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Diffusion Tensor Imaging Findings and Postconcussion Symptom Reporting Six Weeks Following Mild Traumatic Brain Injury

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Abstract

The purpose of this study is to examine the relation between the microstructural architecture of white matter, as measured by diffusion tensor imaging (DTI), and postconcussion symptom reporting 6–8 weeks following mild traumatic brain injury (MTBI). Participants were 108 patients prospectively recruited from a Level 1 Trauma Center (Vancouver, BC, Canada) following an orthopedic injury [i.e., 36 trauma controls (TCs)] or MTBI ($n = 72$). DTI of the whole brain was undertaken using a Phillips 3T scanner at 6–8 weeks postinjury. Participants also completed a 5 h neurocognitive test battery and a brief battery of self-report measures (e.g., depression, anxiety, and postconcussion symptoms). The MTBI sample was divided into two groups based on ICD-10 criteria for postconcussional syndrome (PCS): first, PCS-present ($n = 20$) and second, PCS-absent ($n = 52$). There were no significant differences across the three groups (i.e., TC, PCS-present, and PCS-absent) for any of the neurocognitive measures ($p = .138–.810$). For the self-report measures, the PCS-present group reported significantly more anxiety and depression symptoms compared with the PCS-absent and TC groups ($p < .001, d = 1.63–1.89$, very large effect sizes). For the DTI measures, there were no significant differences in fractional anisotropy, axial diffusivity, radial diffusivity, or mean diffusivity when comparing the PCS-present and PCS-absent groups. However, there were significant differences ($p < .05$) in MD and RD when comparing the PCS-present and TC groups. There were significant differences in white matter between TC subjects and the PCS-present MTBI group, but not the PCS-absent MTBI group. Within the MTBI group, white-matter changes were not a significant predictor of ICD-10 PCS.

Keywords: Mild traumatic brain injury; Diffusion tensor imaging; Postconcussion symptoms; Neurocognitive; Biomarkers

Introduction

Postconcussion symptoms are common in the acute recovery phase following mild traumatic brain injury (MTBI). Patients who sustain MTBI report more acute symptoms than healthy control and trauma control (TC) subjects in the initial days and weeks postinjury in most (Iverson, Silverberg, Lange, & Zasler, 2013), but not all studies (e.g., Landre, Poppe, Davis, Schmaus, & Hobbs, 2006). Fortunately, in the majority of cases, these symptoms resolve within weeks to a few months (Iverson et al., 2013). However, the diagnostic significance of postconcussion symptom reporting following MTBI is controversial. Clinicians often assume that postconcussion symptoms reported many months or years postinjury are directly related to the biological

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consequences of that brain injury. However, there are many factors unrelated to brain injury that can potentially account for these symptoms (e.g., other medical problems (Lees-Haley & Brown, 1993), personal injury litigation (Lees-Haley & Brown, 1993), posttraumatic stress disorder (Foa, Cashman, Jaycox, & Perry, 1997), orthopedic injuries (Meares et al., 2008; Mickeviciene et al., 2004), chronic pain (Iverson & McCracken, 1997), depression (Iverson, 2006; Suhr & Gunstad, 2002b), and myofascial injury (whiplash) (Sullivan, Hall, Bartolacci, Sullivan, & Adams, 2002). Complicating matters further, the perception and reporting of symptoms can be influenced by a diverse range of psychological and social-psychological factors that may cause, maintain, or worsen the myriad of symptoms that are reported postinjury (e.g., premorbid personality [Hibbard et al., 2000], clinical methods used to elicit symptoms [Iverson, Brooks, Ashton, & Lange, 2010], nocebo effect [Hahn, 1997], "expectation as etiology" [Gunstad & Suhr, 2001], diagnosis threat [Suhr & Gunstad, 2002a], and "good old days" bias [Gunstad & Suhr, 2001; Iverson, Lange, Brooks, & Rennison, 2010]). Some studies have illustrated that preinjury mental health problems and postinjury difficulties with anxiety are strongly related to symptoms that persist for many months following injury (Ponsford et al., 2012).

To date, there is limited evidence to support a direct causal link between macrostructural brain injury and symptom reporting. In general, neuroimaging studies have not documented a relationship between greater postconcussion symptom reporting and intracranial abnormalities identified on structural computed tomography (CT) or magnetic resonance imaging (MRI) scans within the first few days (Hughes et al., 2004; Kurca, Sivak, & Kucera, 2006), 3–6 months (Hofman et al., 2001; Lannsjo, Backheden, Af Johansson, Geijerstam, & Borg, 2013; Sigurdardottir, Andelic, Roe, Jerstad, & Schanke, 2009; Taylor et al., 2010), or 6–12 months (Deepika, Munivenkatappa, Devi, & Shukla, 2013; Sigurdardottir et al., 2009; Taylor et al., 2010) following injury. In fact, de Guise and colleagues (2010) found, paradoxically, greater postconcussion symptom reporting 20 weeks following MTBI in those patients who had *normal* day-of-injury CT scans (rather than abnormal scans). Of course, the lack of association between postconcussion symptoms and intracranial abnormalities on structural CT or MRI scan may be due, in part, to the lack of sensitivity of these methods to detect diffuse microstructural changes often associated with MTBI (Bruns & Jagoda, 2009; Gaetz & Weinberg, 2000; e.g., Hofman et al., 2001; Lewine et al., 2007).

Diffusion tensor imaging (DTI) is useful for detecting white-matter changes in the brain following TBI (Belanger, Vanderploeg, Curtiss, & Warden, 2007; Xu, Rasmussen, Lagopoulos, & Haberg, 2007) and it has become an important tool for the evaluation of MTBI in the acute, subacute, and chronic phases of the recovery trajectory (Inglese, Bomsztyk, et al., 2005; Inglese, Makani, et al., 2005; Kraus et al., 2007; Kumar et al., 2009; Lipton et al., 2009; Rutgers et al., 2008; Shenton et al., 2012). To date, a number of researchers have established the sensitivity of DTI to differentiate healthy controls from those individuals who have sustained MTBI and who report postconcussion symptoms 3–6 years following injury (Lipton et al., 2008; Niogi et al., 2008). The methodology of these small, cross-sectional, correlational studies, however, does not allow one to assume a causal link between microstructural white-matter findings and postconcussion symptoms. In recent years, the number of DTI studies that have examined the relationship between postconcussion symptom reporting and MTBI has increased steadily. These studies can be characterized into two categories: correlational studies and group studies.

Results from correlational studies have found a relatively consistent relationship between postconcussion symptom reporting and various DTI metrics. For example, researchers have reported that increased postconcussion symptom reporting is associated with (a) increased fractional anisotropy (FA) and decreased apparent diffusion coefficients (ADCs) and radial diffusivity (RD) in the corpus callosum in 10 adolescents within the first 6 days following MTBI (Wilde et al., 2008); (b) low trace values in the whole brain at 72 h and 1 month postinjury in six patients following MTBI (Bazarian et al., 2007); (c) pre–post season changes in FA and mean diffusivity (MD) in nine high school athletes who sustained repeated multiple subconcussive blows (Bazarian, Zhu, Blyth, Borrino, & Zhong, 2012); and (d) increased MD in the inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, and superior longitudinal fasciculus; and decreased FA in uncinate fasciculus, inferior fronto-occipital fasciculus, internal capsule, corpus callosum, and the parietal and frontal subcortical white matter in 20 patients 1 month postinjury (Smits et al., 2011). One exception to this is a study by Levin and colleagues (2010) who found no relationship between FA and ADC and postconcussion symptoms in 37 mild–moderate TBI service members 2.3 years postinjury using fiber-tracking and region of interest (ROI) methodology. It is important to appreciate, however, that despite the significant correlations found between postconcussion symptom reporting and some DTI metrics in the above studies, there were many other DTI metrics that were *not* associated with postconcussion symptom reporting.

In contrast to correlational studies, there are mixed findings in group studies that have compared DTI metrics across subgroups defined by postconcussion symptom reporting. Messe and colleagues (Messé et al., 2011, 2012) found some DTI differences in a small sample of patients with MTBI divided into poor outcome (Postconcussion Syndrome [PCS] present [i.e., PCS+]) versus good outcome (PCS absent [i.e., PCS-]) groups. These differences were found for MD only, and not for FA, axial diffusivity (AD), or RD (Messé et al., 2011). At 3 months postinjury ($n = 23$), participants in the PCS+ group had higher MD compared with the PCS− group in the forceps major and minor, the corpus callosum, the inferior-occipital fasciculus bilaterally, and inferior longitudinal fasciculus bilaterally. The PCS+ group (but not the PCS− group) also had higher MD compared with a healthy control sample in some ROIs (i.e., superior longitudinal fasciculus, corticospinal tract bilaterally, and left anterior thalamic radiation). In a

follow-up longitudinal study of 53 MTBI patients evaluated in the acute phase of recovery (8–21 days [T1]) and subacute (6 months [T2]), Messe and colleagues (2012) (Messe et al., 2012) reported that the PCS+ group had a greater number of abnormal brain regions on DTI than the PCS− group when compared with healthy controls. These authors did not provide detailed information regarding a direct comparison between PCS+ vs. PCS− groups; however, they concluded that "significant structural differences were found between PCS+ and PCS− groups at T1 and less at T2 for the MD and AD measures, that involved primarily the corpus callosum, the longitudinal fasciculus, and the internal capsules." (p. 288). There were no differences found for FA or RD measures. Similarly, Hartikainen and colleagues (2010) examined 18 patients with mild–moderate TBIs at 6 months postinjury and found that those who reported persistent postconcussion symptoms ($n = 7$) had lower ADC ($d = 2.33$) and higher FA ($d = 1.86$) compared with those who reported no symptoms ($n = 11$) in the midbrain structures (i.e., thalamus, internal capsule, centrum semiovale, and mesencephalon).

