) on the basis of symptoms endorsed at a mild level or greater, and 11.8% met *ICD-10* criteria on the basis of symptoms endorsed at a moderate level or greater.

TABLE 2 *Descriptive statistics, group comparisons, and effect sizes for diffusion tensor imaging measures across 3 regions of the corpus callosum*[a]

	Mild TBI		Trauma Control				
	M	SD	*M*	SD	*P*	*d*[b]	Effect size
DTI Measures							
FA genu	0.765	0.032	0.764	0.024	.888	0.03	Very small
FA body	0.773	0.021	0.774	0.021	.948	0.01	Very small
FA splenium	0.799	0.020	0.804	0.036	.421	0.18	Small
MD genu	0.819	0.031	0.816	0.029	.577	0.12	Small
MD body	0.815	0.031	0.809	0.028	.358	0.20	Small
MD splenium	0.781	0.035	0.767	0.031	.050	0.42	Medium
Postconcussion symptoms							
BC-PSI total	12.2	11.9	5.5	8.2	.001	0.64	Medium-large

Abbreviations: BC-PSI, British Columbia Postconcussion Symptom Inventory; DTI, diffusion tensor imaging; FA, fractional anisotropy; MD, mean diffusivity; TBI, traumatic brain injury.
[a] $N = 94$ (Mild TBI, $n = 60$; Trauma Control, $n = 34$).
[b] Cohen's[44] effect size (d): small (.20), medium (.50), large (.80).

The cumulative percentages of the number of endorsed symptoms (13 maximum) in the trauma control group and the MTBI group are presented in Table 3. χ^2 analyses revealed that there were a greater number of symptoms endorsed at a mild or greater level by the MTBI group compared with the trauma control group for many comparisons (ie, 1, 2, 3, 4, 5, 6, and 7, or more symptoms). For example, 70.0% of the MTBI group endorsed the presence of 3 or more symptoms, compared with 38.2% of the trauma control group. There were also a greater number of symptoms endorsed at a moderate or greater level by the MTBI group than the trauma control group for many comparisons (ie, 1, 2, and 3 or more symptoms).

PCD present versus PCD absent

The MTBI group was divided into 2 groups based on *ICD-10* symptom criteria for postconcussion disorder: (*a*) present ($n = 21$), and (*b*) absent ($n = 39$). Participants were categorized into the PCD present group if they

TABLE 3 *Cumulative percentages and comparison of the number of symptoms endorsed on the BC-PSI by group*[a]

	Mild Symptom Rating or Greater			Moderate Symptom Rating or Greater		
Number of symptoms	Mild TBI	Trauma Controls	*P*	Mild TBI	Trauma Controls	*P*
13	1.7	2.9	.595[b]	0	0	. . .
12	11.7	2.9	.141[b]	1.7	0	.638[b]
11	15.0	2.9	.064[b]	3.3	0	.405[b]
10	21.7	5.9	.045	6.7	0	.160[b]
9	23.3	8.8	.079	8.3	0	.099[b]
8	26.7	11.8	.090	8.3	2.9	.290[b]
7	36.7	14.7	.024	8.3	5.9	.503[b]
6	45.0	17.6	.008	13.3	5.9	.223[b]
5	50.0	26.5	.026	18.3	8.8	.213
4	65.0	32.4	.002	20.0	8.8	.155
3	70.0	38.2	.003	31.7	8.8	.012
2	85.0	55.9	.002	33.3	11.8	.021
1	90.0	73.5	.036	53.3	17.6	.001
0	100.0	100.0	. . .	100.0	100.0	. . .

Abbreviations: BC-PSI, British Columbia Postconcussion Symptom Inventory; TBI, traumatic brain injury.
[a] $N = 94$ (60 Mild TBI, 34 Trauma Controls).
[b] Fisher Exact Test.

