A Prospective Biopsychosocial Study of the Persistent Post-Concussion Symptoms Following Mild Traumatic Brain Injury

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Abstract

This study examined multiple biopsychosocial factors relating to post-concussion symptom (PCS) reporting in patients with mild traumatic brain injuries (MTBI), including structural (CT and MRI) and microstructural neuroimaging (diffusion tensor imaging; DTI).

Patients with MTBIs completed several questionnaires and cognitive testing at approximately one month (N=126) and one year post injury (N=103). At approximately three weeks post injury, DTI was undertaken using a Siemens 3T scanner in a subgroup (N=71). Measures of fractional anisotropy (FA) were calculated for 16 regions of interest (ROIs) and measures of apparent diffusion coefficient (ADC) were calculated for 10 ROIs. Patients were compared to healthy control subjects.

Using ICD-10 postconcussional syndrome (PCS) criteria and mild or greater symptom reporting, 59% of the MTBI sample met criteria at one month and 38% met criteria at one year. However, 31% of the healthy control sample also met criteria for the syndrome—illustrating a high false positive rate. Significant predictors of ICD-10 PCS at one month were pre-injury mental health problems and the presence of extra-cranial bodily injuries. Being symptomatic at one month was a significant predictor of being symptomatic at one year, and depression was significantly related to PCS at both one month and one year. Intracranial abnormalities visible on MRI were present in 12.1% of this sample, and multifocal areas of unusual white matter as measured by DTI were present in 50.7% (compared to 12.4% of controls). Structural MRI abnormalities and microstructural white matter findings were not significantly associated with greater post-concussion symptom reporting.

The personal experience and reporting of post-concussion symptoms is likely individualized, representing the cumulative effect of multiple variables, such as genetics, mental health history, current life stress, medical problems, chronic pain, depression, personality factors, and other psychosocial and environmental factors. The extent to which damage to the structure of the brain contributes to the persistence of post-concussion symptoms remains unclear.

Key words: cognitive function, diffusion tensor imaging, traumatic brain injury, outcome measures, prospective study

Introduction

It is well established that mild traumatic brain injury (MTBI) is associated with cognitive impairment in the initial days following injury in athletes and civilians,[1-3] and by three months post injury there is substantial recovery and cognitive deficits are no longer present in group studies.[4-8] A minority of patients with MTBIs who undergo day-of-injury computed tomography (CT) show evidence of macroscopic abnormalities [e.g., 5% in patients with a Glasgow Coma Scale Score (GCS) of 15, 20% for those with a GCS of 14, and 30% for those with GCS of 13[9]]. The term complicated MTBI has been used to refer this subgroup of patients who have evidence of trauma-related intracranial abnormality (e.g., hemorrhage, contusion, or edema).[10] Some studies have shown that those with complicated MTBIs, as a group, have worse short-term (i.e., 1 week to 3 months)[11-14] and long-term outcome.[15-17] Some researchers, however, have reported that patients with complicated MTBIs do not report more post-concussion symptoms at one month,[18] three months,[19] or six months[20] following injury than those with uncomplicated MTBIs.

The rate at which people recover subjectively, in regards to post-concussion symptoms, varies from study to study—but it is clear that a substantial minority of people continue to report symptoms at one,[21-23] three,[24-27] six,[28] and 12 months[29-31] following injury. Post-concussion-like symptoms tend to be persistent in some people; many of those who are highly symptomatic at one month will also be highly symptomatic at one year.[21,31,32] Of course, there is considerable individual variability in how people endorse their symptoms over time.[27,31,33] There is even evidence that some people who do not report significant post-concussion symptoms shortly following the injury report post-concussion-like symptoms many months or year post-injury.[33,34] The situation is complicated because these symptoms are non-specific; they are reported fairly frequently by healthy adults[35,36] and people with chronic pain,[37,38] post-traumatic stress

disorder,[39,40] and depression.[41-46] Therefore, it is not surprising that in clinical practice and research it is difficult to predict the rate at which a person will improve and recover following an MTBI. The etiology of persistent symptoms is likely diverse, multifactorial, and characterized by considerable individual variability. Therefore, a perspective that integrates biological, social, cognitive, affective, and behavioral factors into a biopsychosocial framework might be useful for conceptualizing rapid, typical, or slow recovery in individual patients.[47-53]

The purpose of this study was to adopt a biopsychosocial perspective for examining the natural history of post-concussion symptom reporting using a prospective, longitudinal, inception cohort design. A biopsychosocial approach facilitates the integration and synthesis of a large and diverse literature into a set of specific hypotheses that can be tested on a single large prospective cohort. Numerous clinical and methodological factors that are relevant to studying outcome from MTBI will be controlled or statistically analyzed, such as pre-existing mental health problems,[4,35,54-59] injury severity and structural neuroimaging,[10,13,15,60-62] the nonspecificity of post-concussion-like symptoms,[35,55,56,63] and the role of post-injury mental health.[49,64,65] Researchers have reported that pre-injury psychiatric problems[55,57] are associated with persistent post-concussion symptom reporting in some people. Moreover, brain injuries of all severities are associated with increased risk for developing depression,[41-46] especially in those with pre-existing mental health problems.[66] Therefore, the relationship between depression and post-concussion symptom reporting is important to analyze. Studies examining the relationship between persistent symptom reporting and macrostructural intracranial abnormalities (e.g., complicated vs. uncomplicated MTBI)[11-20] and microstructural changes in white matter (diffusion tensor imaging; DTI) have yielded mixed results. Waljas and colleagues[67] summarized the findings from 50 studies involving DTI in MTBI. They reported that 88% of authors reported

DTI abnormalities associated with MTBI. However, 82% of the studies did not study the relation between the abnormalities and post-concussion symptoms. Most published studies have found a relationship between white matter abnormalities and PCS,[68-74] although some reported no association.[46,67,75]

This prospective study will include diverse outcome measures, including structural (CT and MRI) and microstructural neuroimaging (DTI), cognition, depression, and post-concussion symptom reporting. There are five primary hypotheses. First, patients who sustain complicated MTBIs (i.e., those with trauma-related abnormalities on day of injury CT or subacute MRI), compared to those with uncomplicated MTBIs, will perform more poorly on memory testing and report greater post-concussion symptoms at one month, but not at one year, following injury. Second, patients with pre-existing mental health problems will report greater post-concussion symptoms than those without pre-injury mental health problems following MTBI. Third, post-concussion-like symptoms at both one month and one year following MTBI will have a medium to high correlation with affective symptoms of depression. Fourth, patients with MTBIs will show more areas of abnormality on diffusion tensor imaging (DTI) than control subjects. Finally, patients with abnormalities on DTI will endorse more symptoms than patients with broadly normal DTI findings following MTBI at three weeks but not one year following injury.

Method

Participants

Participants were 126 consecutively enrolled patients who were evaluated in the Emergency Department (ED) of Tampere University Hospital, Finland. All patients fulfilled the Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine[76] and the World Health

Organization (WHO) Collaborating Center Task Force on Mild Traumatic Brain Injury (page 115) criteria for an MTBI[59]). Inclusion criteria were (i) biomechanical force applied to the head, (ii) loss of consciousness, if present, for less than 30 minutes, (ii) GCS score between 13 and 15 after 30 minutes following injury, and (iii) post-traumatic amnesia, if present, of less than 24 hours. Exclusion criteria were: age under 16 or over 65, history of previous major substance abuse, history of psychiatric disorder, or past neurological condition or disease. MTBI patients underwent day-of-injury head computed tomography (CT) and magnetic resonance imaging (MRI) at average 29 days (SD = 19.9 days) post injury. This sample included patients (N=17; 13.5%) who had an intracranial trauma-related abnormality on day-of-injury CT or follow-up MRI (i.e., a complicated MTBI).

