Diffusion Tensor Imaging Abnormalities in Patients With Mild Traumatic Brain Injury and Neurocognitive Impairment

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Objective: To determine if diffusion tensor imaging can differentiate patients with chronic cognitive impairment after mild traumatic brain injury (TBI) from normal controls.

Methods: Ten patients with persistent cognitive impairment after mild TBI were evaluated at least 2 years after injury. Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) were measured at white matter regions susceptible to axonal injury after TBI. Comparison was made to 10 normal controls.

Results: Fractional anisotropy was significantly lower (4.5%; $P = 0.01$) and ADC higher (7.1%; $P = 0.04$) in patients at the left side of the genu of the corpus callosum. The mild TBI group also demonstrated a significant increase in FA within the posterior limb of the internal capsule bilaterally (left, 5.1%; $P = 0.03$; right, 1.9%; $P = 0.04$).

Conclusions: These results demonstrate low FA and high ADC in the genu of the corpus callosum of mild TBI patients with persistent cognitive impairment, suggesting that permanent white matter ultrastructural damage occurs in mild TBI, and that such damage may be associated with persistent cognitive disability. Further longitudinal studies are warranted to elucidate the full importance of the findings.

Key Words: traumatic brain injury, diffusion tensor imaging, cognitive impairment

(*J Comput Assist Tomogr* 2009;33: 293–297)

Traumatic brain injury (TBI) is a major cause of morbidity and mortality in the United States. An estimated 1.5 million Americans sustain TBI each year, and 80,000 to 90,000 of them will experience long-term disability.[1] The US Centers for Disease Control defines mild TBI as a head injury resulting from blunt trauma or acceleration or deceleration forces where there is transient impaired consciousness, dysfunction of memory, or neuropsychological dysfunction. Reports indicate that mild injuries account for as much as 75% of all TBI.[1,2] However, the prevalence of TBI is likely to be much higher; patients may not seek medical attention because the injury is so mild, and initial symptoms are few and nonspecific. Prior studies have demonstrated that 3 months is an accepted time frame for the resolution of mild TBI-related symptoms.[3,4] Nonetheless, a significant number of mild TBI patients will develop persistent cognitive impairment in the months and years after injury. Prior studies of mild TBI have estimated that up to 30% of patients will suffer long-term cognitive, psychiatric, or behavioral impairment.[5–8] Despite the significant number of patients who will have long-term cognitive impairment, there is currently no method to identify those at risk for a poor outcome. Early identification is crucial because it has been shown that early rehabilitation after TBI may improve clinical outcome.[9,10]

Although conventional computed tomography (CT) and magnetic resonance imaging (MRI) can detect intracranial hematoma and petechial hemorrhage after mild TBI, most often, conventional imaging is normal.[11] Such normal imaging findings are discordant with histological studies where axonal damage is a common finding after mild, moderate, and severe TBI.[12,13] Diffusion-weighted MRI is a technique that quantifies motion of water molecules. The role of diffusion-weighted MRI in TBI has been studied, but results have been nonspecific. Both increases and decreases in diffusivity, measured as the apparent diffusion coefficient (ADC), have been reported at locations known to be affected by diffuse axonal injury.[14,15] This variability has been attributed to vasogenic and cytoxic edema in the acute and subacute phases of injury.[16] In the chronic phase of repeated head injury, increases in the average brain ADC have been reported in professional boxers.[17]

Diffusion tensor imaging (DTI) is a relatively new technique used to detect white matter abnormalities that may not be discernible on conventional MRI. Diffusion tensor imaging characterizes the direction of movement of water molecules. In white matter, the parallel arrangement of axons and fibers leads to preferential diffusion parallel to the long axis of the fiber, with restriction of diffusion across the fiber. After injury, alteration or disruption of the axonal microarchitecture removes the anatomical feature conferring a preferential direction of diffusion. As a result, more random direction of diffusion will be detected at the site of injury. Fractional anisotropy (FA) quantifies the degree to which the diffusion of water is unidirectional. High values of FA indicate unidirectional diffusion typical of normal white matter structure. Low values of FA indicate random direction of diffusion, consistent with white matter injury. Previous studies have demonstrated low white matter FA after TBI.[18–21] However, most of these studies assessed patients with moderate or severe TBI during the acute phase of injury.[18,19]

Our objective was to study a group of patients with persistent cognitive impairment in the chronic phase of mild TBI to determine if DTI can differentiate these patients from normal subjects. We hypothesized that decreases in FA and increases in ADC would be present in TBI patients within white matter regions known to be susceptible to axonal injury after TBI.