TABLE 4 *Demographic and injury characteristics of mild TBI postconcussion groups*

	Mild TBI PCD Absent		Mild TBI PCD Present		
	M	**SD**	***M***	**SD**	***P* (*d*)**
Age, y	30.1	9.6	32.3	10.6	.409 (0.23)
Education, y	14.7	2.7	14.3	2.3	.535 (0.17)
Days tested postinjury	47.1	6.8	46.7	5.3	.822 (0.06)
Lowest valid GCS >30 mins postinjury	14.3	0.6	14.2	0.9	.739 (0.09)
	n	**%**	***n***	**%**	***P***
Gender					
Male	32	82.1	11	52.4	.015
Female	7	17.9	10	47.6	
Ethnicity					
Caucasian	30	76.9	18	85.7	.325[b]
Asian/East-Indian/Other	9	23.1	3	14.3	
Mechanism of injury					
MVA	17	43.6	8	38.1	.681
Non-MVA	22	56.4	13	61.9	
Preinjury alcohol					
Low-Moderate	15	38.5	11	52.4	.299
Heavy	24	61.5	10	47.6	
Day-of-injury BAL					
Intoxicated (>21 mmol/L)	23	59.0	13	61.9	.825
Sober (0 mmol/L)	16	41.0	8	38.1	
LOC					
Positive	27	69.2	10	47.6	.211[c]
Negative	2	5.1	3	14.3	
Equivocal	10	25.6	8	38.1	
GCS category					
15	14	35.9	10	42.9	.310
13–14	25	64.1	11	57.1	
PTA					
Positive	39	100	21	100	.350[b]
Negative	0	0	0	0	
MTBI classification					
Uncomplicated	32	82.1	13	61.9	.086
Complicated	7	17.9	8	38.1	
CT scan					
Normal	29	74.4	12	57.1	.225[c]
Abnormal	7	17.9	8	38.1	
Not ordered	3	7.7	1	4.8	

Abbreviations: BAL, blood alcohol level in millimoles per liter; CT, computed tomography; GCS, Glasgow Coma Scale; LOC, loss of consciousness; MVA, motor vehicle accident; PCD, DSM-IV postconcussion disorder; PTA, posttraumatic amnesia; TBI, traumatic brain injury.

[a] $N = 60$ (PCD Present, $n = 21$; PCD Absent, $n = 39$).

[b] Fisher exact test.

[c] Fisher exact test statistic reported by comparing 2 × 2 of (a) LOC Positive versus LOC Negative/Equivocal, and (b) CT Abnormal versus CT Normal/Not Ordered categories.

endorsed symptoms as a moderate problem or greater on 3 of the 6 *ICD-10* Category C criteria. Descriptive statistics for demographic variables and injury severity characteristics across the 2 PCD groups are presented in Table 4. Group comparisons (ie, ANOVA [continuous variables] and χ^2 analyses [categorical variables]), revealed no significant differences for age, education, days tested postinjury, GCS scores, day-of-injury alcohol intoxication, preinjury alcohol use, ethnicity, mechanism of injury, presence/absence of posttraumatic amnesia, loss of consciousness, or day-of-injury intracranial abnormalities on CT. There was, however, a significant difference for gender ($P = .015$). There was a greater proportion of women in the PCD present group

compared with the PCD absent group. Examination of the effects of gender on symptom reporting in each group separately (ANOVA) revealed no significant differences in BC-PSI total scores between men and women in the PCD present ($P = .114$) or PCD absent group ($P = .174$). However, there was a trend for women to report higher symptoms in both the PCD present ($d = .80$, large effect size; men: $M = 20.8$ [SD = 9.2] vs women: $M = 29.1$ [SD = 11.8]) and PCD Absent group ($d = .63$; medium-large effect size; men: $M = 4.9$ [SD = 4.2] vs women: $M = 7.7$ [SD = 5.1]).

Descriptive statistics, group comparisons, and the Cohen effect sizes[44] for the 6 DTI measures (ANOVA) and BC-PSI total score (Mann-Whitney *U* test due to nonnormal distribution) by PCD group are presented in Table 5. There were no significant main effects for any of the 6 DTI measures. Further analyses using ANCOVA revealed no significant group differences for all DTI measures when gender was used as a covariate ($P > .05$). There was, however, a small-medium effect size for FA in the genu and body of the corpus callosum. For these measures, there was a nonsignificant trend for lower FA in the PCD Present group compared with the PCD Absent group. For the BC-PSI, as expected, the PCD Present group reported a significantly greater number of symptoms on the BC-PSI compared with the PCD Absent.