The average age of the MTBI sample was 37.8 years (SD = 13.5; Range = 16-64), their average education was 12.6 years (SD = 2.7; Range = 8-22), and 56.3% of the sample was female. At the time of injury, the employment status of the sample was as follows: 67.5% working full time, 2.4% working part time, 15.9% students, 4.0% retired/partly retired, 9.5% unemployed, and 0.8% on sick leave. The percentages of patients with previous MTBIs were as follows: none = 65.1%, one = 32.5%, two = 2.4%. The psychiatric history of this sample was as follows: 90.5% none, 7.1% yes, 2.4% unknown. The mechanisms of injury were as follows: 32.5% motor vehicle accident (MVA), 4.0% pedestrian-MVA, 8.7% sports, 36.5% fall (low), 7.1% fall (high), 7.1% assault, and 4.0% other. Their average GCS score was 14.96 (SD = 0.20, Range = 14-15, 96% = 15). Duration of loss of consciousness (LOC) was as follows: 71.6% no LOC, 12.0% LOC $\leq$ 1 min, 13.8% LOC > 1min $\leq$ 5 min, 1.8% LOC > 5 min $\leq$ 10 min, and 0.9% LOC > 10 min; the average duration of LOC was 0.8 min (SD = 2.2, Range = 0 – 15). Duration of post-traumatic amnesia was as follows: 48% no PTA, 22% PTA $\leq$ 2hours, 30% PTA > 2

hours, average duration of PTA was 196.2 minutes (SD = 353.2 minutes, Range = 0-1440 minutes). The average duration of sick leave after the injury was 42.1 days (SD = 112.1, IQR = 3.0 – 30.5, Range = 0 – 729). Four patients were missing data of duration of sick leave. None of the patients were involved in litigation. All participants were Caucasian. This sample was also used in a recent study examining return to work following MTBI,[77] and a subgroup of this sample was used to examine short-term outcome from uncomplicated MTBI.[67]

Two separate healthy control groups were recruited from the community for the study: (a) a neuroimaging control group, and (b) a neuropsychological control group. The neuroimaging control group initially consisted of 30 age- and gender-matched participants with no history of brain injury, neurological disease, or psychiatric disorders who completed a neuroimaging protocol using MRI with diffusion tensor imaging (DTI). In the control sample, 26.7% (8/30) had incidental MRI findings. Of the 8, 6 participants were excluded due to major incidental findings [e.g., cavernotic angioma with hemosiderin or numerous white matter hyperintensities (e.g., more than 10)]. Twenty-four neuroimaging control subjects were included in the final sample (Age: M=36.6 years, SD=10.1, female 66.7%). Of those 24, two had incidental white matter hyperintensities (8.3%; one had a single nonspecific hyperintensity and the other had two).

The neuropsychological control group consisted of 36 age and sex matched individuals (63.9% female) with no history of head injury or psychiatric disorders. The mean age of the controls was 36.9 years (SD = 13.6 years, Range = 17-61) and their average education was 15.1 (SD = 2.5 years, Range = 8-19) years. The employment status of the control sample was as follows: 64% of the participants were working full time, 33% were full-time students and 3% were unemployed. Participants in the neuropsychological control group completed self-report

measures (e.g., post-concussion symptoms and depression) and a test of verbal learning and memory. The MTBI and control group did not differ on age ($t[160] = .336$, $p = .737$) or gender ($\chi 2 = .654$, $p = .419$). The MTBI group differed from the control group on education ($t[160] = -4.890$, $p = .001$). The mean years of education for MTBI patients and control subjects were 12.6 (SD = 2.7) and 15.1 (SD = 2.5), respectively.

All participants provided written informed consent according to the Declaration of Helsinki. The study protocol was approved by the Ethical Committee of the Tampere University Hospital, Finland

Procedures

All the MTBI patients in this study were recruited from the ED of Tampere University Hospital. Brain CT scans were performed in all patients within 24 hours of admission. For the MTBI group, MRI scanning was conducted between two weeks and two months post injury for the majority of participants (n= 119, 7 individuals missing MRI) (M=29.1 days, SD=19.9 days; IQR = 21.0-32.0 days, Range=1-159 days). MTBI patients participated in an interview and completed several questionnaires at approximately one month (N=126) and one year post injury (N=103). The average number of days from injury to the first interview and questionnaires was 24.1 days (SD = 5.4, Range = 8-38). Most of the patients (n = 103, 82%) were seen for an annual follow-up. This session occurred on average 12.6 months post injury (Mean = 383.8 days, SD = 30.6 days, Range = 316 – 488 days). For the control group, testing was completed as soon as possible following enrolment in the study.

Measures

Neuroimaging. MRI was performed either on a 1.5 Tesla (Magnetom Avanto A TIM system Siemens Medical Solutions, Erlangen, Germany) (n = 37, 29.4%) or a 3T Siemens Trio

(Siemens AG Medical Solutions, Erlangen, Germany) (n = 89, 70.6%) machine. MRI sequences were evaluated by a certified neuroradiologist. The MRI protocol included sagittal T1-weighted 3D IR prepared gradient echo, axial T2 turbo spin echo, conventional axial and high resolution sagittal fluid-attenuated inversion recovery (FLAIR), axial T2*, and axial susceptibility weighted imaging (SWI) series. White matter hyperintensities (WMHI) were recorded from FLAIR sequences. The parameters for FLAIR sequences were TI 2216 ms, TR 7000 ms, TE 87 ms, FOV 199 ×220 ms, matrix 232 ×256, slice/gap 4.0/1.2 mm. The DTI sequence was single-shot diffusion-weighted echo planar imaging. The parameters for DTI were TR 5144 ms, TE 92 ms, FOV 230 mm, matrix 128 ×128, 3 averages, slice/gap 3.0/0.9 mm, voxel dimension 1.8 x 1.8 x 3.0 mm, b-factor 0 and 1000 s/mm^2, and 20 diffusion gradient orientations. A 12-channel head matrix coil was used. Only trauma related findings in CT and MRI were counted as abnormal; minor incidental findings, such as isolated white matter hyperintensities, were not considered as abnormal.

Of the 89 patients who underwent 3T MRI, DTI was acquired on 84 of them. A subset of these subjects (n=13) were excluded due to the presence of major incidental findings (e.g., ischemic lesions, numerous white matter hyperintensities, or enlarged lateral ventricles); 3 for incidental findings on CT, and 10 for incidental findings on MRI. The final subsample consisted of 71 MTBI patients (at one year follow-up n= 60). Those who had 1.5T did not differ from those with 3T on age (p=.106), education (p=.980), PTA (p=.603), RA (p=.858) LOC (p=.723), BDI-II at one month (p=.269), BDI-II at one year (p=.396), AUDIT at one month (p=.170), AUDIT at one year (p=.082), sex (p=.214), previous psychiatric symptoms (p=.726), previous brain injuries (p=.204), or previous diseases (p=.564). There was a significant difference in

duration of time off work: the 1.5T group has a significantly greater number of days off work (mean 87.4, SD=182.4) than the 3T group (mean 23.1, SD=54.5) (t[120]=2.08, p=.044).