In contrast to these studies, Waljas et al. (2014) examined 48 patients with uncomplicated MTBI and found no differences across 16 ROIs for FA, or 10 ROIs for ADC, between those who did and did not report postconcussion symptoms at 3 weeks following injury. Similarly, Lange, Iverson, Brubacher, Madler, and Heran (2012) examined the relation between DTI of the corpus callosum and reporting in 60 patients who had sustained MTBI, and 34 patients with orthopedic/soft-tissue injuries (i.e., TCs). At 6–8 weeks postinjury, there were no significant differences between the MTBI and TC groups for FA or for MD in the genu, body, and splenium of the corpus callosum. Similarly, in the MTBI sample, there were no significant differences on any DTI measures between those who did and did not meet ICD-10 symptom criteria for postconcussion syndrome (PCS). In the MTBI sample, Cohen's effect sizes ranged from very small ($d = 0.02$) to small ($d = 0.16$) for all DTI measures; with the exception of small–medium effect size found for FA in the genu ($d = 0.39$) and body ($d = 0.37$) of the corpus callosum.

The purpose of this study is to expand the study by Lange and colleagues (2012) that examined the relation between DTI and postconcussion symptom reporting by: first, using DTI to examine the whole brain; second, include a larger number of DTI metrics such FA, MD, RD, and AD; third, use more advanced and comprehensive DTI analysis methods including tract-based spatial statistics (TBSS) and standard brain atlas generated ROI analyses; fourth, include neurocognitive tests and more symptom scales as outcome measures; fifth, include a sample of individuals in the MTBI group that do not have intracranial abnormalities that predate their injury; and finally, include a sample of participants in the TC group that do not include minor intracranial abnormalities (e.g., T2 hyperintensities).

The hypotheses are threefold. First, compared with the TC group, patients with MTBI will (a) report a greater number of postconcussion, depression, and anxiety symptoms; (b) perform comparably on neurocognitive measures; and (c) have reduced white-matter integrity in the whole brain as measured by DTI metrics. Second, in the MTBI group, patients who meet ICD-10 criteria for PCS (i.e., PCS-present) will report a greater number of depression and anxiety symptoms compared with those patients who do not meet ICD-10 PCS criteria (i.e., PCS-absent). Third, in the MTBI group, there will be no differences across all neurocognitive measures and DTI metrics when comparing the PCS-present vs. PCS-absent groups.

Method

Participants

Participants were 108 patients (72 MTBI and 36 TC) prospectively recruited from the Emergency Department of Vancouver General Hospital (Level 1 Trauma Center) between June 2007 and April 2012. Patients were identified for potential inclusion in the study via daily reviews of consecutive Emergency Department admissions. Patients were targeted for recruitment and consent if they presented to the Emergency Department after sustaining a MTBI (i.e., MTBI group), or they had sustained a soft-tissue or orthopedic injury without brain injury (i.e., TC group).

All participants were enrolled in the study if they were first, between 19 and 55 years of age, second, injured as a result of a traumatic injury (e.g., fall, motor vehicle accident, assault, etc.), and third, had a blood alcohol level (BAL) obtained at the time of injury by hospital staff on admission to the Emergency Department. General exclusion criteria included first, lack of proficiency in conversational English; second, educated in a language other than English after age 10 (Note that the second and more stringent criterion for ESL was only introduced in 2009 after the evaluation of a series of patients whose neurocognitive profile was considered to be affected by a lack of English-based education (e.g., intact scores on all measures except language-based measures).); (c) history of a neurological disorder (e.g., stroke or multiple sclerosis), TBI, learning disability, or psychiatric illness requiring hospitalization; (d) presence of any contraindication 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 were included in the *TC group* 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 (e.g., absence of lacerations/contusions to the head, absence of

complaints of head, neck, or back pain). In a small number of cases ($n = 2$), TC participants had undergone a head CT but had no evidence of intracranial abnormality.

Participants were included in the *MTBI group* if they (a) presented to the Emergency Department following head trauma, and (b) had evidence of MTBI as indicated by *at least* one of the following: (i) witnessed LOC of at least 1 min duration but not >30 min, (ii) PTA of at least 15 min duration but not >24 h, and/or (iii) GCS score of 13 or 14. Patients were further classified into uncomplicated and complicated MTBI groups as follows: (a) uncomplicated MTBI: GCS = 13–15, PTA < 24 h, LOC <30 min, and no trauma-related intracranial abnormality on day-of-injury CT or 6–8 weeks structural MRI scan; (b) complicated MTBI: GCS = 13–15, PTA <24 h, LOC <30 min, and trauma-related intracranial abnormality on day-of-injury CT scan or 6–8 week structural MRI scan. Of the 72 MTBI patients included in this study, there were 38 (52.8%) with uncomplicated MTBI and 34 (47.2%) with complicated MTBI.

For the purpose of this study, the MTBI group was divided into two groups based on ICD-10 criteria for PCS: PCS-present ($n = 20$) and PCS-absent ($n = 52$)—see *Self-reported symptoms* for classification criteria.

Participant Selection

Participants were selected from a larger sample of 170 patients enrolled in the study (105 MTBI and 65 TC) in a three-step manner. First, participants were initially included in the sample if they met the following criteria: (1) completed the entire neuropsychological test battery (99.4% of sample), (2) neurocognitive test performance was not considered influenced by reduced English language proficiency (95.9% of sample), (3) scored above the recommended cutoff for good effort on the Test of Memory Malingering (100% of entire sample), (4) behavioral observations during the neuropsychological evaluation did not provide suspicion of questionable motivation or attention that may have negatively influenced test performance (98.8% of sample), (5) successfully completed MRI scanning (99.4% of sample), (6) there was no evidence of obvious incidental neurological abnormalities on MRI such as meningioma, cistern mass, venous anomaly (95.8% of sample), and (7) structural MRI scans were considered complete and readable by a neuroradiologist (98.8% of sample). In addition, in the MTBI group, participants were only included if (8) there was no evidence of intracranial abnormality that was considered to predate the current injury (97.1% of the MTBI sample). Similarly, in the TC group, participants were only included if (9) they had ≤1 white-matter hyperintensity (WMHIs [76.2% of TC sample]). Researchers have reported that healthy adults with two or more WMHIs have abnormalities on DTI metrics (distal from the hyperintensities) compared with adults with zero or one of hyperintensity (Iverson et al., 2011; Lange, Brickell, et al., 2013; Lange, Shewchuk, et al., 2013). Application of these criteria resulted in retaining 130 participants (39 TC, 91 MTBI [26 PCS-present, 65 PCS-absent]).

Second, in order to control for the influence of age, handedness, and preinjury alcohol consumption, participants were further excluded if they were 50 years or older, left-handed, or whose preinjury alcohol consumption was considered to be unusually high (defined as drinking >30 drinks per week and/or drinking five or more drinks per occasion during four or more days per week). These additional criteria were applied following an exploratory frequency analysis that identified a number of outliers that were considered to bias the analyses. Application of these criteria resulted in retaining 120 participants (39 TC and 81 MTBI [i.e., 22 PCS-present, 59 PCS-absent]).

Third, prior to DTI postprocessing, the MRI scans were inspected for image quality. Scans were excluded if they exhibited significant motion artifact or brain coverage was inadequate. Application of these criteria resulted in retaining a final sample of 108 participants (36 TC and 72 MTBI [i.e., 20 PCS-present, 52 PCS-absent]).

Some of the participants in this study were included in a previous study by Lange and colleagues (2012). In the current MTBI group, 54.2% ($n = 39$) were included in the previous study. In the current TC group, 50.0% ($n = 18$) were included in the original study. There were two primary reasons why participants from the original study were not included here. First, the inclusion of the neuropsychological variables in this study resulted in the exclusion of some participants due to unsuccessful test completion, poor English proficiency, and/or fluctuating attention (i.e., criteria 1–4 above). Second, more stringent criteria was applied to the TC and MTBI groups in this study with regard to the structural MRI scans, in order to create "cleaner" groups (i.e., criteria 8 and 9 above).

Measures and Procedure

Participants completed a 1-h MRI brain scan and a 5-h neuropsychological assessment battery that included measures of neurocognitive functioning and self-reported mental health and postconcussion symptoms, ~6–8 weeks postinjury ($M = 46.6$ days, $SD = 6.0$). All participants gave written informed consent in accordance with the Clinical Research Ethics Board at the University of British Columbia, Vancouver, Canada.