METHODS

Subjects and Design

The study comprised a review of MRI scans performed in 10 mild TBI patients (Table 1) and 10 control subjects. All

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Received for publication August 6, 2007; accepted March 12, 2008.

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TABLE 1. Patient Characteristics and Neuropsychological Deficits

Demographics (at Injury)				Time From Injury, yrs		Neuropsychological Domains				
Subject	Sex	Age	Mechanism	Neuropsychology	MRI	Language	Memory	Attention	Executive	Sensorimotor
1	M	46.3	Fall	7.5	10.2	XX	XX	XX	XX	X
2	F	20.2	MVA	1.2	6.7	Intact	Intact	X	X	Intact
3	M	34.6	MVA	3.3	3.8	X	XX	XXX	XXX	Intact
4	F	51.2	MVA	8.5	9.3	Intact	XX	XX	XX	Intact
5	F	45.8	MVA	7.8	10.1	Intact	XX	XX	XXX	Intact
6	M	41.4	MVA	9.3	10.8	Intact	XX	XX	XX	X
7	F	37.0	MVA	3.5	6.1	Intact	XX	XXX	XXX	Intact
8	F	38.6	Fall	1.6	2.6	Intact	X	XX	XX	Intact
9	M	28.2	MVA	5.8	8.1	Intact	XX	XXX	XXX	Intact
10	M	38.3	MVA	6.0	6.1	X	XX	X	X	Intact

Demographic characteristics of the patient group at the time of injury and the time from injury to neuropsychological evaluation and MRI are shown. Deficits on each of the 5 major neuropsychological domains are shown, graded as mild (X), moderate (XX), severe (XXX), or intact, based on the impression of the evaluating neuropsychologist.

F indicates female; M, male; MVA, motor vehicle accident.

aspects of the study were approved and supervised by the local institutional review board. Mild TBI patients were referred for MRI by a treating physician to evaluate for structural brain abnormalities that might explain symptomatic cognitive impairment. Before their injury, these patients had no history of neurological or psychiatric disease or cognitive impairment. Injuries were due to falls and motor vehicle accidents. All patients were evaluated by a physician, and each patient demonstrated a Glasgow Coma Scale score of 13 or higher at the time of injury. None of the patients required hospitalization at the time of injury. Of the patients who had CT and/or conventional MRI at the time of injury, the results were normal. All patients developed persistent cognitive impairment several months after the injury, with deficits including memory, attention, impulsivity, executive function, and personality changes. The diagnosis of cognitive impairment due to mild TBI was made during a clinical neuropsychological examination in each case. The neuropsychological examinations were not standardized because patients were evaluated in the course of their clinical workup by different neuropsychologists; patients were not administered the same test components in each case. Nevertheless, impairments were determined based on 2 or more standard deviations less than the mean (based on the normalized z scores for each test). We reviewed the neuropsychology reports to ascertain impairment and classified each subject's impairment on each of the 5 major neuropsychological domains (verbal, memory, attention, executive function, and sensorimotor) as intact, mildly impaired, moderately impaired, or severely impaired. Patients were referred for imaging more than 1 year after the injury due to their persistent neurocognitive impairment. Time from injury to neuropsychological evaluation and MRI is shown in Table 1. Ten age- and sex-matched control subjects (5 men, 5 women; mean age, 44 years; range, 18–54 years; SD = 10.9) were recruited for the study. The controls were patients referred for MRI due to headache and had no history of head trauma.