DISCUSSION

The purpose of this study was to examine the relation between postconcussion symptom reporting following MTBI and associated possible loss of white matter integrity of the corpus callosum using DTI. It was hypothesized that patients who sustained an MTBI would report a greater number of postconcussion symptoms, and have lower FA and higher MD in the corpus callosum, compared with patients who sustained orthopedic, soft tissue injuries (ie, trauma controls), or both. It was further hypothesized that in the MTBI group, patients who reported symptoms consistent with *ICD-10* criteria for postconcussion disorder would have lower FA and higher MD in the corpus callosum compared with those patients who did not meet symptom criteria for this disorder. Overall, support for these hypotheses was mixed.

Patients who sustained an MTBI reported a greater number of postconcussion symptoms compared with trauma controls at 6 to 8 weeks postinjury. The majority of the MTBI sample (81.7%) met *ICD-10* Category C symptom criteria for postconcussional disorder based on symptoms endorsed at a mild level of greater, and 35.0% met *ICD-10* criteria based on symptoms endorsed at a moderate level or greater. This is consistent with previous studies that have reported greater postconcussion symptom reporting following MTBI compared to healthy control participants (eg, Wilde et al[45]). Of interest, however, was the prevalence of postconcussion symptom reporting in the trauma control group. A substantial number of patients in this group reported a large number of postconcussion-like symptoms. One-half of the trauma control group (52.9%) met *ICD-10* criteria for postconcussion disorder on the basis of symptoms endorsed at a mild level of greater, and 11.8% met *ICD-10* criteria on the basis of symptoms endorsed at a moderate level or greater. The high symptom reporting by the trauma control group is consistent with previous research indicating that postconcussion symptoms are not specific to MTBI and those are commonly reported by

TABLE 5 *Descriptive statistics, group comparisons, and effect sizes by ICD-10 PCD group*[a]

	Mild TBI PCD Absent		Mild TBI PCD Present				
DTI Measures	***M***	**SD**	***M***	**SD**	***P***	***d*[b]**	**Effect size**
FA genu	0.769	0.027	0.757	0.038	.161	0.39	Small-Med
FA body	0.776	0.020	0.768	0.024	.179	0.37	Small-Med
FA splenium	0.799	0.021	0.800	0.019	.928	0.02	Very small
MD genu	0.820	0.035	0.818	0.023	.759	0.08	Very small
MD body	0.813	0.030	0.818	0.034	.549	0.16	Small
MD splenium	0.781	0.039	0.779	0.025	.840	0.06	Very small
Postconcussion measure							
BC-PSI total	5.4	4.5	24.8	11.1	<.001	2.85	Very large

Abbreviations: BC-PSI, British Columbia Postconcussion Symptom Inventory; DTI, diffusion tensor imaging; FA, fractional anisotropy; MD, mean diffusivity; PCD, DSM-IV postconcussion disorder; TBI, traumatic brain injury.

[a] $N = 60$ (PCD Present, $n = 21$; PCD Absent, $n = 39$).

[b] Cohen's (1988) effect size (*d*): small (.20), medium (.50), large (.80).

healthy adults,[2] patients with orthopedic injuries,[6,7] and various other non-TBI clinical groups.[3–6,8,9]

With regards to the DTI measures, there was a lack of support for all hypotheses. Inconsistent with the first hypothesis, patients in the MTBI group did not have significantly lower FA, or higher MD, in the corpus callosum compared with the trauma controls. There was, however, a nonsignificant trend (ie, $P = .05$) and medium effect size ($d = 0.42$) toward higher MD in the splenium for the MTBI groups than for the trauma control group. The effect size noted for MD in the splenium is somewhat consistent with the majority of the literature that has reported higher MD in the corpus callosum following MTBI when compared with healthy control participants.[26,28,32,33] For those studies that included appropriate data (ie, means and standard deviations),[26,28] we calculated the Cohen effect sizes for all group comparisons using MD in the splenium. Comparison of these effect sizes with our own study revealed that the effect sizes in our sample were generally smaller than one study,[26] but greater than another study.[28] It should also be noted that the majority of researchers have also reported lower FA in the corpus callosum following MTBI than in healthy controls.[26,28,32,33] The results from our study are inconsistent with previous research in this regard.