Self-Reported symptoms. Participants completed the Beck Depression Inventory-Second Edition (BDI-II), Beck Anxiety Inventory (BAI), and the British Columbia Postconcussion Symptom Inventory (BC-PSI). The BDI-II (Beck, Steer, & Brown, 1996) and BAI (Beck & Steer, 1993) are widely used measures designed to assess depressive and anxiety symptoms, respectively. Total scores for each measure were obtained by summing the individual responses to all items on each scale separately. In addition, for the purposes of this study, an additional total score was calculated for the BDI-II using 10 selected symptoms that are believed to have the least overlap with symptoms of MTBI, and that are considered most representative of depression (i.e., BDI-II 10-item total score). These items included sadness, loss of interest, loss of pleasure, pessimism, past failure, guilt feelings, punishment feelings, self-criticalness, crying, and suicidal thoughts or wishes. The BDI-II 10-item total score was calculated by summing the responses to these 10 individual items.

The BC-PSI (Iverson, Zasler, & Lange, 2007) is a symptom inventory designed based on ICD-10 (American Psychiatric Association, 2000) symptom criteria for PCS that requires the test taker to rate the frequency (0 = "not at all" to 5 = "constantly") and intensity (0 = "not at all" to 5 = "very severe problem") of 13 symptoms (e.g., headaches, dizziness, nausea, fatigue, sensitivity to noises, etc.) as well as the effect of three co-occurring life problems on daily living (i.e., effects of alcohol consumption, worrying/ dwelling on symptoms, and self-perception of brain damage). For each of the 13 symptoms, the two ratings are multiplied together (frequency × intensity) to create a single score for each item. These product-based scores were then converted to item scores that reflect both the frequency and intensity of symptom endorsement (range = 0–4). Item scores of 3 are interpreted as falling in the moderate range.

Responses on the BC-PSI were classified into two categories based on ICD-10 criteria for PCS: (a) PCS-present and (b) PCS-absent. Participant responses were classified as PCS-present if they endorsed BC-PSI items as moderate or greater on ≥3 of the six ICD-10 Category C criteria. Similarly, participant responses were classified as PCS-absent if they endorsed BC-PSI items as a moderate or greater on <3 of the six ICD-10 Category C criteria. The percentages of patients who endorsed each individual symptom domain were as follows: physical symptoms = 28.7%, emotional symptoms = 15.7%, cognitive symptoms = 16.7%, poor sleep = 20.4%, sensitivity to alcohol = 18.5%, and being overly focused on and concerned about their symptoms = 35.2%.

It is important to appreciate that symptom endorsement on the BC-PSI cannot be used in isolation to evaluate whether a person meets ICD-10 criteria for PCS. The diagnosis of PCS is complicated, challenging, and requires a comprehensive clinical evaluation (see Iverson et al., 2013 for a comprehensive discussion). This was not done here. Rather, endorsement of BC-PSI items that meet ICD-10 symptom criteria for PCS simply reflects clinically elevated postconcussion symptom reporting and not a diagnosis *per se*.

Neurocognitive measures. The neurocognitive measures consisted of 16 tests from the Neuropsychological Assessment Battery (NAB; Stern & White, 2003). The NAB is a comprehensive, co-normed (across all tests) neuropsychological test battery that consists of 24 individual tests designed to assess cognitive functioning across five domains: attention, language, memory, spatial, and executive functioning. The normative sample is large and the coverage of neuropsychological abilities assessed is broad. The NAB can be used in a fixed or flexible manner. Only 16 of the 24 tests were selected for use in order to reduce administration time. The 16 selected tests result in 23 scores of interest. In order to reduce the number of cognitive variables for the analyses, the 23 scores of interest were used to generate index scores for each of the five cognitive domains. The Attention and Memory indexes were generated as per the instructions in the manual. For the Language, Spatial, and Executive Functioning Indexes, however, not all tests included in these indexes were administered. As such, these indexes were prorated. These three indexes were calculated by generating a prorated "sum of *T*-scores" which was converted to a standard score using the look-up table (i.e., Table 7.1) in the NAB normative manual (Stern & White, 2003). The prorated sum of *T*-scores for the three indexes was calculated by averaging the demographically adjusted *T*-scores across all available tests that are included in each index. The mean *T*-score was then multiplied by the number of subtests that are used to generate the full version of the index. For the Language Index, two of five possible subtests were used (i.e., Oral Production and Naming). For the Spatial Index, two of four possible subtests were used (i.e., Visual Discrimination and Design Construction). For the Executive Functioning Index, three of four possible subtests were used (Categories, Mazes, and Word Generation). A NAB Total Score Index was also generated using the standard scores derived for the five indexes above as per the instructions in the manual.

As part of the larger neurocognitive test battery, participants were also administered the (a) Test of Memory Malingering (Tombaugh, 1996) to evaluate the possibility of poor effort during neuropsychological testing, (b) Reynolds Intellectual Screening Test (Reynolds & Kamphaus, 2003) to assess current level of intellectual ability, and (c) Wechsler Test of Adult Reading (The Psychological Corporation, 2001) to assess premorbid level of intellectual ability. In addition, participants completed a semi-structured interview designed to gather information about their past and present medical, psychiatric, and personal history. Detailed information regarding the duration of PTA was obtained during this interview and reconstructed, when possible, using collateral information obtained from hospital records.

Neuroimaging. All MRI data were acquired on a Philips Achieva 3T scanner equipped with Dual Nova Gradients (maximum gradient strength 80 mT/m, max. slew rate 200 mT/m/s) and an eight-channel head coil. Partial parallel imaging was performed using sensitivity encoding (SENSE) (Pruessmann, Weiger, Scheidegger, & Boesiger, 1999). The total data acquisition time was 43 min. The MRI protocol included: (a) axial T2-weighted turbo spin echo scan ($TR = 3000$ ms, $TE = 80$ ms, flip angle $= 90^\circ$, acquisition matrix $= 320 \times 245$, field of view $= 240 \times 192 \times 139$ mm^3, acquired voxel size $= 0.75 \times 0.78 \times 4$ mm^3, reconstructed voxel size $= 0.47 \times 0.47 \times 4$ mm^3, SENSE factor of 1.2 along the left–right direction, 2 averages); (b) axial T2-weighted fluid attenuated inversion recovery [FLAIR] scan, $TR = 10{,}000$ ms, $TE = 10$ ms, acquisition matrix $= 304 \times 194$, field of view $= 240 \times 193 \times 139$ mm^3, acquired voxel size $= 0.79 \times 0.99 \times 4.00$ mm^3, reconstructed voxel size $= 0.47 \times 0.47 \times 4.00$ mm^3, SENSE factor of 1.6 along the left–right direction); and (c) DTI scan ($TR = 5618$ ms, $TE = 75$ ms, flip angle $= 90^\circ$, acquisition matrix $= 96 \times 95$, field of view $= 240 \times 240 \times 125$ mm^3, acquired voxel size $= 2.50 \times 2.50 \times 2.50$ mm^3, reconstructed voxel size $= 1.88 \times 1.88 \times 2.50$ mm^3, SENSE factor of 2.4 along the anterior–posterior direction, 15 diffusion directions, 3 averages, b factor $= 1{,}000$ s/mm^2). Sagittal 3D T1-weighted, axial T1-weighted spin echo, and axial and coronal 2D T2*-weighted gradient echo scans were also obtained but are not directly relevant to this study.

The structural T1 and FLAIR images were reviewed by a board certified radiologist (JRS or MKSH) who determined whether any visible trauma-related intracranial pathology was present. Common pertinent MRI pathologies that were coded included number and location of susceptibility and T2 hyperintense foci, encephalomalacia, and extra-axial collections.

Tract-based spatial statistics and randomize. The TBSS (Smith et al., 2006) and randomize (Winkler, Ridgway, Webster, Smith, & Nichols, 2014) part of the FMRIB Software Library (FSL, Analysis Group, FMRIB, Oxford, UK) (Smith et al., 2004) were used for comparisons of FA, MD, AD, and RD. DTI sequences with poor field-of-view resulting in significant deficits in whole brain coverage or artifacts were not considered in the analysis. Motion and artifacts in the diffusion data were corrected using affine registration of all gradient volumes with the first $b = 0$ volume (FLIRT; FMRIB Software Library, Oxford, UK), and gradient directions were compensated for rotations (Landman et al., 2007). This was followed by creation of a manual brain mask based on the first $b = 0$ image using 3D Slicer version 2.7 (Gering et al., 2001). Voxel-based comparisons (on the TBSS skeleton using randomize) of FA, MD, AD, and RD were performed using FSL Version 4.1.9 (Smith et al., 2006). Briefly, individual FA maps were nonlinearly registered via FSL-FNIRT to the Montreal Neurological Institute International Consortium Brain Mapping (ICBM)-152 template provided by FSL, followed by creation of a mean FA skeleton. Individual FA values were then projected onto this mean skeleton. MD, AD, and RD values were projected onto the same template using the previously created FA transformation. FA threshold was set to 0.35 and the number of permutations was set at 5,000. The conservative threshold of 0.35 was chosen based on a visual inspection of the mean TBSS skeleton and represented the best qualitative compromise between skeletal continuity and peripheral white-matter inclusion. Threshold-free cluster enhancement with correction for family wise error rate was employed. The $p < .05$ T-contrast maps were projected on the mean FA images. To identify which specific anatomical areas were implicated, the mean FA skeleton and contrast map were overlaid with the Johns Hopkins University (JHU) ICBM-DTI-81 white-matter label atlas (Hua et al., 2008; Mori, Wakana, Nagai-Poetscher, & va Zigl, 2005; Wakana et al., 2007).