Image Acquisition

Magnetic resonance imaging was performed on a 1.5-T system (Signa Excite MR/i; GE Medical Systems, Milwaukee, Wis). Pulse sequences included a 3-plane localizer (excitations, 1; 22 × 22-cm field of view [FOV]; 256 × 256 imaging matrix; 4-mm section thickness with a 1-mm gap), sagittal 3-dimensional fast spoiled gradient echo (repetition time [TR], 7.6 ms; time to echo [TE], 4.2 ms; excitations, 2; 30-degree flip angle; 26 × 26-cm FOV; 256 × 256 imaging matrix; 1-mm section thickness), sagittal fast spin echo (TR, 550 ms; TE, 20 ms; excitations, 1; echo train, 3; FOV, 24 × 24 cm; 256 × 224 imaging matrix; 5-mm section thickness with a 1-mm gap), axial fast recovery fast spin echo (TR, 4350 ms; TE, 120 ms; excitations, 1; echo train, 16; FOV, 26 × 26 cm; 256 × 192 imaging matrix; contiguous 5-mm sections); axial fluid-attenuated inversion recovery (TR, 800 ms; TE, 120 ms; excitations, 1; delay time, 2250 ms; FOV, 22 × 22 cm; 256 × 224 imaging matrix; 5-mm section thickness with a 1-mm gap), axial gradient echo (TR, 750 ms; TE, 17 ms; excitations, 2; 15-degree flip angle; FOV, 22 × 22 cm; 256 × 192 imaging matrix; 5-mm section thickness with a 1-mm gap); and coronal fast spin echo (TR, 3155 ms; TE, 104 ms; excitations, 2; echo train, 17; FOV, 23 × 23 cm; 512 × 224 imaging matrix; 5-mm section thickness with a 1-mm gap).

Whole brain diffusion tensor echoplanar imaging was performed using 25 noncolinear directions and a b value 1000 s/mm^2. Echoplanar imaging parameters were TR, 8700 ms; TE, 89 ms; excitations, 1; FOV, 26 × 26 cm; 128 × 128 imaging matrix; contiguous 5-mm sections.

Image Analysis

In all patients, conventional MRI as well as FA and ADC images were reviewed by 2 Certificate of Added Qualification–certified neuroradiologists to identify hemorrhage or other evidence of gross brain pathology. Any discrepancy between the 2 interpretations was resolved by consensus.

Images were analyzed off-line on a LINUX workstation running the Functional Magnetic Resonance Imaging of the Brain (FSL) software package.[22] Two investigators blind to the group assignment (patient or control) drew regions of interest (ROIs) on the B0 images using the FSLview module of FSL. Polygonal ROIs were placed in the genu and splenium of the corpus callosum, posterior limb of the internal capsule, and in the pontine tegmentum. Region of interest placement was supervised by 2 Certificate of Added Qualification–certified neuroradiologists. For each structure, ROIs were placed on both right and left. Samples of the locations of ROI placement are shown in Figure 1. Anatomical landmarks determined the shape and size of the polygonal region of interest in each case. Care was taken to exclude adjacent gray matter and cerebral spinal

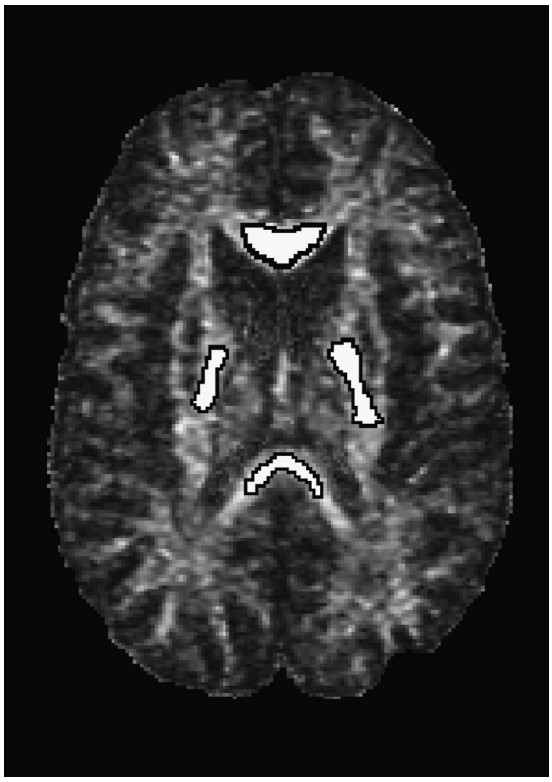

FIGURE 1. Region of interest placement on an FA image: ROI markers (white with black outline) were placed in the genu and splenium of the corpus callosum and the posterior limb of the internal capsule. Region of interest markers were also placed in the pons (not shown). For clarity, the ROIs are shown superimposed on an FA image but were actually drawn on the B0 image.

fluid. Average FA and ADC were computed for each ROI using the AVWmaths module of FSL.

