Title

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Journal

Journal of the American Academy of Child & Adolescent Psychiatry, 51(11)

ISSN

0890-8567

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Publication Date

2012-11-01

DOI

10.1016/j.jaac.2012.08.026

Peer reviewed

Published in final edited form as:
J Am Acad Child Adolesc Psychiatry. 2012 November ; 51(11): 1208–1217. doi:10.1016/j.jaac.2012.08.026.

Neuroimaging Correlates of Novel Psychiatric Disorders after Pediatric Traumatic Brain Injury

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Disclosure: Drs. Max and Bigler independently provide expert testimony in cases of traumatic brain injury on an ad hoc basis for plaintiffs and defendants on a more or less equal ratio. This activity constitutes approximately 5% of their respective professional activities. Drs. Wilde, Thompson, Merkley, Hunter, Chu, Hotz, Chapman, Yang, and Levin, and Ms. MacLeod, Ms. Vasquez, and Ms. Yallampalli report no biomedical financial interests or potential conflicts of interest.

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Abstract

Objective—To study magnetic resonance imaging (MRI) correlates of novel (new-onset) psychiatric disorders (NPD) following traumatic brain injury (TBI) and orthopedic injury (OI).

Method—Participants were age 7–17 years at the time of hospitalization for either TBI or OI. The study used a prospective, longitudinal, controlled design with standardized psychiatric assessments conducted at baseline (reflecting pre-injury function) and 3 months post-injury. MRI assessments including diffusion tensor imaging (DTI)–derived fractional anisotropy (FA), volumetric measures of gray and white matter regions, volumetric measures of lesions, and cortical thickness were conducted. Injury severity was assessed by standard clinical scales. The outcome measure was the presence of an NPD identified during the first 3 months following injury.

Results—There were 88 participants (TBI=44; OI=44). NPD occurred more frequently in the TBI (21/44; 48%) versus the OI (6/44; 14%) group (Fisher's Exact p=.001). NPD in TBI participants was not related to injury severity. Multivariate analysis of covariance of the relationship between FA in hypothesized regions of interest (bilateral frontal and temporal lobes, bilateral centrum semiovale, bilateral uncinate fasciculi) and NPD and group (TBI versus OI) was significant, and both variables (NPD: p<.05; group: p<.001) were jointly significantly related to FA. NPD was not significantly related to volumetric measures of white or gray matter structures, volumetric measures of lesions, or to cortical thickness measures.

Conclusions—Lowered white matter integrity may be more important in the pathophysiology of NPD than indices of gray matter or white matter atrophic changes, macroscopic lesions, and injury severity.

Keywords

TBI; pediatric; psychiatric disorders; prospective; diffusion tensor imaging

Introduction

Traumatic brain injury (TBI) in children and adolescents is a major public health problem. Psychiatric disorders are a common and important complication of pediatric TBI. Research has focused on understanding the risk factors for post-injury development of a general category of new-onset psychiatric disorders, called novel psychiatric disorders (NPD)[1, 2], and specific psychiatric disorders such as attention-deficit/hyperactivity disorder (ADHD), personality change due to a general medical condition, and anxiety disorders[1, 3, 4]. The catch-all category, NPD, is important because new-onset disorders after pediatric TBI are typically heterogeneous, and repeated studies show they occur at a significantly higher rate than in children with orthopedic injury (OI)[1, 2, 5]. This study concentrates on magnetic resonance imaging (MRI) correlates of the broad category of NPD in children who participated in a prospective longitudinal psychiatric interview study of pediatric TBI and OI.

This manuscript is a follow-up paper to one which analyzed the relation of NPD to group (TBI versus OI), pre-injury lifetime psychiatric disorder, pre-injury adaptive function, pre-injury family stressors, pre-injury family resources, family psychiatric history,

socioeconomic status, age at injury, and gender (Max JE, Wilde EA, Bigler ED. Psychiatric Disorders After Pediatric Traumatic Brian Injury [unpublished manuscript]. 2012.). NPD occurred significantly more frequently in the TBI (32/65; 49%) versus the OI (7/53; 13%) group (Fisher's Exact $p<.0005$). None of the other psychosocial variables was associated with NPD in this study. Furthermore, TBI severity, measured by the Glasgow Coma Scale (GCS)[6], was not associated with NPD. This raised the following question, "If not injury severity as defined by the GCS, what MRI-defined brain markers differentiate between children who develop NPD versus those who do not?"