FSL statistics were then used to compute the mean FA values for each individual for each of the ROIs on the mean FA skeleton. Mean values for MD, AD, and RD were done similarly. Forty-eight individual ROIs were identified according to the JHU ICBM-DTI-81 white-matter labels atlas (Hua et al., 2008; Mori et al., 2005; Wakana et al., 2007).

The ROIs from the ICBM-DTI-81 atlas included the (a) genu, body, and splenium of corpus callosum; (b) pontine crossing tract, fornix, and middle cerebellar peduncle; and (c) two unilateral symmetrical ROIs (left/right) each for the corticospinal tract, medial lemniscus, inferior cerebellar peduncle, superior cerebellar peduncle, cerebral peduncle, anterior limb of internal capsule, posterior limb of internal capsule, retrolenticular part of internal capsule, anterior corona radiata, superior corona radiata, posterior corona radiata, posterior thalamic radiation, sagittal stratum, external capsule, cingulum (cingulate gyrus), cingulum (hippocampus), fornix/stria terminalis, superior longitudinal fasciculus, superior fronto-occipital fasciculus, uncinate fasciculus, and tapetum.

Due to the large number of ROIs, four summary scores were calculated for each participant and used in all statistical analyses. The four summary scores represent the number of ROIs with FA, MD, AD, and RD values that fell below/above a specified cutoff score for each participant. Cutoff scores were identified by calculating the means and *SD* for FA, MD, AD, and RD values in each of the 48 ROIs based on DTI of 36 participants who were recruited for this study, that had sustained an orthopedic injury, but not a TBI. FA values that were >2 *SD*s below the mean, and MD, AD, and RD values that were >2 *SD*s above the mean, were classified as reflecting an ROI with "reduced white-matter integrity" (i.e., abnormal score).

Results

Demographic and Injury Characteristics

Descriptive statistics and group comparisons (using ANOVA and χ^2 analyses) of demographic and injury characteristics are presented in Table 1 (continuous variables) and Table 2 (categorical variables). In the MTBI group, there were no significant differences between the PCS-present and PCS-absent group for GCS scores, duration of LOC, duration of PTA, intracranial abnormality on day-of-injury CT scans, or intracranial abnormality on MRI scans 6–8 weeks postinjury (range: $p = .233–.999$). When comparing the remaining variables across the three groups (i.e., PCS-present, PCS-absent, and TC), there were no significant effects for age, education, gender, ethnicity, preinjury alcohol use, day-of-injury BAL, mechanism of injury, days tested postinjury, current intellectual ability, or estimated premorbid intellectual ability (all $p > .05$).

There was a significantly greater proportion of women in the PCS-present group (45.0%) compared with men (21.2%; $p = .043$). There was a significantly greater proportion of individuals who were intoxicated at the time of injury in the PCS-absent group (76.0%) compared with those who were sober (52.4%; $p = .042$). The effect sizes (phi-coefficient; φ) for these two findings were relatively small (i.e., gender: $\varphi = 0.24$; intoxication: $\varphi = 0.22$). Further, the PCS-absent group had a significantly higher level of education, and higher BALs at the time of injury, compared with the TC group (both $p < .05$, $d = 0.51$ and 0.50, respectively).

Neuropsychological Measures

Descriptive statistics, group comparisons, and Cohen's effect sizes (Cohen, 1988) for the self-reported symptoms and neurocognitive measures, by group, are presented in Table 3. For the *self-reported symptoms*, there were significant main effects (using Kruskal–Wallis *H* tests due to non-normal distribution) for the BC-PSI total, BAI total, and BDI-II total scores. As expected, pairwise comparisons (using Mann–Whitney *U*-tests) revealed that the PCS-present group had higher total scores on the BC-PSI, BAI, and BDI-II compared with both the PCS-absent group ($d = 1.63–1.89$ [Of course, the significant difference between the PCS-present and PCS-absent group for the BC-PSI total score is not meaningful. This group difference is a direct consequence of group classification. As such, the Cohen's effect size for this comparison is not reported here.], very large effect sizes) and TC group ($d = 1.22–2.46$, very large effect sizes). There were no significant differences, or substantial effect sizes, when comparing the PCS-absent group and TC group across the three measures.

For the *neurocognitive* variables, there were no significant main effects (using ANOVA) for the NAB Total Index ($p = .761$) or for the five NAB Indexes (range: $p = .138–.810$). Pairwise comparisons revealed no significant differences between groups, though there were a number of meaningful effect sizes. There was a trend for the PCS-present group to have better scores on the Language Index compared with the PCS-absent group ($d = 0.50$, medium effect size). There was a trend for the PCS-absent group to have better scores on the Attention, Memory, and Language Indexes compared with the TC group ($d = 0.25–0.34$, small–medium effect sizes).

Comparison of the prevalence of the number of low neurocognitive scores was undertaken by considering all 23 individual NAB measures simultaneously. The cumulative percentages of the number of low scores (using <16th and <10th percentile

Table 1. Descriptive statistics, group comparisons, and effect sizes of demographic and injury severity characteristics (continuous variables) by group

	1. Mild TBI: PCS-absent		2. Mild TBI: PCS-present		3. Trauma control			Cohen's effect size		
	M	*SD*	*M*	*SD*	*M*	*SD*	*p*	1 versus 2	1 versus 3	2 versus 3
Age (years)	34.1	11.3	34.1	10.4	31.6	10.2	.521	0.01	0.23	0.25
Education (years)	15.3	2.1	14.4	2.3	14.2	2.0	.055	0.40	0.51_a	0.09
Day-of-injury BAL	17.5	25.6	17.8	26.5	6.7	16.1	.074	0.01	0.50_a	0.56
Days tested postinjury	46.8	6.5	46.7	5.5	46.2	5.7	.920	0.02	0.09	0.08
Lowest GCS >30 min	14.4	0.7	14.4	0.7	—	—	.999	0.01	—	—
RIST Index	110.3	9.6	107.8	8.0	106.9	10.9	.271	0.27	0.33	0.09
Premorbid IQ (WTAR)	107.6	7.1	106.2	7.4	107.6	6.9	.713	0.20	0.00	0.21

Notes: $N = 108$ (mild TBI PCS-absent, $n = 52$; mild TBI PCS-present, $n = 20$; TC, $n = 36$). BAL = blood alcohol level; GCS = Glasgow Coma Scale; RIST = Reynolds Intellectual Screening Test; IQ = intelligence quotient; WTAR = Wechsler Test of Adult Reading.
Significant pairwise comparisons: [a]$p < .05$.

Table 2. Descriptive statistics and group comparisons of demographic and injury severity characteristics (categorical variables) by group

	Mild TBI: PCS-absent		Mild TBI: PCS-present		Trauma control		χ^2
	N	%	*n*	%	*n*	%	
Gender							
Men	41	78.8[a]	11	55.0[a]	26	72.2	0.129
Women	11	21.2[a]	9	45.0[a]	10	27.8	
Ethnicity							
Caucasian	44	84.6	15	75.0	30	83.3	0.634
Asian/East-Indian/other	8	15.4	5	25.0	6	16.7	
Mechanism of injury							
MVA	21	40.4	8	40.0	14	38.9	0.990
Non-MVA	31	59.6	12	60.0	22	61.1	
Preinjury alcohol[1]							
Low-moderate	17	32.7	3	15.0	12	33.3	0.283
Heavy	35	67.3	17	85.0	24	66.7	
Day-of-injury BAL							
Sober (<21 mmol/l)	33	63.5[b]	13	65.0	30	83.3[b]	0.113
Intoxicated (≥21 mmol/l)	19	36.5[b]	7	35.0	6	16.7[b]	
LOC							
None	3	5.8	2	10.0	—	—	0.527[‡]
Transient	14	26.9	2	10.0	—	—	
1–30 min	35	67.3	16	80.0	—	—	
PTA							
<15 min	5	9.6	4	20.0	—	—	0.233
>15 min	47	90.4	16	80.0	—	—	
GCS							
15	27	51.9	10	50.0	—	—	0.884
13–14	25	48.1	10	50.0	—	—	
DOI CT scan							
Normal	39	75.0	15	75.0	—	—	0.826
Abnormal	12	23.1	4	20.0	—	—	
Not ordered	1	1.9	1	5.0	—	—	
DOI CT or 6-week MRI							
Normal	26	50.0	12	60.0	—	—	0.446
Abnormal	26	50.0	8	40.0	—	—	
#MRI Sus foci							
None	29	55.8	14	70.0	—	—	0.443[†]
1	5	9.6	1	5.0	—	—	
2–5	7	13.5	1	5.0	—	—	
>5	11	21.2	4	20.0	—	—	
#MRI T2 foci							
None	37	71.2	15	75.0	—	—	0.968[†]
1	7	13.5	2	10.0	—	—	
2–5	3	5.8	2	10.0	—	—	
>5	5	9.6	1	5.0	—	—	

Notes: $N = 108$ (mild TBI PCS-absent, $n = 52$; mild TBI PCS-present, $n = 20$; TC, $n = 36$). CT = computed tomography; GCS = Glasgow Coma Scale; PTA = posttraumatic amnesia; LOC loss of consciousness; TBI = traumatic brain injury; MVA = motor vehicle accident; BAL = blood alcohol level.
[1]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 >52 times per year; (b) males: 15 or more drinks per week or 5 or more drinks on a single occasion >52 times per year.
[a]$p = .043$; [b]$p = .042$; [‡]2 × 2 comparison completed by collapsing "Transient" and "1–30 min" categories together; [†]2 × 2 comparison completed by collapsing "None" and "1" categories together, and "2–5" and ">5" categories together.

as cutoff scores) by group are presented in Table 4. Using χ^2 analyses, there were no significant differences in the percentage of patients that had multiple low scores across groups. However, there were a number of notable comparisons that approached significance. Using a <16th percentile cutoff score: (a) 15.0% of PCS-present group had 3 or more low scores, compared with 38.5% of PCS-absent group ($p = .056$), and 33.3% of TC group; and (b) 40.0% of PCS-present group had 2 or more low scores, compared with 66.7% of TC group ($p = .053$), and 57.7% of PCS-absent group. Therefore, there was a trend for the PCS-present group to perform *better* across the battery of neuropsychological tests than the other two groups.