Statistical Analysis

Student *t* test for nonpaired data was used to compare mean FA and ADC extracted from each ROI between subject and control groups.

RESULTS

Table 1 reports demographic features of the patient group, time from injury to neuropsychological evaluation, and MRI and severity of neuropsychological impairment. On the conventional MRI sequences, suggestion of a small focal area of lobar gliosis was present in 1 of the subjects. No other abnormality and, specifically, no evidence of hemorrhage were found in the remaining subjects. Visual assessment of the FA and ADC images disclosed no abnormality. Intergroup differences between the controls and subjects in mean FA and ADC for each ROI are summarized in Tables 2 and 3, respectively. The TBI group demonstrated a 4.2% absolute reduction in FA within the left side of the genu of the corpus callosum compared with the control group. This finding was statistically significant ($P = 0.04$). The corresponding mean ADC of the TBI group at this location demonstrated a 6.7% increase when compared with the control group, which was statistically significant ($P = 0.03$). The mild TBI group also demonstrated a significant increase in FA within the posterior limb of the internal capsule bilaterally (left, 5.1%; $P = 0.03$; and right, 1.9%; $P = 0.04$).

TABLE 2. Fractional Anisotropy (Mean ± SD) for Mild TBI Patients and Controls

Location	Patients	Controls	*P*
Genu (L)	0.737 ± 0.086	0.772 ± 0.045	0.01
Genu (R)	0.748 ± 0.114	0.743 ± 0.054	0.41
Internal Capsule (L)	0.700 ± 0.094	0.666 ± 0.032	0.03
Internal Capsule (R)	0.687 ± 0.088	0.666 ± 0.032	0.04
Splenium (L)	0.800 ± 0.091	0.780 ± 0.056	0.23
Splenium (R)	0.811 ± 0.097	0.796 ± 0.065	0.27
Pons (L)	0.524 ± 0.112	0.532 ± 0.074	0.39
Pons (R)	0.514 ± 0.117	0.515 ± 0.065	0.48

L indicates left; R, right.

DISCUSSION

Our results demonstrate a significant decrease in FA within the genu of the corpus callosum in patients with persistent cognitive impairment after mild TBI. Although expert visual assessment of FA and ADC images (Fig. 2) revealed no qualitative difference between the control and trauma patients, highly significant quantitative intergroup differences are present. These results agree with previous studies showing low FA after TBI.[18–21,23] However, only 2 of the published studies evaluated subjects with mild TBI.[20,21] Additionally, those studies that did include subjects with mild TBI included patients with structural brain abnormalities on CT or MRI consistent with TBI or diffuse axonal injury. The prevalence of these gross abnormalities in prior studies, including petechial hemorrhage, contusion, or hematoma, suggests that the patients studied had more severe TBI than our study population. The extremely mild degree of TBI in our sample may be why significant reductions in FA were not detected in other areas known to be susceptible to DAI.[24,25]

Persistent cognitive, psychiatric, and behavioral dysfunction after TBI has been well described in the literature. Nonspecific and variable symptoms reported by patients after trauma are often categorized as postconcussion syndrome. The subjective and nonspecific nature of the symptoms have led some authors to question whether mild TBI is in fact a real cognitive disorder.[26,27] However, existing evidence strongly indicates that up to 30% of patients experiencing mild TBI develop neurocognitive impairment related to the initial injury. Although acute and subacute changes in FA after TBI have been studied, our study is the first to address the important problem of chronic cognitive impairment after mild TBI. Our study shows that DTI

TABLE 3. Apparent Diffusion Coefficient (Mean ± SD, $10^{-5}cm^2/s$) for Mild TBI Patients and Controls

Location	Patients	Controls	*P*
Genu (L)	0.673 ± 0.100	0.614 ± 0.059	0.04
Genu (R)	0.618 ± 0.106	0.636 ± 0.061	0.22
Internal Capsule (L)	0.541 ± 0.720	0.535 ± 0.019	0.31
Internal Capsule (R)	0.526 ± 0.069	0.583 ± 0.012	0.44
Splenium (L)	0.577 ± 0.090	0.600 ± 0.052	0.17
Splenium (R)	0.584 ± 0.089	0.583 ± 0.060	0.48
Pons (L)	0.547 ± 0.067	0.555 ± 0.052	0.33
Pons (R)	0.554 ± 0.064	0.560 ± 0.043	0.39

L indicates left; R, right.

can be used to detect differences between patients with cognitive impairment after mild TBI and controls.