Region-of-interest (ROI) based DTI measurements were performed in eight different anatomical locations of each hemisphere and in three locations within the corpus callosum. Quantitative DTI parameters, including apparent diffusion coefficient (ADC) and fractional anisotropy (FA), were calculated symmetrically for multiple ROIs in the pyramidal tract (i.e., basal pons, cerebral peduncle, posterior limb of the internal capsule, corona radiata, and centrum semiovale) and frontobasal area (i.e., uncinate fasciculus, forceps minor, and anterior corona radiata). In the corpus callosum, the ROIs included three regions: the genu, body, and splenium. ROIs were selected on the basis of prior studies that have demonstrated abnormalities on DTI parameters in these areas.[69,70,78-81]

All diffusion parameter analyses were performed by one observer (a physicist with long experience of brain ROI measurements; UH) on a workstation using commercially available software (Neuro 3D; Siemens Medical Solution, Malvern, USA). Circular ROIs were manually placed on color-coded axial fractional anisotropy (FA) maps and automatically transferred on the non-diffusion-weighted b_0 and ADC maps. The ROIs of the corpus callosum were drawn onto the median-line sagittal images. The size of the ROI was modified to the axial structure of each fiber tract. The circular ROIs were centered in the region taking care to avoid border areas, such as overlapping with cerebrospinal fluid spaces and neighboring tracts. The data quality was excellent in most cases, except in certain regions that had artifacts caused by air cavities and fluid flow. Mean values for FA and ADC for each region were calculated from the mean values of the right and left hemispheres.

A reliability study of this method was undertaken using the control sample (n=30).[82] Each ROI was sampled twice by the same rater to evaluate intrarater reliability. Intraclass correlation coefficients (ICCs) were calculated for all FA and ADC using a two-way random-model analysis with absolute agreement. The ICC values were considered as excellent agreement if greater than 0.8, as substantial agreement if they were from 0.60 to 0.79, and as fair/poor agreement if below 0.6. All ROIs that did not met criteria for substantial agreement for intrarater reliability (>0.65) were excluded from the analyses, including the Cerebral Peduncle-ADC (0.19), Centrum Semiovale-FA (0.48), Centrum Semiovale-ADC (0.63), Forceps Minor-ADC (0.64), Anterior Corona Radiata-ADC (0.27), Corpus Callosum Body-FA (0.23), Corpus Callosum-Body-ADC (0.26).

Initially, 19 ROIs were measured and ADC and FA values were calculated symmetrically for each ROI. Based on results from the reliability study, two regions were excluded for FA analysis (Centrum Semiovale, Corpus Callosum Body). Five regions were excluded for ADC analysis (Cerebral Peduncle, Centrum Semiovale, Forceps Minor, Anterior Corona Radiata, and Corpus Callosum Body). The number of ROIs retained for the analysis was 16 ROIs for FA and 10 ROIs for ADC.

Self-Report Questionnaires: Post-concussion symptoms were assessed with the Rivermead Post Concussion Questionnaire (RPSQ).[83] The RPSQ is a 16-item self-report questionnaire that measures the severity of common post-concussion symptoms on a 5-point Likert scale. The patients rated the presence of the symptoms over the past 24 hours on a scale from 0 to 4 (0 = not experienced at all after the injury, 1 = experienced but no more of a problem compared with before the injury, 2 = a mild problem, 3 = a moderate problem, and 4 = a severe

problem). A total score was calculated by adding all items with a score greater than 1. High test-retest reliability has been reported for 7-10 day (r=.90) and 6-month (r= .87) intervals.[83]

Depressive symptoms were assessed using the Beck Depression Inventory-Second Edition (BDI II [84] a 21-item self-report questionnaire). Subjects are asked to rate each item on a four-point scale ranging from zero to three. It should be noted that many symptoms on this questionnaire overlap with post-concussion symptom measured by the RPSQ and clinically it is often not possible to differentiate depression from persistent post-concussion symptoms. Therefore, 10 of the 21 symptoms from the BDI-II, believed to have the least overlap with symptoms of MTBI and being most representative of depression, were selected. These symptoms were: sadness, loss of interest, loss of pleasure, pessimism, past failure, guilt feelings, punishment feelings, self-criticalness, crying, and suicidal thoughts or wishes. In this study, we used the total score which is the sum of all 10 items, giving a range from zero to 30. Higher total scores indicate more severe depressive symptoms.

The Alcohol Use Disorders Identification Test (AUDIT) was used to detect alcohol problems.[85] The AUDIT is a widely used brief screening test to identify persons who have risky drinking, harmful drinking, or alcohol dependence. The AUDIT is a self-report measure that consists of 10 questions. Each of the questions has a set of responses to choose from, and each response has a score ranging from 0 to 4 (questions 1 – 8). Questions 9 and 10 are scored 0, 2, or 4 only. All the response scores are added to create a total score. Total score of $\geq$ 10 on the AUDIT is considered indicative of harmful or hazardous drinking. One subject did not complete this questionnaire.

Neurocognitive measure: The Rey Auditory Verbal Learning Test (RAVLT)[86] was used to assess verbal memory. RAVLT is a widely used test for learning and memory. In this study,

immediate recall (total number of words recalled in trials 1-5) was used. The normative data applied in this study were from Mitrushina and co-workers.[87]

Postconcussion Symptom Classification

Classification of the ICD-10 symptom criteria for the post-concussion syndrome (PCS) was based on the Rivermead Post Concussion Symptoms Questionnaire. We defined the syndrome, based on ICD-10 criteria, two ways: (a) based on mild or greater symptom reporting in each domain, and (b) based on moderate or greater symptom reporting in each domain.

We defined the DSM-IV criteria for postconcussion disorder (PCD) two ways as follows: (a) mild cognitive impairment AND mild or greater report of 3 Category C symptoms AND not having returned to work by one month (30 days); or (b) mild cognitive impairment AND moderate or greater report of 3 Category C symptoms AND not having returned to work by approximately one month (30 days). The methodology of this study did not permit an exact application of the DSM-IV criteria at 3 months because the symptom and cognition data were collected prior to that point in time. In the total sample, 75.4% had returned to work by one month and 93.4% had returned to work by three months following injury. We operationally defined mild cognitive impairment in memory as scoring more than 1.5 standard deviations below the normative mean on the Rey Auditory Verbal Learning Test total score.[87] The RAVLT is recommended as a common data element for TBI research.[88] Using 1.5 standard deviations below the normative mean cut-off score, the percentages of the MTBI sample with low scores were as follows: RAVLT total score = 7.1% at one month following injury and 1.9% at one year. Applying this cut-off to the control sample, the percentages with low scores were as follows: RAVLT total score = 5.6%.

Withdrawal During the Study

Twenty three patients (18.3%) dropped out of the study during the one-year follow-up. Those who did not come to the follow-up (i.e., Attrition group) were compared to those who came to the follow-up (i.e., Follow-up group). The Attrition group did not differ from the Follow-up group on age (p=.205), education (p=.211), AUDIT at one month (p=.397), BDI-II at one month (p=.302), RAVLT total score at one month (p=.113), RPSQ total score at one month (p=.609), gender (p=.342), previous psychiatric symptoms (p=1.0) previous brain injuries (p=.456), abnormal CT findings (p=.206), abnormal MRI findings (p=.737), or duration of time off work (p=.325). There was a significant difference in PTA, retrograde amnesia (RA), and LOC: the Attrition group had a significantly shorter PTA (mean=30.8 minutes, SD=81.5) than the Follow-up group [mean=232.2 minutes, SD=378.7; t(121)=4.85, p<.001]. Also, the Attrition group had a significantly shorter RA (mean=.03 minutes, SD=.11) than the Follow-up group [mean=9.5 minutes, SD=36.5; t(101)=2.61, p=.010]. On LOC, the Attrition group had a significantly shorter duration (mean=.16 minutes, SD=.47) than the Follow-up group [mean=.96 minutes, SD=2.39; t(107)=2.94, p=.004]. Therefore, by traditional injury severity criteria, those who completed the study had more severe MTBIs than those who dropped out.