There are no data on neuroimaging correlates of NPD after pediatric TBI. There are data on several specific new-onset disorders (ADHD, personality change, obsessive compulsive disorder/symptoms, post-traumatic disorder symptoms, anxiety disorder, mania/hypomania) where the findings are varied depending on the specific NPD[1, 3, 4, 7, 8]. We reasoned that if there were to be neuroimaging correlates for NPD, which is a diverse group of clinically-significant disorders, the correlates would likely have a systemic character. For example, if NPD were related to degraded white matter (WM) integrity, then bilateral frontal and temporal lobe WM tracts, tracts linking these lobes (uncinate fasciculi), and the extensive centrum semiovale bilaterally would show differences between children who acquire NPD versus those who do not as these a priori selected regions of interest are commonly damaged in TBI[9]. Diffusion tensor imaging (DTI) metrics such as fractional anisotropy (FA) would be expected to be a sensitive tool to detect WM integrity degradation[9]. DTI has not been used previously to detect potential correlates for new-onset psychiatric disorders in TBI populations. However, a TBI-OI study examined 3-month post-injury self-reported anxiety scores, which did not distinguish new-onset anxiety versus pre-injury anxiety scores, and found a relation of higher left amygdala mean diffusivity and anxiety in the TBI but not in the OI group[10]. If NPD were also related to compromised gray matter (GM) regions, then multiple GM regions would show significantly greater involvement with lesions or tissue loss especially in frontal and temporal areas[1, 7]. Cortical thickness differences in multiple regions would be an additional metric to document a potential systemic relationship of GM involvement and NPD. MRI volumetric analyses of lesions have been applied to specific new-onset psychiatric disorders[1, 3, 4, 7] but there are no studies reporting the relation of the general category of NPD to lesion volumes, region of interest volumes, or cortical thickness.

The preceding review led us to the following specific hypotheses. 1) NPD is related to lower WM integrity, measured by FA, and detected in frontal, temporal, uncinate fasciculi, and centrum semiovale WM that appears normal without obvious lesions in conventional neuroimaging. 2) NPD is related to WM volume loss in multiple regions. 3) NPD is related to compromised GM, measured by regional volume, and cortical thickness, and detected in multiple GM areas. We anticipated that the first three hypotheses would hold independent of group (TBI versus OI) and age. 4) NPD is related to total lesion volume.

METHOD

Study procedures were approved by the institutional review boards of the participating organizations and complied with the National Institutes of Health (NIH) policies on human subjects. Participants with TBI or OI were recruited from consecutive admissions to medical centers in Houston, Dallas, and Miami. Inclusion of the OI group was intended to control for factors predisposing children to injury and for stress resulting from hospitalization. Children were aged 7–17 years at the time of injury. Participants with TBI were included if they had a complicated mild to severe TBI. Severity of TBI classification was based on the lowest post-resuscitation score on the GCS[6] which was recorded from clinical notes. The GCS is the standard measure of severity of acute brain injury associated with TBI. Scores range from 3 (unresponsive) to 15 (normal). Severe TBI was defined by GCS scores of 3–8, moderate

TBI by GCS scores of 9–12, and complicated mild TBI by GCS scores of 13–15 with brain lesions indicated by computed tomography. The OI patients had mild-to-moderate injuries as defined by the Abbreviated Injury Scale[11]. The current investigation examined participants at baseline within 1 month after injury and 3 months post-injury. Baseline assessments were conducted only after children emerged from posttraumatic amnesia documented by the Children's Orientation and Amnesia Test[12]. All participants were English-speaking. Children were excluded if they had a previous head injury, penetrating gunshot wounds to the brain, history of child abuse, pre-existing neurologic disorders (e.g., cerebral palsy, mental retardation), pervasive developmental disorders, prematurity (gestation <37 weeks) or low birth weight (<2,500g), contraindication to undergoing MRI, hypoxia, or hypotension.