It is generally established that reductions in FA in anatomical regions prone to TBI are due to changes in the microarchitecture that restricts movement of water molecules across white matter tracts. However, in our study of patients with chronic TBI, it is unclear why a persistent reduction of FA in the genu of the corpus callosum in particular was identified, whereas other regions also known to be susceptible to axonal injury such as the splenium of the corpus callosum, internal capsule, and pons did not demonstrate a statistically significant reduction. One possible explanation is that, in some regions, FA normalized during the time between initial injury and the DTI examination. Using an animal impact-acceleration model, Barzo et al[16] reported normalization of ADC 4 weeks after TBI. However, the mechanisms relevant to our study may be different because the initial changes in ADC in the study of Barzo et al of moderate/severe TBI were due to vasogenic and cytoxic edema. In our study, however, subjects were imaged well beyond the acute phase of injury when edema would be present. Alternatively, due to the small sample size and the inherent limitations of ROI analysis, our study may not have been powered to detect a significant effect in the other anatomical regions prone to TBI.

Interestingly, FA was higher in patients than in controls in the internal capsules. No associated abnormality of ADC was found in this region. Although the mechanism leading to increases in FA beyond that found in normals is not entirely clear, such findings have been described in other white matter disorders; an increase in FA greater than normal may be a manifestation of recovery from injury.[28,29] Alternatively, with loss of a subset of corticospinal tract fibers, but preservation of other fibers such as in Wallerian degeneration due to lesions in the cerebral hemisphere, FA might be enhanced. In such a scenario, the extracellular space would be increased but with preservation of a linear arrangement of cellular structure (remaining axons) and consequent greater facilitation of diffusion along the direction of the fiber. Measurement of the component eigenvalues of the diffusion tensor might shed light on this possibility. Finally, it is plausible that the increase in FA reflects a compensatory alteration related to reduced FA in the left side of the genu of the corpus callosum. A longitudinal study may be helpful in addressing these possibilities.

A limitation of this study is its small sample size. Our findings need to be replicated in a larger group. In addition, the study sample is somewhat heterogenous with different mechanisms of TBI, varying time intervals between injury and the DTI examination, and varying degrees of cognitive impairment. Nonetheless, the fact that we did detect significant group differences, despite these limitations, suggests that significant abnormalities are likely to be found in a future study of a larger and more homogeneous patient group.

The ROI analysis method used in this study is similar to ROI analyses that have been described in all prior reports of DTI in TBI. It is important to recognize that the ROI approach carries several limitations. Placement of the ROI, even by a trained and blinded observer as in our study, inevitably introduces observer bias. Furthermore, due to the low resolution of the FA images, it is extremely difficult to be sure that ROIs are placed precisely. Finally, partial volume effects are inevitable whenever an ROI is placed. Given the very small size of TBI lesions, one important consequence of such partial volume effects is a loss of sensitivity to small lesions. Although we were extremely careful to exclude adjacent CSF and gray matter, partial volume effects can still bias the mean FA within the ROI. We used a relatively large ROI based on the appearance of the anatomy on the B0 images. This approach facilitates standardization of ROI placement and avoids the potential for bias if ROIs were drawn on the FA and ADC images. The ROI method, however, may decrease