Table 3. Descriptive statistics, group comparisons, and effect sizes for neuropsychological measures: self-report measures and NAB Indexes

	1. Mild TBI: PCS-absent		2. Mild TBI: PCS-present		3. Trauma control			Effect size		
	M	*SD*	*M*	*SD*	*M*	*SD*	*p*	1 versus 2	1 versus 3	2 versu 3
Symptom questionnaires[1]										
BC-PSI total	6.5	4.6	24.3	10.4	4.9	6.5	<.001	n/a[†]	0.30	2.46[c]
BAI total	5.2	4.8	15.5	10.2	5.9	6.6	<.001	1.63[c]	0.13	1.22[c]
BDI-II total	6.1	5.0	19.2	11.7	6.5	7.4	<.001	1.89[c]	0.07	1.41[c]
Neurocognitive[2]										
Total Index	105.5	13.5	107.3	13.6	107.4	13.3	.761	0.13	0.15	0.01
NAB Attention Index	105.7	13.8	104.5	10.3	102.1	13.6	.455	0.10	0.26	0.19
NAB Memory Index	101.5	13.2	103.1	13.4	104.7	11.9	.526	0.12	0.25	0.13
NAB Language Index*	100.1	14.8	108.6	22.8	105.7	18.8	.138	0.50	0.34	0.14
NAB Spatial Index*	107.5	16.0	107.3	15.2	110.0	14.2	.714	0.01	0.16	0.19
NAB Executive Index*	106.9	15.9	104.5	14.9	106.8	13.7	.810	0.16	0.01	0.16

Notes: $N = 108$ (mild TBI PCS-absent, $n = 52$; mild TBI PCS-present, $n = 20$; TC, $n = 36$); *Cohen's (1988) effect size (*d*): small (0.20), medium (0.50), and large (0.80). BAI = Beck Anxiety Inventory; BDI-II = Beck Depression Inventory-Second Edition; BC-PSI = British Columbia Postconcussion Inventory; NAB = Neuropsychological Assessment Battery.

[1]Group comparisons for the neurobehavioral measures were undertaken using Kruskal–Wallis *H* tests (across three groups) and Mann–Whitney *U* tests (pairwise comparisons) due to non-normal distribution of scores. [2]Group comparisons for the neurocognitive measures were undertaken using ANOVA.

Significant pairwise comparisons: [a]$p < .05$; [b]$p < .01$; [c]$p \leq .001$; [†]Data not reported because comparison is not meaningful. This variable was used for group classification. *Prorated Index scores.

Table 4. Base rate of low neurocognitive scores by group

Number of Low Scores	<16th percentile						<10th percentile					
	1. MTBI PCS-absent (%)	2. MTBI PCS-present (%)	3. Trauma ctrl (%)	Percent diff. (%)			1. MTBI PCS-absent (%)	2. MTBI PCS-present (%)	3. Trauma ctrl (%)	Percent diff. (%)		
				1 versus 2	1 versus 3	2 versus 3				1 versus 2	1 versus 3	2 versus 3
9 low scores	—	—	2.8	—	2.8	2.8	—	—	—	—	—	—
8 or more	1.9	—	2.8	1.9	0.9	2.8	—	—	2.8	—	2.8	2.8
7 or more	3.8	5.0	2.8	1.2	1.0	2.2	—	5.0	2.8	5.0	2.8	2.2
6 or more	5.8	5.0	2.8	0.8	3.0	2.2	—	5.0	2.8	5.0	2.8	2.2
5 or more	13.5	10.0	11.1	3.5	2.4	1.1	1.9	5.0	2.8	3.1	0.9	2.2
4 or more	28.8	10.0	25.0	18.8	3.8	15.0	9.6	5.0	8.3	4.6	1.3	3.3
3 or more	38.5	15.0	33.3	23.5	5.2	18.3	23.1	10.0	16.7	13.1	6.4	6.7
2 or more	57.7	40.0	66.7	17.7	9.0	26.7	46.2	25.0	38.9	21.2	7.3	13.9
1 or more	76.9	85.0	77.8	8.1	0.9	7.2	65.4	55.0	58.3	10.4	7.1	3.3
0 scores	100	100	100	—	—	—	100	100	100	—	—	—

Notes: $N = 108$ (mild TBI PCS-absent, $n = 52$; mild TBI PCS-present, $n = 20$; TC, $n = 36$).

Diffusion Tensor Imaging

Tract-based spatial statistics analysis. The TC group was compared with the PCS-absent group on DTI measures of FA, MD, AD, and RD using TBSS. There were no statistically significant differences (using *t*-tests) between the groups in FA, MD, AD, or RD at the $p < .05$ level.

TBSS comparisons between the PCS-present group and the TC group revealed multiple areas of significant differences (using *t*-tests) in MD and RD. RD was significantly increased ($p < .05$) in the PCS-present group in widespread areas including the genu, body, and splenium of the corpus callosum; bilateral anterior, superior, and posterior corona radiata; bilateral superior longitudinal fasciculus; bilateral cingulum; bilateral posterior thalamic radiations; bilateral anterior limb of the internal capsule; and bilateral external capsule (see Fig. 1). MD values were also significantly increased ($p < .05$) in the PCS-present group in the genu and body of the corpus callosum, bilateral superior corona radiata, right anterior corona radiata, right anterior and posterior limb of the internal capsule, and the right superior longitudinal fasciculus (see Fig. 2). No significant differences were observed for AD values, although a trend ($p < .10$) of decreased FA in the PCS+ group was noted in multiple regions (data not shown).