Inconsistent with our second hypothesis, patients in the MTBI group who reported symptoms consistent with *ICD-10* postconcussion disorder did not have significantly lower FA, or higher MD, in the corpus callosum compared with those patients who did not meet symptom criteria for this disorder. However, although not statistically significant, there was a nonsignificant trend (ie, small-medium effect size) toward lower FA in the genu and body of the corpus callosum of the PCD present group than of the PCD absent group. There are a handful of studies that suggest that there may be an association between postconcussion symptom reporting and reduced white matter integrity of the corpus callosum.[26,32,35,37] However, one thing that is lacking in the literature is convincing evidence to suggest that the biological consequences of MTBI are strongly related to postconcussion symptom reporting. That is, structural damage to the brain, inferred using neuroimaging tools such as DTI, cannot reliably predict postconcussion symptoms in individual subjects. Our study is no exception. We found only 2 nonsignificant trends toward lower FA in the PCD present group.

The lack of association between postconcussion symptom reporting and MTBI is further highlighted by a scatter plot (Figure 1) of individual DTI scores for each patient in the PCD Present and PCD Absent group (and

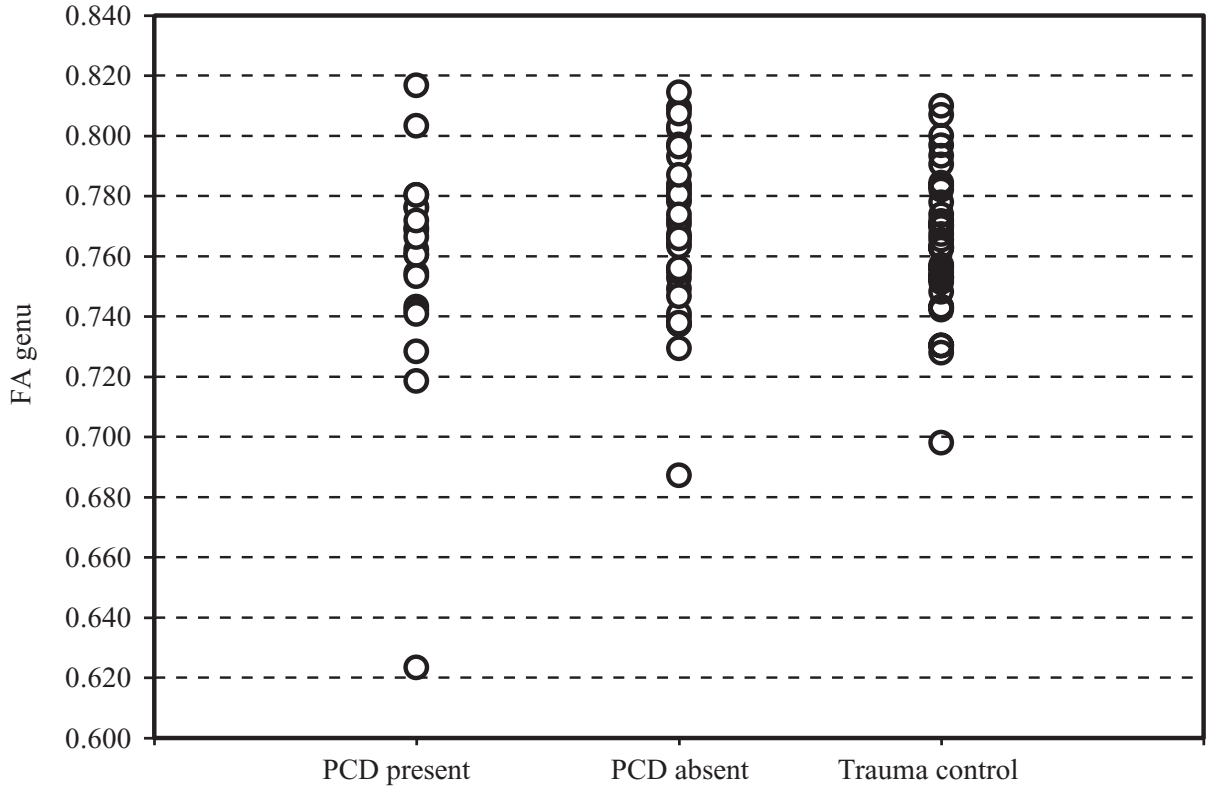

Figure 1. Scatter plot of FA genu by PCD group. $N = 90$ (PCD present, $n = 21$; PCD absent, $n = 39$; Trauma controls, $n = 34$); FA indicates fractional anisotropy; PCD, *ICD-10* postconcussion disorder.

trauma controls) using the DTI measure that had the largest effect size between the 2 groups (FA Genu from Table 5). This scatter plot clearly shows that there is little differentiation of DTI scores between the 2 PCD groups (and for that matter, the PCD and trauma control groups). Contrary to the biological explanation, there is very weak evidence from this relatively large study supporting a potent relationship between white matter changes and the postconcussion disorder.