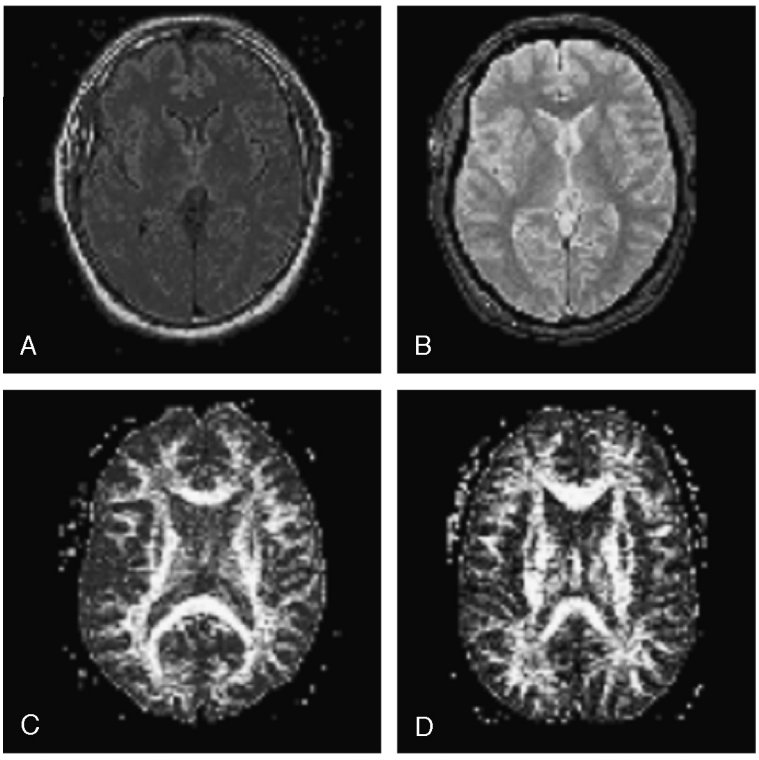

FIGURE 2. Image appearance in mild TBI (A–C) and controls (D): Fluid-attenuated inversion recovery imaging (A) and gradient echo (B) image from a mild TBI patient show no signal abnormality or evidence of hemorrhage. Fractional anisotropy images in the mild TBI patient (C) and control (D) are qualitatively similar, with no visual evidence of white matter lesions.

sensitivity to small lesions even where there is a significant difference between groups. Voxel-based analyses may be more sensitive and can help better delineate the full extent of injury.

Finally, a prospective longitudinal study with standardized neurocognitive testing and imaging at the time of injury and at set intervals post injury is needed to characterize temporal change in FA and its relationship to neurocognitive impairment. Such a design may separate subgroups of TBI patients who develop persistent neurocognitive impairment and those who recover and remain symptom-free. The results of the present study indicate that such a longitudinal study is likely to be informative.

CONCLUSIONS

The patient group with persistent cognitive impairment after mild TBI was distinguished from matched controls by evaluating the mean FA and ADC within regions prone to axonal injury after trauma. These results build on prior studies demonstrating FA reduction in similar regions immediately after trauma. The present findings are important in that they address a serious adverse outcome of a very common disorder: cognitive impairment due to mild TBI. Longitudinal studies will be required to confirm and elucidate the full importance of our findings, which suggest that permanent white matter ultrastructural damage occurs in mild TBI, and that such damage may be a substrate of persistent cognitive disability.