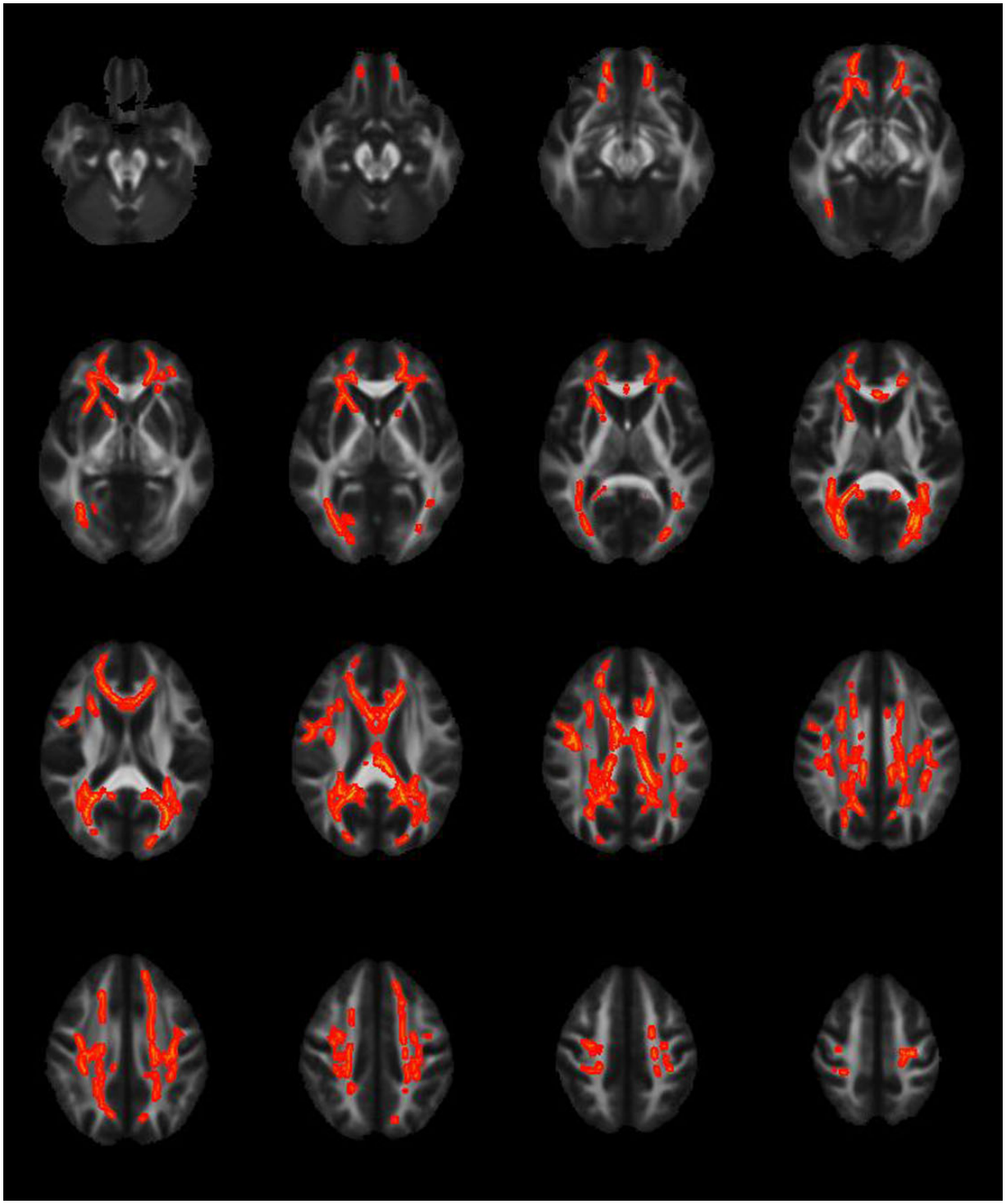

Fig. 1. Tract-based spatial statistics lightbox comparing MTBI-PCS-present patients and controls on RD. Voxels highlighted in yellow/orange indicated areas of significant increase in RD at the $p < .05$ level in the MTBI-PCS-present patients. Neuroanatomical areas where significant increases were noted include the genu, body, and splenium of the corpus callosum, bilateral anterior, superior and posterior corona radiata, bilateral superior longitudinal fasciculus, bilateral cingulum, bilateral posterior thalamic radiations, bilateral anterior limb of the internal capsule, and bilateral external capsule.

The PCS-absent group was then compared with the PCS-present group on the four DTI indices. There were no statistically significant differences in FA, MD, AD, or RD. In summary, TBSS revealed significant white-matter differences between the PCS-present group and the TC group. There were no significant differences between the PCS-absent group and the TC group, or between the two MTBI groups.

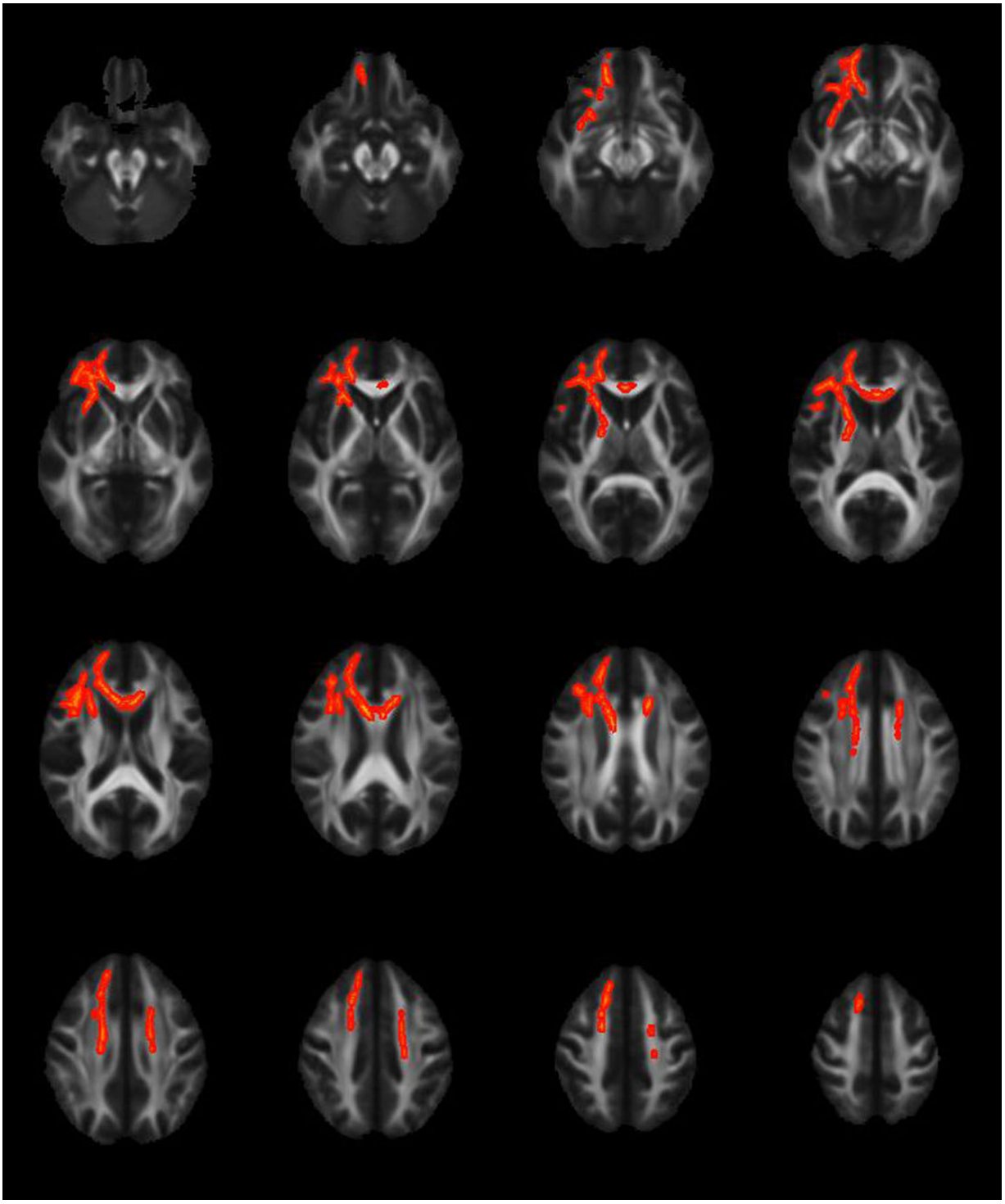

Fig. 2. Tract-based spatial statistics lightbox comparing MTBI-PCS-present patients and controls on MD. Voxels highlighted in yellow/orange indicated areas of significant increase in MD at the $p < .05$ level in the MTI-PCS-present group. Neuroanatomical areas where significant increases were observed included genu and body of the corpus callosum, bilateral superior corona radiata, right anterior corona radiata, right anterior and posterior limb of the internal capsule and the right superior longitudinal fasciculus.

Region of interest analyses. An atlas-based multivariate ROI analysis, based on 48 regions, was conducted by determining the number of abnormal areas of white matter in each individual as defined by mean DTI values that were >2 *SD*s from the means of the TC group. Descriptive statistics, group comparisons, and Cohen's effect sizes (Cohen, 1988) for the number of abnormal

FA, AD, RD, and MD brain regions, by group, are presented in Table 5. There were no significant main effects (Kruskal–Wallis *H* tests) for the number of regions with abnormal FA, AD, RD, or MD across the three groups. However, pairwise comparisons (Mann–Whitney *U* tests) revealed that participants in the PCS-present group had a statistically ($p < .05$) greater number of locations with abnormal RD and MD compared with the TC group ($d = 0.36$ [small–medium effect size] and $d = 0.56$ [medium effect size], respectively). Although not statistically significant ($p = 0.056$), there was also a medium effect size ($d = 0.45$) found for the number of regions with abnormal FA between these two groups (i.e., PCS-present >TC). Similarly, there was a medium effect size ($d = 0.49$) found for the number of regions of abnormal MD between the TC group and the PCS-absent group. There was a non-significant trend for the PCS-absent group to have a greater number of abnormal MD regions compared with the TC group ($p = .073$). There were no significant differences when comparing the number of abnormal FA, AD, RD, or MD scores across the PCS-present and PCS-absent groups. The largest effect sizes were found for FA and AD ($d = 0.25$ and 0.23, respectively) between these groups.

The cumulative percentages of the number of abnormal FA, AD, RD, and MD regions by group are presented in Tables 6 and 7. Using χ^2 analyses, there were significant pairwise comparisons when comparing the PCS-present and TC groups on FA, RD, and MD, but not AD. For FA, the proportion of the PCS-present group that had two or more (50.0%) abnormal areas was significantly greater ($p = .033$) compared with the TC group (22.2%). Similarly, the proportion of the PCS-present group that had three or more (35.0%) abnormal areas was significantly greater ($p = .041$; Fisher's exact test) compared with the TC group (11.1%). For RD, there was a statistically greater proportion of the PCS-present group that had one or more abnormal areas (65.0%, $p = .038$) and two or more abnormal areas (50.0%, $p = .008$) when compared with the TC group (36.1% and 16.7%, respectively). For MD, the

Table 5. Descriptive statistics, group comparisons[1], and effect sizes for the number of abnormal ROIs

	1. Mild TBI: PCS-absent		2. Mild TBI: PCS-present		3. Trauma control			Effect size		
	M	*SD*	*M*	*SD*	*M*	*SD*	*p*	1 versus 2	1 versus 3	2 versus 3
Fractional anisotropy	1.5	2.7	2.2	2.9	1.1	2.3	.153	0.25	0.17	0.45
Axial diffusivity	1.4	2.1	1.0	1.5	0.9	1.4	.812	0.23	0.25	0.00
Radial diffusivity	2.1	4.0	2.7	4.9	1.3	3.3	.064	0.13	0.21	0.36*
Mean diffusivity	2.0	3.3	2.2	4.5	0.7	1.5	.084	0.05	0.49	0.56*

Notes: $N = 108$ (mild TBI PCS-absent, $n = 52$; mild TBI PCS-present, $n = 20$; TC, $n = 36$); *Cohen's (1988) effect size (*d*): small (0.20), medium (0.50), and large (0.80). ROI = region of interest; TBI = traumatic brain injury.