Results

Complicated Versus Uncomplicated MTBI

The MTBI group's RAVLT total score mean 53.3 (SD=9.3) did not differ from the healthy control's RAVLT total score mean 55.6 (SD=9.0) at one month post injury [t(160)=-1.31, p=.193; Cohen's d=.25] or one year post injury [t(137)=1.04, p=.300; d=.20] (RAVLT total score mean=57.4, SD=9.0 for the MTBI group at one year). Alpha was adjusted for the four primary comparisons for the first hypothesis (.05/4=.0125). The RAVLT total score for those with complicated MTBIs (n=17, mean=55.5, SD=12.8) did not differ from those with

uncomplicated MTBIs (n=109, mean=52.9, SD=8.7) at one month following injury [t(124)=-1.06, p=.299; d=.28]. Similarly, the total score for those with complicated MTBIs (n=15, mean=59.8, SD=10.7) did not differ from those with uncomplicated MTBIs (n=88, mean=57.0, SD=8.7) at one year following injury [t(101)=-1.12, p=.266; d=.31].

Regarding symptoms, the RPSQ total score for those with complicated MTBIs (mean=7.3, SD=6.3) did not differ from those with uncomplicated MTBIs (mean=10.9, SD=11.2) at one month following injury [t(34)=1.92, p=.064; d=.34]. Similarly, the total score for those with complicated MTBIs (mean=4.0, SD=4.3) did not differ from those with uncomplicated MTBIs (mean=7.3, SD=10.2) at one year following injury [t(46)=2.11, p=.040; d=.35]. The percentages of patients who met ICD-10 criteria, using "mild or greater" symptom reporting, for a PCS at one month and one year post injury were as follows: uncomplicated MTBI=59.8% and 39.8%, and complicated MTBI (MRI abnormality)=52.9% and 26.7%, respectively. The percentages of patients who met ICD-10 criteria, using "moderate or greater" symptom reporting, for a PCS at one month and one year post injury were as follows: uncomplicated MTBI=21.9% and 13.6%, and complicated MTBI (MRI abnormality)=5.9% and 0%, respectively. Chi square analyses did not reveal any significant differences in the rates of the ICD-10 diagnosis in relation to the presence or absence of MRI abnormalities. Also, the effect sizes (phi-coefficient; φ) for this finding were very small (φ ranged from .05 to .15 indicating little or no association).

Depression

There was a significant positive Pearson correlation between the BDI-II subscale scores and the RPSQ total scores in the MTBI group at one month post injury (r=.51; p<.001) and at one year post injury (r=.59; p<.001). The correlation between BDI-II subscale scores and RPSQ

total scores in the control group was .48 (p=.003). At one month, the MTBI group had higher mean BDI-II subscale scores (sum of all 10 selected items; mean=2.2, SD=3.3) than the control group [mean=1.3, SD=1.8; t(101)=2.10, p=.042, d=.30] – but this finding is not significant after considering multiple comparisons. At one year, the MTBI group's BDI-II subscale scores (mean=1.7, SD=3.4, d=.13) did not differ from the control group mean subscale BDI-II score (p=.548). Patients who met ICD-10 criteria for postconcussional syndrome had significantly higher BDI-II subscale total scores than those patients who did not meet the ICD-10 criteria at one month based on "mild or greater" symptom reporting [t(94)=-5.59, p<.001, Cohen's d=.96] and "moderate or greater" symptom reporting [t(27)=-3.59, p=.001, Cohen's d=1.19]. Similarly, at one year post-injury, patients who met ICD-10 criteria for the syndrome had significantly higher BDI-II subscale total scores than those patients who did not meet the ICD-10 criteria using both "mild or greater" symptom reporting [t(56)=-2.68, p=.010, Cohen's d=.63] and "moderate or greater" symptom reporting [t(12)=-3.59, p=.004, Cohen's d=2.01]. Correcting for multiple comparisons (.05/4=.0125), three of the four above mentioned findings are statistically significant.

Regarding pre-injury history of mental health problems, the RPSQ total score for those with pre-injury mental health problems (n=9, mean=21.0, SD=11.1) was much higher than for those without mental health problems (n=117, mean=9.6, SD=10.3) at one month following injury [t(124)=-3.19, p=.002; d=1.10]. At one year, the RPSQ total score for those with pre-injury mental health problems (n=7, mean=12.9, SD=16.9) did not differ from those without mental health problems [n=96, mean=6.4, SD=8.83; t(6)=-1.01, p=.351; d=.69], most likely due to small sample size. Of the 73 patients who met ICD-10 criteria for PCS at one month post injury based on "mild or greater" symptom reporting, 10.9% (n=8) had previous mental health

problems [$\chi 2$ (1,126)=3.61, p=.080]. Of those 8 patients, who had a history of mental health problems, 88.9% met the ICD-10 criteria for PCS based on "mild or greater" symptom reporting. Using symptom endorsement as "moderate or greater" in those with a pre-injury mental health problem (n=8), 62.5% [$\chi 2$ (1,122)=9.94, p=.007] met the PCS criteria at one month. At one year, there was not a significant association between PCS group membership and previous mental health problems.

Descriptive Analysis of Post-Concussion Symptoms

Descriptive statistics, percentages, and group comparisons for the RPSQ total score and individual symptoms at one month and one year post injury are presented in Table 1. The RPSQ total score was significantly higher in the MTBI group compared to controls at both one month [t(129)=5.32, p<.001, d=.71] and one year [t(119)=2.48, p=.015, d=.36] following injury. In the MTBI group, significantly lower RPSQ total scores were found at one year post injury compared to one month post injury [t(102)=3.57, p<.001, d=.35]. At one month, the individual symptoms that differentiated the MTBI group from the control group with the largest effect sizes were fatigue, taking longer to think, dizziness, headaches, blurred vision, and nausea. At one year, the individual symptoms that differentiated the MTBI group from the control group, with the largest effect sizes, were fatigue, taking longer to think, and blurred vision.

Insert Table 1 About Here

Considering the total number of symptoms endorsed by the MTBI and the control group, two important issues emerge (see Figure 1). First, it is typical for control patients to endorse post-concussion-like symptoms. When using the criteria "mild or greater" symptom reporting, over 50% of controls endorsed one to five symptoms and approximately 6% endorsed six to ten symptoms. Commonly reported symptoms included feeling frustrated or impatient, sleep

disturbance, being irritable, and headaches. Second, there is a subgroup of MTBI patients who endorse an extremely high number of symptoms (11 or more) at both one month and one year following injury. None of the controls endorsed this level of symptoms.