This study has several methodological limitations. First, this study does not address medium- or long-term postconcussion symptom reporting, nor does it address the course of recovery following MTBI. Longitudinal studies would assist in understanding the role of microstructural white matter abnormality on the short-, medium-, and long-term outcome from MTBI. There are no such studies reported in adults to date. Second, although the focus of this study was on the relation between postconcussion symptom reporting and DTI, it is not possible to exclude the influence of other factors that may have had a contributory role (eg, "good old days" bias,[15] diagnosis threat,[16]). However, we did include trauma control patients in our study (rather than a healthy control group) because these patients tend to share many preinjury characteristics to their head-injured counterparts.[46] As such, the potential bias of these factors influencing the results in one group, but not the other, is mitigated. Third, it would be a mistake to assume that the results from this study generalize to all people who sustain an MTBI. Our patients were recruited from a level 1 trauma center. The majority of people who sustain an MTBI in daily life are not evaluated in the emergency department of a hospital.[47] Our patients had clear evidence of an MTBI. The vast majority of our patients (93.3%) underwent day-of-injury CT scanning and 25.0% of our sample had a day-of-injury intracranial abnormality. This is a substantial minority of patients with complicated MTBIs. Therefore, the patient sample used in this study represents a minority of the more seriously injured MTBI population. Fourth, the DTI acquisition protocol used in this study is limited to one structure (ie, corpus callosum) and to one form of DTI analysis. It is possible that examining additional structures might result in different conclusions. Finally, despite the fact that these results show a lack of association between structural brain damage and postconcussion symptom reporting in the entire group, this does not necessarily preclude the very real possibility that there are subgroups of individuals where the presumed "biological explanation" may be more robust. Our results suggest that there may be some weak association between reduced white matter integrity in the corpus callosum and self-reported postconcussion symptoms 6 to 8 weeks post-MTBI in some patients. However, our data certainly do not support a clear association between postconcussion syndrome and white matter disruption following MTBI. The results from this study once again highlight the need to evaluate many factors other than brain injury to account for self-reported postconcussion symptoms.