REFERENCES

1. National Center for Injury Prevention and Control. Report to Congress on Mild Traumatic Brain Injury in the United States: Steps to Prevent a Serious Public Health Problem. Atlanta, GA: Centers for Disease Control and Prevention; 2003.
2. Mittl RL, Grossman RI, Hiehle JF, et al. Prevalence of MR evidence of diffuse axonal injury in patients with mild head injury and normal head CT findings. *AJNR AM J Neuroradiol*. 1994;15:1583–1389.
3. Levin HS, Mattis S, Ruff RM, et al. Neurobehavioral outcome following minor head injury: a three-center study. *J Neurosurg*. 1987;66:234–243.
4. Ponsford J, Willmott C, Rothwell A, et al. Factors influencing outcome following mild traumatic brain injury in adults. *J Int Neuropsychol Soc*. 2000;6:568–579.
5. Sterr A, Herron KA, Hayward C, et al. Are mild head injuries as mild as we think? Neurobehavioral concomitants of chronic post-concussion syndrome. *BMC Neurol*. 2006;6:7.
6. Bohnen N, Twijnstra A, Jolles J. Persistence of postconcussional symptoms in uncomplicated, mildly head-injured patients: a prospective cohort study. *Neuropsychiatry Neuropsychol Behav Neurol*. 1993;6: 193–200.
7. Kreutzer JS, Seel RT, Gourley E. The prevalence and symptom rates of depression after traumatic brain injury: a comprehensive examination. *Brain Inj*. 2001;15:563–576.
8. Rao V, Lyketsos C. Neuropsychiatric sequelae of traumatic brain injury. *Psychosomatics*. 2000;41:95–103.
9. Cicerone KD, Dahlberg C, Malec JF, et al. Evidence-based cognitive rehabilitation: updated review of the literature from 1998 through 2002. *Arch Phys Med Rehabil*. 2005;86:1681–1692.
10. Palmese CA, Raskin SA. The rehabilitation of attention in individuals with mild traumatic brain injury, using the APT-II programme. *Brain Inj*. 2000;14:535–548.
11. McAllister TW, Sparling MB, Flashman LA, et al. Neuroimaging findings in mild traumatic brain injury. *J Clin Exp Neuropsychol*. 2001;23:775–791.
12. Medana IM, Esiri MM. Axonal damage: a key predictor of outcome in human CNS diseases. *Brain*. 2003;126:515–530.
13. Gentleman SM, Roberts GW, Gennarelli TA, et al. Axonal injury: a universal consequence of fatal closed head injury? *Acta Neuropathol*. 1995;89:537–543.
14. Hergan K, Schaefer PW, Sorensen AG, et al. Diffusion-weighted MRI in diffuse axonal injury of the brain. *Eur Radiol*. 2002;12:2536–2541.
15. Liu A, Maldijian J, Bagley L, et al. Traumatic brain injury: diffusion weighted imaging findings. *AJNR Am J Neuroradiol*. 1999;20: 1636–1641.
16. Barzo P, Marmarou A, Fatouros P, et al. Contribution of vasogenic and cellular edema to traumatic brain swelling measured by diffusion-weighted imaging. *J Neurosurg*. 1997;87:900–907.
17. Zhang L, Ravdin LD, Relkin N, et al. Increased diffusion in the brain of professional boxers: a preclinical sign of traumatic brain injury. *AJNR Am J Neuroradiol*. 2003;24:52–57.
18. Huisman TA, Schwamm LH, Schaefer PW, et al. Diffusion tensor imaging as potential biomarker of white matter injury in diffuse axonal injury. *AJNR Am J Neuroradiol*. 2004;25:370–376.
19. Ptak T, Sheridan RL, Rhea JT, et al. Cerebral fractional anisotropy score in trauma patients: a new indicator of white matter injury after trauma. *AJR Am J Roentgenol*. 2003;181:1401–1407.
20. Inglese M, Makani B, Johnson G, et al. Diffuse axonal injury in mild traumatic brain injury: a diffusion tensor imaging study. *J Neurosurg*. 2005;103:298–303.
21. Arfanakis K, Haughton VM, Carew JD, et al. Diffusion tensor MR imaging in diffuse axonal injury. *AJNR Am J Neuroradiol*. 2002;23: 794–802.
22. Smith SM, Jenkinson M, Woolrich MW, et al. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage*. 2004;23 Supp 1:S208–S219.
23. Salmond CH, Menon DK, Chatfield DA, et al. Diffusion tensor imaging in chronic head injury survivors: correlation with learning and memory indices. *Neuroimage*. 2006;29:117–124.
24. Gentry LR. Imaging of closed head injury. *Radiology.* 1994;191:1–17.
25. Gentry LR, Godersky JC, Thompson B. MR imaging of head trauma: review of the distribution and radiopathologic features of traumatic lesions. *AJR Am J Roentgenol*. 1988;150:663–672.
26. Smith-Seemiller L, Fow NR, Kant R, et al. Presence of post-concussion syndrome symptoms in patients with chronic pain vs. mild traumatic brain injury. *Brain Inj*. 2003;17:199–206.
27. Barth JT, Diamond R, Errico A. Mild head injury and post concussion syndrome: does anyone really suffer? *Clin Electroencephalogr*. 1996;27:183–186.
28. Houenou J, Wessa M, Douaud G, et al. Increased white matter connectivity in euthymic bipolar patients: diffusion tensor tractography between the subgenual cingulate and the amygdalo-hippocampal complex. *Mol Psychiatry* 2007;12:1001–1010.
29. Yu C, Shu N, Li J, et al. Plasticity of the corticospinal tract in early blindness revealed by quantitative analysis of fractional anisotropy based on diffusion tensor tractography. *Neuroimage*. 2007;32:411–417.