Insert Figure 1 About Here

Diagnostic Rates for the Post-Concussion Syndrome

The percentages of the sample that met ICD-10 symptom criteria for postconcussion syndrome (PCS) and DSM-IV criteria for postconcussional disorder (PCD) are presented in Table 2. Using the mild or greater ICD-10 criteria for PCS, 59% of the MTBI cases met criteria at one month post injury and 38% met criteria at one year post injury. In the control group, 31% met the criteria. Using the moderate or greater ICD-10 criteria for the PCS, 20% of the MTBI cases met criteria at one month post injury and 12% met criteria at one year. In the control group, 0% met the criteria. At one month post injury, a significantly greater proportion of MTBI patients met PCS criteria than control participants using symptom endorsement as "mild or greater" [$\chi2(1,160) = 8.97$, p=.003] and "moderate or greater" [$\chi2(1,158) = 8.35$, p=.007]. At one year post-injury, a significantly greater proportion of MTBI patients met PCS criteria compared to controls when using "moderate or greater" criterion [$\chi2(1,139) = 4.59$, p=.036].

Using the mild or greater DSM-IV criteria for PCD, only 1.6% of the MTBI cases met criteria at one month post injury, and 1.0% met criteria at one year. In the control group, 0% met the criteria. Using the moderate or greater DSM-IV criteria for the syndrome, 0% of the MTBI cases met criteria one month post injury, and 1.0% met criteria at one year. None of the controls met the criteria. There were too few cases of PCD to run statistical analysis. All patients who met DSM-IV PCD criteria also fulfilled ICD-10 PCS criteria.

Insert Table 2 About Here

Postconcussion Symptom Reporting Trajectory

The natural history of post-concussion symptom reporting from one month to one year post-injury was examined in each individual MTBI subject (n=101). Of the 58 patients who met criteria for ICD-10 PCS at one month based on "mild or greater" symptom reporting, 53.4% (31 patients) met and 46.6% (27 patients) did not meet the PCS criteria at one year. Of those 43 patients who did not meet the ICD-10 PCS criteria ("mild or greater" symptom reporting") at one month, 16.3% (7 patients) met and 83.7% (36 patients) did not meet the PCS criteria at one year. Thus, of those who initially met the criteria ICD-10 criteria for PCS (n=58), 46.6% improved and 53.4% remained symptomatic. Of those who did not meet ICD-10 criteria at one month (n=43), 16.3% worsened and met criteria at one year.

Correlates of Post-Concussion Symptom Reporting (Exploratory Analyses)

Descriptive statistics and group comparisons for numerous demographic and injury variables by ICD-10 PCS groups (e.g., mild or greater vs. moderate or greater) are presented in Table 3 for exploratory purposes. There were no significant differences for age, sex, or education across PCS groups at one month or one year post injury. The duration of post-traumatic amnesia was not related to PCS group membership at one month or one year post injury. Those with previous head trauma were not more likely to meet PCS criteria at one month or one year. Those with multiple bodily injuries were more likely to have PCS (based on "mild or greater" symptom reporting) at one month [$\chi 2(1,124)=5.99$, $p=.014$]. Presence of multiple bodily injuries was not related to PCS group membership at one month based on "moderate or greater" symptom reporting or at one year post injury. Those with structural abnormalities on day-of-injury CT or four-week MRI were not more likely to meet PCS criteria at one month or one year. Post-injury

alcohol abuse at one month was not associated with post-concussion symptom reporting at one month or one year.

Insert Table 3 About Here

Diffusion Tensor Imaging and Post-Concussion Symptom Reporting

To examine the relation between self-reported post-concussion symptoms and DTI measures, the MTBI subsample was divided into four groups based on ICD-10 criteria for PCS: (a) PCS-Present at one month, mild or greater symptom reporting (n=39), (b) PCS-Absent at one month, mild or greater symptom reporting (n=32), (c) PCS-Present at one year, mild or greater symptom reporting (n=18), and (d) PCS-Absent at one year, mild or greater symptom reporting (n=42).

A multivariate ROI analysis was used to examine the relation between post-concussion symptoms and DTI measures. This methodology is described in detail by Iverson and colleagues.[89] For these analyses, the 16 ROIs for FA and 10 ROIs for ADC were considered simultaneously. To examine the prevalence of low (FA) or high (ADC) scores, when all ROIs were considered simultaneously, a cut-off score for each ROI was set at 1.28 SDs below or above the mean of control values. The 1.28 SDs below the mean for each FA score for each ROI was selected as a cutoff score for unusually low FA scores (i.e., 10^{th} percentile) and 1.28 SDs above the mean for each ADC score for each ROI was selected as a cutoff score for unusually high ADC scores (i.e., 90^{th} percentile). The 10^{th} and 90^{th} percentiles were selected because the control sample was relatively small and this would create more variability, and mediate the effects of possible outliers, in the control sample. The cumulative percentages of the number of low FA scores and high ADC scores by group are presented in Table 4.

Insert Table 4 About Here

Overall, there were a greater number of low FA scores in the MTBI group compared to the control group. Chi-square analyses revealed that there was a significantly greater number of low FA scores when using 2 or more low scores as the criterion [$X^2(1,95) = 12.72$, $p<.001$; 70.4% MTBI, 29.2% controls]. Also, there was a greater number of low FA scores in the MTBI group when using 3 or more low scores as the criterion [$X^2(1,95) = 4.63$, $p=.046$; 40.9% MTBI, 16.7% controls]. Similarly, there were also a greater number of high ADC scores in the MTBI group compared to the control group. Chi-square analyses revealed that there was a significantly greater number of high ADC scores when using 2 or more high scores [$X^2(1,95) = 10.60$, $p=.002$; 54.9% MTBI, 16.7% controls] and 3 or more high scores [$X^2(1,95) = 7.57$, $p=.006$; 32.4% MTBI, 4.2% controls] as the criterion. However, there were no significant differences in DTI measures between those who met ICD-10 criteria for PCS and those who did not meet criteria for PCS.

To further examine the relation between post-concussion symptoms and DTI measures, a multifocal abnormal WM group was defined as follows: 4 or more areas of abnormally low FA values or 3 or more areas of abnormally high ADC values. The broadly normal WM group was defined as follows: less than 4 areas of abnormally low FA values and less than 3 areas of abnormally high ADC values. Based on this definition, multifocal abnormal WM was found in 12.5% of the control group (3/24) and 50.7% of the MTBI group (36/71). Patients in the MTBI group were significantly more likely to show evidence of multifocal diminished white matter than participants in the control group [$X^2(1,95)=10.82$, $p=.001$; RR=4.06, 95% CI (1.44-16.01)]. However, the presence of multifocal diminished white matter was not significantly associated with the presence or absence of ICD-10 PCS (see Table 5).

Insert Table 5 About Here

Multivariable Prediction of ICD-10 Postconcussional Syndrome

Two logistic regression analyses were used to determine the extent to which ICD-10 PCS, based on mild or greater symptom reporting, could be predicted at one month and one year following injury. To predict PCS at one month post injury, the variables entered into the model were: (a) pre-injury mental health problems, (b) presence/absence of MRI abnormality, (c) presence/absence of bodily injuries, (d) one-month BDI-II subscale score, and (e) total number of low FA scores and high ADC scores on DTI. The only significant predictor of ICD-10 PCS (mild or greater symptom reporting) was the one-month BDI-II subscale score [$p<.001$, 95% CI (1.75-7.20)]. Presence of bodily injuries neared significance ($p=.052$). The overall classification rate was 81.7% (74.4% PCS Present, 90.6% PCS Absent; Cox & Snell $R^2=.397$, Nagelkerke $R^2=.531$).