REFERENCES

1. Bigler ED, Brooks M. Traumatic brain injury and forensic neuropsychology. *J Head Trauma Rehabil.* 2009;24(2):76–87.
2. Iverson GL, Lange RT. Examination of "postconcussion-like" symptoms in a healthy sample. *Appl Neuropsychol.* 2003;10(3):137–144.
3. Fox DD, Lees-haley PR, Earnest K, Dolezal-wood S. Post-concussive symptoms: Base rates and etiology in psychiatric patients. *Clin Neuropsychol.* 1995;9:89–92.
4. Lees-Haley PR, Brown RS. Neuropsychological complaint base rates of 170 personal injury claimants. *Arch Clin Neuropsychol.* 1993;8:203–209.
5. Foa EB, Cashman L, Jaycox L, Perry K. The validation of a self-report measure of posttraumatic stress disorder: the posttraumatic diagnostic scale. *Psychol Assess.* 1997;9(4):445–451.
6. Mickeviciene D, Schrader H, Obelieniene D, et al. A controlled prospective inception cohort study on the post-concussion syndrome outside the medicolegal context. *Eur J Neurol.* 2004;11(6):411–419.
7. Meares S, Shores EA, Taylor AJ, et al. Mild traumatic brain injury does not predict acute postconcussion syndrome. *J Neurol Neurosurg Psychiatry.* 2008;79(3):300–306.
8. Iverson GL, McCracken LM. 'Postconcussive' symptoms in persons with chronic pain. *Brain Inj.* 1997;11(11):783–790.
9. Sullivan MJ, Hall E, Bartolacci R, Sullivan ME, Adams H. Perceived cognitive deficits, emotional distress and disability following whiplash injury. *Pain Res Manag.* 2002;7(3):120–126.
10. Hibbard MR, Bogdany J, Uysal S, et al. Axis II psychopathology in individuals with traumatic brain injury. *Brain Inj.* 2000;14(1):45–61.
11. Iverson GL, Brooks BL, Ashton VL, Lange RT. Interview versus questionnaire symptom reporting in people with the postconcussion syndrome. *J Head Trauma Rehabil.* 2010;25(1):23–30.
12. Iverson GL. Misdiagnosis of the persistent postconcussion syndrome in patients with depression. *Arch Clin Neuropsychol.* 2006;21(4):303–310.
13. Suhr JA, Gunstad J. Postconcussive symptom report: the relative influence of head injury and depression. *J Clin Exper Neuropsychol.* 2002;24(8):981–993.
14. Hahn RA. The nocebo phenomenon: concept, evidence, and implications for public health. *Prev Med.* 1997;26(5 Pt 1):607–611.
15. Gunstad J, Suhr JA. "Expectation as etiology" versus "the good old days": postconcussion syndrome symptom reporting in athletes, headache sufferers, and depressed individuals. *J Int Neuropsychol Soc.* 2001;7(3):323–333.
16. Suhr JA, Gunstad J. "Diagnosis Threat": the effect of negative expectations on cognitive performance in head injury. *J Clin Exp Neuropsychol.* 2002;24(4):448–457.