[1]Group comparisons for the neurobehavioral and neuroimaging measures were undertaken using Kruskal–Wallis *H* tests (across three groups) and Mann–Whitney *U* tests (pairwise comparisons) due to non-normal distribution of scores: *$p < .05$.

Table 6. Base rate of the number of abnormal DTI-ROI scores by group—FA and AD

Number of low scores	Fractional anisotropy						Axial diffusivity					
	1. MTBI PCS-absent (%)	2. MTBI PCS-present (%)	3. Trauma ctrl (%)	Percent diff. (%)			1. MTBI PCS-absent (%)	2. MTBI PCS-present (%)	3. Trauma ctrl (%)	Percent diff. (%)		
				1 versus 2	1 versus 3	2 versus 3				1 versus 2	1 versus 3	2 versus 3
15 or more[a]							—	—	—	—	—	—
14 or more	1.9	—	—	—	—	—	—	—	—	—	—	—
13 or more	1.9	—	—	—	—	—	—	—	—	—	—	—
12 or more	1.9	—	2.8	—	0.9	—	—	—	—	—	—	—
11 or more	1.9	5.0	2.8	3.1	0.9	2.2	1.9	—	—	—	—	—
10 or more	1.9	5.0	2.8	3.1	0.9	2.2	1.9	—	—	—	—	—
9 or more	3.8	5.0	2.8	1.2	1.0	2.2	1.9	—	—	—	—	—
8 or more	5.8	5.0	2.8	0.8	3.0	2.2	1.9	—	—	—	—	—
7 or more	7.7	10.0	2.8	2.3	4.9	7.2	1.9	—	—	—	—	—
6 or more	7.7	10.0	2.8	2.3	4.9	7.2	1.9	5.0	—	3.1	—	—
5 or more	9.6	15.0	8.3	5.4	1.3	6.7	9.6	5.0	5.6	4.6	4.0	0.6
4 or more	13.5	20.0	8.3	6.5	5.2	11.7	17.3	5.0	8.3	12.3	9.0	3.3
3 or more	15.4	35.0	11.1	19.6	4.3	23.9	23.1	10.0	8.3	13.1	14.8	1.7
2 or more	32.7	50.0	22.2	17.3	10.5	27.8	30.8	25.0	25.0	5.8	5.8	0
1 or more	46.2	60.0	38.9	13.8	7.3	21.1	48.1	45.0	47.2	3.1	0.9	2.2
0 scores	100.0	100.0	100.0	0	0	0	100.0	100.0	100.0	0	0	0

Notes: $N = 108$ (mild TBI PCS-absent, $n = 52$; mild TBI PCS-present, $n = 20$; TC, $n = 36$).

[a]Table has been limited to 15 or more scores.

Table 7. Base rate of the number of abnormal DTI-ROI scores by group—RD and MD

Number of low scores	Radial diffusivity						Mean diffusivity					
	1. MTBI PCS-absent (%)	2. MTBI PCS-present (%)	3. Trauma ctrl (%)	Percent diff. (%)			1. MTBI PCS-absent (%)	2. MTBI PCS-present (%)	3. Trauma ctrl (%)	Percent diff. (%)		
				1 versus 2	1 versus 3	2 versus 3				1 verusu 2	1 versus 3	2 versus 3
15 or more[a]	1.9	5.0	2.8	3.1	0.9	2.2	1.9	5.0	—	3.1	1.9	—
14 or more	1.9	5.0	2.8	3.1	0.9	2.2	1.9	5.0	—	3.1	1.9	—
13 or more	1.9	5.0	2.8	3.1	0.9	2.2	1.9	5.0	—	3.1	1.9	—
12 or more	1.9	5.0	2.8	3.1	0.9	2.2	1.9	5.0	—	3.1	1.9	—
11 or more	5.8	5.0	2.8	0.8	3.0	2.2	3.8	5.0	—	1.2	3.8	—
10 or more	5.8	5.0	5.6	0.8	0.2	0.6	3.8	5.0	—	1.2	3.8	—
9 or more	5.8	5.0	5.6	0.8	0.2	0.6	5.8	5.0	—	0.8	5.8	—
8 or more	9.6	5.0	5.6	4.6	4.0	0.6	7.7	5.0	—	2.7	7.7	—
7 or more	9.6	5.0	5.6	4.6	4.0	0.6	7.7	5.0	2.8	2.7	4.9	2.2
6 or more	11.5	10.0	5.6	1.5	5.9	4.4	13.5	10.0	2.8	3.5	10.7	7.2
5 or more	15.4	15.0	8.3	0.4	7.1	6.7	19.2	10.0	2.8	9.2	16.4	7.2
4 or more	17.3	15.0	8.3	2.3	9.0	6.7	23.1	10.0	5.6	13.1	17.5	4.4
3 or more	19.2	30.0	11.1	10.8	8.1	18.9	25.0	15.0	11.1	10.0	13.9	3.9
2 or more	34.6	50.0	16.7	15.4	17.9	33.3	32.7	40.0	16.7	7.3	16.0	23.3
1 or more	50.0	65.0	36.1	15.0	13.9	28.9	46.2	60.0	30.6	13.8	15.6	29.4
0 scores	100.0	100.0	100.0	0	0	0	100.0	100.0	100.0	0	0	0

Notes: $N = 108$ (mild TBI PCS-absent, $n = 52$; mild TBI PCS-present, $n = 20$; TC, $n = 36$)
[a]Table has been limited to 15 or more scores.

proportion of the PCS-present group that had one or more (60.0%) abnormal brain regions was significantly greater ($p = .032$) compared with the TC group (30.6%).

There were some significant differences when comparing the PCS-absent and TC groups on MD, but not FA, RD, and AD. There was a statistically greater proportion of the PCS-absent group that had four or more abnormal areas on MD (23.1%, $p = .037$; Fisher's exact test) and five or more abnormal areas on MD (19.2%, $p = .024$; Fisher's exact test) compared with the TC group (5.6% and 2.8%, respectively). There was a nonsignificant trend ($p = .063$) towards a greater proportion of the PCS-absent group to have two or more (34.6%) brain areas with abnormal RD compared with the TC group (16.7%).

There were no significant differences when comparing the PCS-present and PCS-absent groups for FA, RD, MD, and AD. There was, however, a nonsignificant trend ($p = .066$) towards a greater proportion of the PCS-present group to have three or more (35.0%) abnormal areas on FA compared with the PCS-absent group (15.4%).

Extended region of interest analyses. Based on the results of the TBSS analyses, further exploratory multivariate ROI analyses were undertaken using only those DTI metrics and ROIs that were identified as significantly different between some groups (i.e., 19 ROIs for RD [see Fig. 1], and 8 ROIs for MD [see Fig. 2]). The number of abnormal areas of white matter was calculated for each individual across the select ROIs and was compared across the three groups. There were significant main effects (Kruskal–Wallis H tests) for the number of abnormal RD regions ($p = .029$), but not MD regions ($p = .131$). Pairwise comparisons (Mann–Whitney U tests) revealed that participants in both the MTBI groups had a significantly greater ($p < .05$) number of abnormal RD regions (i.e., PCS-absent: $M = 0.9$, $SD = 2.1$; PCS-present: $M = 1.5$, $SD = 3.6$) compared with the TC group ($M = 0.5$, $SD = 1.8$; $d = 0.22$ and 0.39, respectively). There were no significant differences between the PCS-present and PCS-absent groups ($p > .05$, $d = 0.20$, small effect size).

Examination of the cumulative percentages of the number of brain regions with abnormal RD and MD by group (data not shown; available on request from RTL) revealed no significant pairwise differences across the three groups for the percentage of patients that had multiple abnormal MD or RD regions. The one exception to this was for RD. The proportion of the PCS-present group (45.0%) and PCS-absent group (30.8%) that had one or more abnormal RD regions was significantly higher ($p < .05$) compared with the TC group (11.1%). There were no significant differences between the PCS-present and PCS-absent groups.

Prediction of PCS-Present versus PCS-Absent Groups

To examine which factors provide the most unique contribution towards the prediction of postconcussion symptom reporting, logistic regression analyses were undertaken to determine if select factors could identify participants in the PCS-present versus

PCS-absent groups. Factors were selected were as follows: (i) gender, (ii) education, (iii) BDI-II 10-item total score, (iv) BAI total score, and (v) the total number of abnormal FA and MD scores combined. For the logistic regression analysis, all five factors were entered simultaneously as the independent variables and group membership as the dependent variable.

Only two of the six variables were significant predictors of group membership (depression [$p = .043$] and BAI total [$p = .043$]) accounting for 52.1% of the variance (Nagelkerke R^2; $p < .001$). Overall, 83.3% of participants were correctly classified using depression and BAI total scores alone. However, classification rates were substantially higher when predicting the PCS-absent group (94.2%) compared with the PCS-present group (55.0%). No DTI metrics entered the prediction model.