To predict PCS at one year post injury, the variables entered into the model were: (a) pre-injury mental health problems, (b) presence/absence of MRI abnormality, (c) presence/absence of bodily injuries, (d) one-month BDI-II subscale score, (e) one-month RPSQ total score, (f) total number of low FA scores and high ADC scores on DTI, and (e) one-year BDI-II subscale score. At one year, only one-month symptom reporting [RPSQ total score, $p=.001$, 95% CI (1.10-1.48)] was a significant predictor of ICD-10 PCS (mild or greater symptom reporting). The overall classification rate was 81.7% (66.7% PCS Present, 88.1% PCS Absent; Cox & Snell $R^2=.391$, Nagelkerke $R^2=.555$).

Discussion

This study prospectively examined the prevalence of, and factors related to, persistent postconcussion symptom reporting following MTBI. We hypothesized that patients who sustained complicated MTBIs would perform more poorly on memory testing and report more

post-concussion symptoms at one month but not one year following injury. Those with complicated MTBIs did not perform more poorly on memory testing and they did not report more post-concussion symptoms at one month or one year post injury. Also, patients with longer periods of post-traumatic amnesia were not more likely to report more post-concussion symptoms. Thus, our results do not provide support for the hypothesis that patients with greater injury severity will report more post-concussion symptoms than patients with milder injuries.

To address the second and third hypotheses, we examined whether MTBI patients with pre-existing mental health problems or current affective symptoms of depression would report greater post-concussion symptoms than those without pre-injury mental health problems or current problems with depression. Pre-injury mental health problems[54-57] and ongoing problems with depression[57,58,90,91] have been identified as risk factors for slow or incomplete recovery following MTBI. In fact, it is well established in the literature that people who sustain a MTBI are at increased risk for developing depression,[41,92] with prevalence rates varying from 12% to 44% in the first three months following injury.[19,93-97] In this study, the prevalence of pre-injury mental health problems was low because patients with a known psychiatric history were initially excluded during recruitment. However, some patients brought up some pre-injury problems with depression and anxiety in the neuropsychological evaluation only after recruiting them into the study.

In the current study, and consistent with our second hypothesis and previous studies,[41,92,98] those with a pre-injury history of mental health problems were more likely to have postconcussion symptoms at one month. At one year follow-up, pre-injury mental health problems were not significantly associated with postconcussion symptom reporting. We tried to reduce the overlap between post-concussion symptom reporting and depression symptom

reporting by conducting the analyses with a reduced item set for the BDI-II. Only ten of the 21 symptoms from the BDI-II, believed to have the least overlap with symptoms of MTBI and being most representative of depression, were selected. As a group, MTBI patients reported more depressive symptoms at one month post-injury compared to controls. At one year, the groups did not differ in depression symptom reporting. In support of the third hypothesis, post-concussion-like symptoms had a significant positive correlation with affective symptoms of depression at both one month and one year following injury. Similar to previous studies,[92,94] our results lend support to the view that depression should be evaluated as part of the assessment protocol after MTBI.

In the present study, the MTBI patients were significantly more likely to show multifocal areas of diminished white matter on DTI compared to control subjects—which is consistent with our fourth hypothesis. Thus, this study is consistent with many previous studies showing that patients with MTBIs show differences on DTI relative to controls.[for a review see 67,99,100] For the fifth hypothesis, we predicted that white matter changes would be associated with post-concussion symptom reporting because some studies have suggested that compromised microstructural white matter might be associated with increased post-concussion symptom reporting following MTBI.[69,101-104] However, inconsistent with the final hypothesis, those MTBI patients who had multifocal white matter changes on DTI did not report more symptoms than those with broadly normal white matter. In other words, the presence of multifocal white matter changes was not associated with the presence of the persistent post-concussion symptoms. Several published studies have found a relationship between white matter abnormalities and PCS,[68-74] although some reported no association.[46,67,75]

The present study was large, carefully controlled, and prospective. We carefully

excluded most obvious premorbid conditions (substance abuse, psychiatric disorders, previous moderate-severe brain injuries, developmental cognitive disorders, and other medical conditions resulting in cognitive changes) to rule out the possible influence of premorbid moderator variables and to avoid possible bias due to these confounding factors. Furthermore, we ensured that none of the patients were involved in litigation, and had no financial incentives to exaggerate their symptoms.

This study has some methodological limitations and issues that should be considered. First, the majority (96%) of patients in the sample had a GCS of 15 with only a few having a GCS of 14. Thus, the sample can be considered to be skewed toward the less severe end of injury severity spectrum in MTBI. Second, the study included age and gender matched community controls as a comparison group instead of an orthopedically-injured trauma control group. In general, trauma control subjects are a better and more generalizable control group. Third, self-reported pain was not examined in the current study. Post-concussion-like symptoms are often endorsed by patients with chronic pain,[37,38] so it is important that pain be taken into account in future studies. Fourth, the imaging control group was a convenience sample that did not undergo psychological testing. Using separate comparison groups for outcome measures and imaging is a weakness that needs to be taken into account when interpreting results. Fifth, the inclusion/exclusion criteria were very strict and resulted in a slight female majority. For this study, a total of 2,479 consecutive patients from the ER were screened for inclusion between October 2006 and May 2009. As expected based on previous literature, the total sample had a male preponderance (males 1,406, females 1,073). However, applying strict inclusion/exclusion criteria excluded 94.8% of MTBI patients, leaving only 126 patients in the final sample. Finally, in this study a cross-sectional, not prospective, design was used for DTI (i.e., subjects were

imaged only once).

In conclusion, the rate at which the post-concussion syndrome is diagnosed varies greatly based on whether ICD-10 or DSM-IV criteria are used,[98,105-107] and whether the researcher or clinician requires the symptoms to be mild or greater or moderate or greater on the rating scale. Using ICD-10 criteria and mild or greater symptom reporting, 59% of the MTBI sample met criteria at one month and 38% met criteria at one year. However, 31% of the healthy control sample also met criteria for the syndrome—illustrating a high false positive rate. Of those who met criteria at one month, 47% improved and 53% remained symptomatic at one year. Notably, of those who did not meet criteria at one month, 16% worsened and met criteria at one year. Significant predictors of ICD-10 PCS at one month were pre-injury mental health problems and the presence of extra-cranial bodily injuries. Age, gender, and prior MTBI were not significant predictors. Being symptomatic at one month was as significant predictor of being symptomatic at one year, and depression was related to PCS at both one month and one year. Intracranial abnormalities visible on MRI were present in 12.1% (15/124) of this sample, and multifocal areas of unusual white matter were present in 50.7% of the subgroup who underwent DTI (compared to 12.4% of controls). However, these structural MRI abnormalities and microstructural white matter findings were not associated with greater post-concussion symptom reporting. Simply put, greater putative damage to the brain was not associated with greater symptom reporting. Clearly, no simple theory relating to the etiology of post-concussion symptom reporting following MTBI has strong explanatory value. The manifestation of post-concussion symptoms likely represents the cumulative effect of multiple variables, such as genetics, mental health history, current life stress, general medical problems, chronic pain, depression, and substance abuse. How people report their symptoms also can be influenced by

personality factors and the presence of possible future financial gain (e.g., personal injury litigation or disability determinations). The extent to which damage to the structure of the brain contributes to the persistence of post-concussion (or post-concussion-like) symptoms following MTBI remains unclear.