17. Iverson GL, Lange RT, Brooks BL, Rennison VL. 'Good old days' bias following mild traumatic brain injury. *Clin Neuropsychol*. 2010;24(1):17–37.
18. Hughes DG, Jackson A, Mason DL, Berry E, Hollis S, Yates DW. Abnormalities on magnetic resonance imaging seen acutely following mild traumatic brain injury: correlation with neuropsychological tests and delayed recovery. *Neuroradiology*. 2004;46(7):550–558.
19. Kurca E, Sivak S, Kucera P. Impaired cognitive functions in mild traumatic brain injury patients with normal and pathologic magnetic resonance imaging. *Neuroradiology*. 2006;48(9):661–669.
20. Hofman PA, Stapert SZ, van Kroonenburgh MJ, Jolles J, de Kruijk J, Wilmink JT. MR imaging, single-photon emission CT, and neurocognitive performance after mild traumatic brain injury. *AJNR Am J Neuroradiol*. 2001;22(3):441–449.
21. Gaetz M, Weinberg H. Electrophysiological indices of persistent post-concussion symptoms. *Brain Inj*. 2000;14(9):815–832.
22. Bruns JJ Jr, Jagoda AS. Mild traumatic brain injury. *Mt Sinai J Med*. 2009;76(2):129–137.
23. Lewine JD, Davis JT, Bigler ED, et al. Objective documentation of traumatic brain injury subsequent to mild head trauma: multimodal brain imaging with MEG, SPECT, and MRI. *J Head Trauma Rehabil*. 2007;22(3):141–155.
24. Belanger HG, Vanderploeg RD, Curtiss G, Warden DL. Recent neuroimaging techniques in mild traumatic brain injury. *J Neuropsychiatry Clin Neurosci*. 2007;19(1):5–20.
25. Xu J, Rasmussen IA, Lagopoulos J, Håberg A. Diffuse axonal injury in severe traumatic brain injury visualized using high-resolution diffusion tensor imaging. *J Neurotrauma*. 2007;24(5):753–765.
26. 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.
27. Inglese M, Bomsztyk E, Gonen O, Mannon LJ, Grossman RI, Rusinek H. Dilated perivascular spaces: hallmarks of mild traumatic brain injury. *AJNR Am J Neuroradiol*. 2005;26(4):719–724.
28. Kumar R, Gupta RK, Hussain M, et al. Comparative evaluation of corpus callosum DTI metrics in acute mild and moderate traumatic brain injury: its correlation with neuropsychometric tests. *Brain Inj*. 2009;23(7):675–685.
29. Rutgers DR, Fillard P, Paradot G, Tadié M, Lasjaunias P, Ducreux D. Diffusion tensor imaging characteristics of the corpus callosum in mild, moderate, and severe traumatic brain injury. *AJNR Am J Neuroradiol*. 2008;29(9):1730–1735.
30. 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(Pt 10):2508–2519.
31. Lipton ML, Gulko E, Zimmerman ME, et al. Diffusion-tensor imaging implicates prefrontal axonal injury in executive function impairment following very mild traumatic brain injury. *Radiology*. 2009; 252(3):816–824.
32. Lipton ML, Gellella E, Lo C, et al. Multifocal white matter ultrastructural abnormalities in mild traumatic brain injury with cognitive disability: a voxel-wise analysis of diffusion tensor imaging. *J Neurotrauma*. 2008;25(11):1335–1342.
33. 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(3):514–519.
34. Mayer AR, Ling J, Mannell MV, et al. A prospective diffusion tensor imaging study in mild traumatic brain injury. *Neurology*. 2010;74(8):643–650.
35. Bazarian JJ, Zhong J, Blyth B, Zhu T, Kavcic V, Peterson D. Diffusion tensor imaging detects clinically important axonal damage after mild traumatic brain injury: a pilot study. *J Neurotrauma*. 2007;24(9):1447–1459.
36. Wilde EA, McCauley SR, Hunter JV, et al. Diffusion tensor imaging of acute mild traumatic brain injury in adolescents. *Neurology*. 2008;70(12):948–955.
37. 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;29(5):967–973.
38. Mild Traumatic Brain Injury Committee, American Congress of Rehabilitation Medicine, and Head Injury Interdisciplinary Special Interest Group. Definition of mild traumatic brain injury. *J Head Trauma Rehabil*. 1993;8(3):86–87.
39. Carroll LJ, Cassidy JD, Holm L, Kraus J, Coronado VG. WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. Methodological issues and research recommendations for mild traumatic brain injury: the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. *J Rehabil Med*. 2004(43 Suppl):113–125.
40. Iverson GL, Zasler ND, Lange RT. Post-Concussive Disorder. In:Zasler ND, Katz D, Zafonte RD, eds. *Brain Injury Medicine: Principles and Practice*. New York: Demos Medical Publishing Inc; 2007:373–405.
41. American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 2000. Text Revision.
42. Tombaugh TN. *Test of Memory Malingering*. North Tonawanda, NY: Multi-Health Systems; 1996.
43. Witelson SF. Hand and sex differences in the isthmus and genu of the human corpus callosum. A postmortem morphological study. *Brain*. 1989;112 (Pt 3):799–835.
44. Cohen J. *Statistical power analysis for the behavioral sciences*. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates; 1998.
45. Wilde EA, Chu Z, Bigler ED, et al. Diffusion tensor imaging in the corpus callosum in children after moderate to severe traumatic brain injury. *J Neurotrauma*. 2006;23(10):1412–1426.
46. Dikmen SS, Machamer JE, Winn HR, Temkin NR. Neuropsychological outcome at 1-year post head injury. *Neuropsychology*. 1995;9:80–90.
47. Sosin DM, Sniezek JE, Thurman DJ. Incidence of mild and moderate brain injury in the United States, 1991. *Brain Inj*. 1996;10(1):47–54.