Discussion

The purpose of this study was to examine the relationship between DTI and postconcussion symptom reporting following MTBI. There were three hypotheses. First, compared with the TC group, patients in both the MTBI groups would (a) report a greater number of depression, anxiety, and postconcussion symptoms; (b) perform comparably on neurocognitive measures; and (c) have reduced white-matter integrity in the brain as measured by DTI metrics. Second, in the MTBI group, patients who met ICD-10 criteria for PCS would report a greater number of depression and anxiety symptoms compared with those who did not meet criteria for PCS. Third, in the MTBI group, there would be no differences across all neurocognitive measures and DTI metrics when comparing those patients who are classified as PCS-present versus PCS-absent.

MTBI versus Trauma Controls

Consistent with the *first hypothesis*, compared with the TC group, the PCS-present group (a) reported a greater number of depression, anxiety, and postconcussion symptoms; (b) had multiple regions of the brain with significant differences in MD and RD using TBSS (but not AD or FA); and (c) had a greater number of brain regions with abnormal RD and MD (but not AD or FA) using ROI analyses. In contrast, these differences were not found when comparing the PCS-absent and TC groups. Although the PCS-absent group had a greater number of abnormal MD regions compared with the TC group, there were no group differences when comparing (a) all DTI measures using TBSS, (b) FA, AD, and RD measures using ROI analyses, and (c) measures of depression, anxiety, and postconcussion symptoms.

Fractional anisotropy is a representation of the directional coherence (anisotropy) of water diffusion, and MD represents the average total diffusion of water within a particular voxel, irrespective of direction. Mean diffusivity values generally increase, and FA values decrease in response to white-matter injury (Hulkower, Poliak, Rosenbaum, Zimmerman, & Lipton, 2013). Radial diffusivity represents the diffusion of water perpendicular to the axon, and thus is thought to be sensitive to processes such as demyelination (Mac Donald, Dikranian, Bayly, Holtzman, & Brody, 2007). AD represents the diffusivity parallel to the axon and hence changes in AD are thought to indicate axonal compromise (Mac Donald et al., 2007). Therefore, an explanation for our results is that the PCS+ group showed evidence of white-matter compromise (increased MD) mainly via a membrane integrity mechanism (increased RD). This is consistent with other research showing increased RD in the subacute period (Hulkower et al., 2013; Mac Donald et al., 2007).

TBSS revealed a nonsignificant trend to lower FA values in the PCS+ groups. Given that increases in mean and RD generally result in lower FA (because they are interrelated mathematical derivations), the nonsignificant findings for FA values could result from insufficient sample size, or simply that MD is a more sensitive measure of white-matter integrity during the subacute period, as has been observed in other studies (Hulkower et al., 2013).

It is possible that some of the differences in DTI metrics in this study between the PCS-present and TC groups could be related, at least in part, to the influence of depression and anxiety on physiology, rather than differences in the microstructure of white-matter attributable to differences in biomechanical forces applied to the brain. Numerous studies have shown that depression and other affective disorders are associated with white-matter abnormalities as identified by DTI. In a systematic review of DTI studies in affective disorders, Sexton, Mackay, and Ebmeier (2009) concluded that "21 of 27 studies found significantly lower [fractional] anisotropy in subjects with affective disorders compared to control subjects" (p. 814).

Nonetheless, the DTI results in this study are relatively consistent with some past studies that have compared controls with MTBI groups divided into PCS-present/absent groups. For example, Messé et al. (2011) found that MTBI patients who were classified as having persistent PCS from <1 month to 3 months postinjury (but not those whose symptoms had improved) had higher MD scores compared with a healthy controls in some ROIs (i.e., superior longitudinal fasciculus, corticospinal tract bilaterally, and left anterior thalamic radiation). In another study, Messe et al. (2012) reported that compared with healthy controls, MTBI patients who met criteria for ICD-10 PCS <1 month and 6 months postinjury had a greater number of abnormal brain regions compared with those who did not meet ICD-10 PCS criteria.

Also consistent with the first hypothesis, there were no significant differences on the neurocognitive measures when comparing the TC group with both MTBI groups. This finding was not surprising or unexpected. Patients with MTBI perform poorly on neuropsychological tests in the initial days (e.g., Hughes et al., 2004; Lovell, Collins, Iverson, Johnston, & Bradley, 2004) and up to the first month following the injury (e.g., Levin et al., 1987; Ponsford et al., 2000), but cognitive deficits typically are not seen after 1–3 months (e.g., Gentilini et al., 1985; Ponsford et al., 2000) in prospective group studies. This has been illustrated repeatedly in reviews and meta-analyses (e.g., McCrea et al., 2009; Rohling, Larrabee, & Millis, 2012). In our study, we examined patients at 6–8 weeks postinjury. Although this time period falls in the middle of when we might expect most, but certainly not all, patients to have normal performance on neuropsychological tests; it is our expectation that there would be no measurable group differences on neuropsychological testing at this time.

PCS-Present versus PCS-Absent

In support of the *second hypothesis*, those individuals in the MTBI group who were classified as PCS-present at 6–8 weeks postinjury reported a greater number of depression and anxiety symptoms on the BAI and BDI-II compared with those patients who were classified as PCS-absent. The effect sizes were very large ($d = 1.63$ and 1.89, respectively). Of course, the relationship between postconcussion symptoms and depression and anxiety found here is not new. Many researchers have reported a strong relation between postconcussion symptoms and other self-reported mental health problems. In a military context, the relation between postconcussion symptoms and depression or PTSD symptoms following MTBI is well established (e.g., Lange, Brickel, et al., 2013; Lange, Shewchuk, et al., 2013; Lange et al., 2014). Similarly, in a civilian context, the relationship between postconcussion symptoms and depression and anxiety following MTBI is also well established (Bryant & Harvey, 1999; Garden & Sullivan, 2010).

Consistent with the *third hypothesis*, there were no significant differences between those patients in the MTBI group that were PCS-present versus PCS-absent across all neurocognitive measures and DTI metrics. The DTI results reported in this study are consistent with some research that has also found no group differences in DTI metrics when an MTBI sample is divided into ICD-10 PCS-present versus PCS-absent groups at 3-week postinjury (Waljas et al., 2014) and 6–8 weeks postinjury (Lange et al., 2012). Of course, these results are not consistent with other studies that have reported differences between MTBI groups when divided into PCS-present versus PCS-absent groups at 3 months (Messé et al., 2011) and 6 months (Hartikainen et al., 2010; Messe et al., 2012) postinjury. Collectively, based on these results, one might argue that differences between PCS-present versus PCS-absent groups are more likely to be detectable after 3 months following injury. However, contrary to this, in a longitudinal study by Messe et al. (2012), these authors concluded that there were "significant structural differences" found between PCS-present versus PCS-absent groups at <1 month postinjury, but less at 6-month postinjury.

Limitations

This study has several methodological limitations. First, TBSS is a conservative DTI approach that we chose because we had no *a priori* hypothesis that some regions would be affected over others. Other approaches that interrogate specific regions, such as user-defined track selection or probabilistic tractography may indeed be more sensitive than a full brain analysis, if driven by a well-informed hypothesis. Second, this study does not address medium- or long-term postconcussion symptom reporting, nor did 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. Third, although the focus of this study was on the relationship between postconcussion symptom reporting and DTI, it is not possible to exclude the influence of other factors that may have had a contributory role (e.g., persistent pain [Smith-Seemiller, Fow, Kant, & Franzen, 2003], "good old days" bias [Gunstad & Suhr, 2001], diagnosis threat [Suhr & Gunstad, 2002a], etc.). However, we did include TC patients (rather than a healthy control group) because these patients tend to share more preinjury characteristics to their head-injured counterparts (Dikmen, Machamer, Winn, & Temkin, 1995). As such, the potential bias of these factors influencing the results in one group, but not the other, is mitigated. Fourth, there were a greater proportion of women in this sample who met ICD-10 criteria for PCS compared with men. Nearly, 1 in 2 women met symptom criteria for PCS compared with 1 in 5 men. This is consistent with research that has found increased postconcussion symptom reporting in women compared with men (e.g., Meares et al., 2008). It is possible that sex differences influenced the results of this study. Fifth, 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 (Sosin, Sniezek, & Thurman, 1996). Our patients had clear evidence of an MTBI. The vast majority of our patients underwent day-of-injury CT scanning and a substantial minority had a day-of-injury intracranial abnormality. Therefore, the patient sample used in this study represents a minority of the more seriously injured MTBI population.

Conclusion

Following an MTBI, there is no doubt that many people experience a range of postconcussion symptoms (e.g., headaches, dizziness, fatigue, and cognitive difficulties). These symptoms typically resolve within the first few days, weeks, or months for most people. However, for some people, these symptoms are reported many months or years postinjury. In this study, symptoms of depression and anxiety differentiated patients with MTBIs who met criteria for the postconcussion symptom versus those who did not. In contrast, these groups did not differ on diverse metrics of DTI. These findings once again highlight that there are many factors that can potentially account for postconcussion symptom reporting, even in the first 6–8 weeks of recovery. It has been recommended that postconcussion symptom reporting be viewed from a biopsychosocial perspective (Iverson et al., 2013). That is, there are a diverse range of biopsychosocial factors (i.e., pre-, peri-, and postinjury factors) that can influence the perception and reporting of symptoms long after an MTBI.

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Conflict of Interest

None declared.

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