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Declaration of Interest

Dr. Iverson has received past research funding from several test publishing companies, including ImPACT Applications, Inc., CNS Vital Signs, and Psychological Assessment Resources (PAR, Inc.). He receives royalties for two books in neuropsychology and one test (WCST-64). He has a clinical practice in forensic neuropsychology involving individuals who have sustained mild TBIs (including athletes). He is a co-investigator, collaborator, or consultant on grants relating to mild TBI funded by several organizations. The authors report no declarations of interest.

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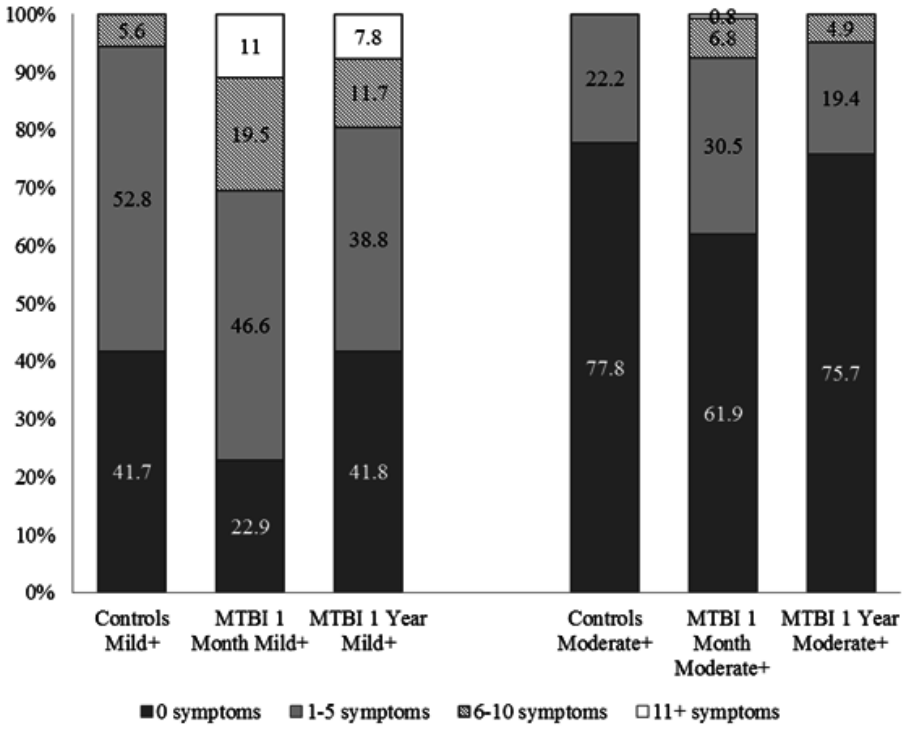

Figure 1. Total number of symptoms endorsed by MTBI and control group presented in percentages

Table 1. Individual RPSQ symptom reporting at one month and one year post injury.

	MTBI 1 Month N = 126		Mild+	Mod+	MTBI 1 Year N = 103		Mild+	Mod+	Controls N = 36		Mild+	Mod+	1 month vs. 1 year		1 month vs. controls		1 year vs. controls	
Symptom	M	SD	%	%	M	SD	%	%	M	SD	%	%	p†	d	p‡	d	p‡	d
1. Headaches	1.33	.99	40.5	11.1	.76	.93	26.2	3.9	.50	.94	19.4	5.6	<.001	.60	<.001	.85	.158	.28
2. Feelings of Dizziness	1.21	.96	34.9	9.5	.76	.91	21.4	3.9	.36	.76	16.7	0.0	<.001	.48	<.001	.93	.021	.46
3. Nausea and/or Vomiting	.66	.83	14.3	3.2	.25	.50	2.9	0.0	.11	.40	2.8	0.0	<.001	.60	<.001	.75	.091	.30
4. Noise Sensitivity	.67	.92	15.9	6.3	.54	.92	15.5	3.9	.11	.52	2.8	2.8	.123	.14	<.001	.67	.001	.53
5. Sleep Disturbance	1.03	1.20	34.1	13.5	.71	1.04	24.3	9.7	.44	.91	16.7	5.6	.007	.28	.002	.52	.179	.27
6. Fatigue, tiring more easily	1.56	1.21	51.6	23.0	.98	1.16	30.1	11.7	.19	.58	8.3	0.0	<.001	.49	<.001	1.28	<.001	.78
7. Being Irritable, easily angered	.98	1.06	33.3	9.5	.64	.95	20.4	4.9	.61	1.05	22.2	5.6	.017	.34	.064	.35	.875	.03
8. Feeling Depressed or Tearful	.67	.94	21.4	5.6	.52	.99	15.5	5.8	.14	.54	2.8	2.8	.192	.16	<.001	.62	.005	.44
9. Feeling Frustrated or Impatient	.87	1.09	30.9	11.4	.54	.93	15.5	5.8	.58	1.08	19.4	8.3	.004	.32	.167	.27	.833	.04
10. Forgetfulness, poor memory	1.02	1.06	36.0	8.0	.86	1.03	32.0	5.8	.39	.69	11.1	0.0	.275	.12	<.001	.64	.003	.50
11. Poor Concentration	1.02	1.07	36.3	9.7	.75	1.04	22.3	7.8	.39	.77	16.7	0.0	.019	.26	<.001	.63	.031	.37
12. Taking Longer to Think	.91	.98	31.2	6.4	.58	.95	17.5	5.8	.06	.23	0.0	0.0	.003	.34	<.001	1.05	<.001	.68
13. Blurred Vision	.49	.81	13.5	3.2	.37	.74	11.7	1.9	.00	.00	0.0	0.0	.113	.15	<.001	.78	<.001	.68
14. Light Sensitivity	.54	.82	14.3	3.2	.44	.81	13.6	1.9	.11	.47	5.6	0.0	.174	.12	<.001	.58	.004	.46
15. Double Vision	.23	.53	4.8	0.0	.15	.41	1.9	0.0	.00	.00	0.0	0.0	.131	.17	<.001	.56	<.001	.49
16. Restlessness	.68	.93	25.4	3.2	.42	.81	11.7	2.9	.39	.77	16.7	0.0	.013	.30	.058	.32	.854	.04
Total score	10.4	10.7	---	---	6.8	9.6	---	---	3.7	4.9	---	---	<.001	.36	<.001	.71	.015	.36

Note: † p values based on Paired Samples T Test, ‡ p values based on Independent Samples T Test; M=mean; MTBI=mild traumatic brain injury; RPSQ=Rivermead Postconcussion Symptom Questionnaire; SD=standard deviation

Table 2. Rates of participants who meet the criteria for post-concussion syndrome (PCS) depending on different diagnostic criteria

	MTBI group				Control group	
	1 Month n (%)		1 Year n (%)		n (%)	
Criteria	PCS Absent	PCS Present	PCS Absent	PCS Present	PCS Absent	PCS Present
ICD-10 Mild or greater symptoms	51 (41.1)	73 (58.9)	64 (62.1)	39 (37.9)	25 (69.4)	11 (30.6)
ICD-10 Moderate or greater symptoms	98 (80.3)	24 (19.7)	91 (88.3)	12 (11.7)	36 (100)	0 (0)
DSM-IV Mild + RTW >30 days	120 (98.4)	2 (1.6)	100 (99.0)	1 (1.0)	36 (100)	0 (0)
DSM-IV Moderate + RTW >30 days	0 (0)	0 (0)	100 (99.0)	1 (1.0)	36 (100)	0 (0)

Note: Sample size for 1 month: n = 124 for ICD-10 mild, 122 for ICD-10 moderate, n= 122 for DSM-IV; Sample size for 1 year: n = 103 for ICD-10; n = 101 for DSM-IV; Sample size for control group: n=36; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders-IV, ICD-10= International Classification of Diseases-10th edition, MTBI= Mild Traumatic Brain Injury, PPCS=Persistent Post-Concussion Syndrome, RTW=Return to Work.

Table 3. Demographic, pre-injury, and injury characteristics of the MTBI patients

	MTBI group											
	1 Month (N=126)						1 Year (N=103)					
	Mild + n=124			Moderate + n=122			Mild + n=103			Moderate + n=103		
	PCS+ n=73, 58.9 %	PCS- n=51, 41.1%	p	PCS+ n=24, 19.7%	PCS- n= 98, 80.3%	p	PCS+ n=39, 37.9%	PCS- n=64, 62.1%	p	PCS+ n=12, 11.7%	PCS- n= 91, 88.3%	p
Women, n (%)	45 (61.6)	25 (49.0)	.163	16 (66.7)	53 (54.1)	.265	22 (56.4)	34 (53.1)	.745	6 (50.0)	50 (54.9)	.747
Age, mean years (SD)	38.9 (13.4)	36.2 (13.6)	.275	39.1 (13.7)	37.4 (13.6)	.583	39.8 (13.6)	37.7 (13.3)	.435	37.8 (13.9)	38.6 (13.4)	.863
Education, years (SD)	12.8 (2.9)	12.3 (2.4)	.281	12.5 (2.3)	12.7 (2.9)	.763	12.8 (3.0)	12.7 (2.7)	.898	12.3 (3.2)	12.8 (2.7)	.500
PTA, minutes (SD)	164.4 (333.2)	234.7 (377.6)	.281	206.2 (397.4)	194.3 (345.1)	.884	147.8 (269.7)	283.1 (425.4)	.053	146.4 (252.2)	243.73 (392.3)	.406
BDI-II subscale score, mean (SD)	3.34 (3.8)	.63 (1.3)	<.001	4.83 (4.4)	1.49 (2.5)	.001	2.91 (4.1)	.95 (2.53)	.010	6.54 (5.2)	1.06 (2.4)	.004
AUDIT												
0-9	56	43	.299	18	79	.542	32	56	.446	8	80	.072
≥ 10	17	8		6	19		7	8		4	11	
CT												
Normal	67	47	1.00	23	89	.685	36	53	.737	12	81	.364
Abnormal	6	4		1	9		3	7		0	10	
MRI												
Normal	65	44	.642	23	84	.299	37	53	.736	12	78	.222
Abnormal	8	7		1	14		2	11		0	13	
Previous psychiatric symptoms												
No	65	50	.080	19	95	.007	36	60	1.00	10	86	.188
Yes	8	1		5	3		3	4		2	5	
Previous head trauma												
No	47	37	.339	14	68	.301	27	44	.959	8	63	1.00
Yes	26	14		10	30		12	20		4	28	
Multiple injury												
No	47	43	.014	14	75	.072	28	48	.719	8	68	.727
Yes	26	8		10	23		11	16		4	23	

Note: AUDIT= The Alcohol Use Disorders Identification Test, CT=computed tomography, PCS += postconcussional syndrome present, PCS - = postconcussional syndrome absent, Mild + = mild or greater symptom reporting, Moderate + = moderate or greater symptom reporting, MRI=magnetic resonance imaging, MTBI = mild traumatic brain injury, PTA=posttraumatic amnesia, SD=standard deviation

Table 4. Cumulative frequency distributions of low FA and high ADC scores, by group, and stratified by the presence or absence of ICD-10 Postconcussional Syndrome (based on symptom rating of "mild or greater").

	Low FA Scores				High ADC Scores				Low FA Scores By ICD-10 Dx At One Month				High ADC Scores By ICD-10 Dx At One Month				Low FA Scores By ICD-10 Dx At One Year				High ADC Scores By ICD-10 Dx At One Year			
	MTBI FA Scores (n = 71)		Controls FA Scores (n = 24)		MTBI ADC Scores (n = 71)		Controls ADC Scores (n = 24)		PCS + (n = 39)		PCS - (n = 32)		PCS + (n = 39)		PCS - (n = 32)		PCS + (n = 18)		PCS – (n = 42)		PCS + (n = 18)		PCS – (n = 42)	
Unusual Scores	f	cp	f	cp	f	cp	f	cp	f	cp	f	cp	f	cp	f	cp	f	cp	f	cp	f	cp	f	cp
6	5	7.0	0	-	1	1.4	0	-	3	7.7	2	6.3	0	-	1	3.1	0	-	3	7.1	0	-	1	2.4
5	6	15.5	1	4.2	1	2.8	0	-	3	15.4	3	15.6	0	-	1	6.3	1	5.6	4	16.7	1	5.6	0	-
4	7	25.4	1	8.4	7	12.7	0	-	4	25.6	3	25.0	4	10.3	3	15.6	3	22.2	4	26.2	1	11.1	5	14.3
3	11	40.9	2	16.7	14	32.4	1	4.2	7	43.6	4	37.5	8	30.8	6	34.4	6	50.0	4	35.7	4	33.3	10	38.1
2	21	70.4	3	29.2	16	54.9	3	16.7	14	79.5	7	59.4	9	53.9	7	56.3	6	88.9	11	61.9	4	55.6	10	61.9
1	15	91.6	12	79.2	19	81.7	12	66.7	6	94.9	9	87.5	12	84.6	7	78.1	2	100.0	11	88.1	5	83.3	7	78.6
0	6	100.0	5	100.0	13	100.0	8	100.0	2	100.0	4	100.0	6	100.0	7	100.0	0	-	5	100.0	3	100.0	9	100.0

Note: dx = diagnosis, cp = cumulative percentage, f = Frequency; FA = fractional anisotropy, ADC=apparent diffusion coefficient, PCS += postconcussional syndrome present, PCS - = postconcussional syndrome absent, MTBI = mild traumatic brain injury

Table 5. The presence of multifocal abnormal white matter by group.

				1 Month ICD-10 Mild or Greater (MTBI)			1 Month ICD-10 Moderate or Greater (MTBI)			1 Year ICD-10 Mild or Greater (MTBI)			1 Year ICD-10 Moderate or Greater (MTBI)		
	MTBI (n=71)	Controls (n=24)	p	PCS + (n=39)	PCS – (n=32)	p	PCS + (n=15)	PCS – (n=56)	p	PCS + (n=18)	PCS – (n=42)	p	PCS+ (n=5)	PCS – (n=55)	p
Broadly Normal WM	35 (49.3%)	21 (87.5%)	.001; RR 4.06, 95% CI	20 (51.3%)	15 (46.9%)	.712; RR 1.09, 95% CI	9 (60.0%)	26 (46.4%)	.351; RR 0.75, 95% CI	9 (50.0%)	19 (45.2%)	.740; RR 0.91, 95% CI	4 (80%)	24 (43.6%)	.175; RR 0.36, CI
Abnormal WM	36 (50.7%)	3 (12.5%)	1.44-16.01	19 (48.7%)	17 (53.1%)	0.68-1.77	6 (40.0%)	30 (53.6%)	0.38-1.45	9 (50.0%)	23 (54.8%)	0.53-1.56	1 (20%)	31 (56.4%)	0.06-2.08

Abbreviations: ADC=apparent diffusion coefficient, CI= confidence interval; FA=fractional anisotropy, PCS=postconcussional syndrome, RR=relative risk, WM=white matter