Psychiatric measures

DSM-IV-TR psychiatric diagnoses were derived by utilizing a semi-structured interview, the Schedule for affective disorders and schizophrenia for school-aged children, present and lifetime version (K-SADS-PL)[13]. Consistent with the methodology of others[14] and our own studies over the last 20 years, diagnoses (including those of depressive and anxiety disorders) were made according to *DSM-IV-TR* criteria excluding the criterion that precludes such a diagnosis in the presence of a related general medical condition. This approach permits the analyses of potential injury variables and pre-injury psychosocial variables as predictors for various psychiatric outcomes at different post-injury intervals. The K-SADS-PL generates diagnoses based on a clinician synthesizing data collected from parent and child separately, querying symptoms that were present in the weeks before injury and pre-injury lifetime symptoms (at baseline) and symptoms present or past from injury to 3 months (at 3 month assessment). The entire interview was completed by the parent. The interview of the child was shortened because the children also completed an extensive neurocognitive battery. All children completed the depression and anxiety disorder sections, while children ≥13 years also answered the conduct disorder, drugs, and alcohol sections.

The Neuropsychiatric Rating Schedule (NPRS)[15] is a semi-structured interview designed to identify symptoms and subtypes of personality change due to TBI (PC). Both parents and children served as informants in the interview that took place at baseline and at 3 months after injury. We specifically waived the one-year duration of symptomatology criterion to allow us to monitor clinically significant symptomatology. The instrument has been shown to provide reliable and valid diagnoses of the common subtypes of PC[15].

Best-estimate psychiatric diagnoses[16] were generated by the interviewer, a trained Master's level clinician at each site, after integrating the reports of the parent and the child from the NPRS and the K-SADS interviews and, when available, from the Behavior Assessment System for Children[17] and Behavior Rating Inventory of Executive Function[18] completed by the teacher. Child psychologists at each site closely supervised the assessments, and fidelity in diagnosis was maintained across sites by frequent telephone conferences and transmission of written summaries of psychiatric assessments that were critiqued by the first author and other interviewers, resulting in a consensus diagnosis.

Socioeconomic Status

The Socioeconomic Composite Index (SCI)[19] was based on three variables: maternal education, coded on a seven point scale with values representing <7 years education to attainment of a graduate degree; the Duncan occupational status index[20]; and annual family income, based off an eight point scale ranging from <$20,000 to >$60,000 as part of the Life Stressors and Resources Scale[21]. These three variables were transformed into z-scores and

then averaged together to yield a composite z-score which was standardized (mean = 0; SD= 1).

Predictive Variables

Imaging—Participants underwent MRI 3-months after injury on Philips 1.5-Tesla Intera scanners[22], using comparable scanner platforms and software. No sedation was used. Regular quality assurance testing was performed on all three scanners, including American College of Radiology phantom and Weisskoff testing[23] for echo-planar imaging sequences, and all scanners were consistently noted to be within an acceptable range throughout the course of the study.

DTI Background [24]: DTI has been used to probe the integrity of WM in the brain through common DTI-derived metrics such as FA. FA is derived from the tendency of water molecules to move preferentially in parallel (rather than perpendicular) to barriers to free diffusion such as axons or other support cells. Higher anisotropic diffusion has been shown to relate to homogeneity in fiber orientation, increased fiber density or axonal diameter, and properties of the intracellular and extracellular space around the axons. FA ranges from 0 to 1, where 0 represents maximal isotropic diffusion (free diffusion in all directions) and 1 represents maximal anisotropic diffusion (movement parallel to the major axis of a WM tract).

DTI Acquisition: Transverse multislice spin echo, single-shot, echo-planar imaging sequences were applied with the following parameters: 10,150.5-ms repetition time (TR); 90-ms echo time (TE); 2.7-mm-thick slices with 0-mm gap; 256-mm field of view (FOV) and a measured voxel size of 2.69×2.69×2.7-mm. Diffusivities were evaluated along 15 directions (number of b-value=2, low b-value=0 s/mm^2, high b-value=860 s/mm^2). A total number of 55 slices were acquired, and each acquisition took approximately 6 minutes. Two acquisitions were obtained and averaged to ensure a better signal-to-noise ratio.

Anatomical Acquisitions for Lesion Analysis: a coronal T2-weighted fluid attenuated inversion recovery (FLAIR) sequence was used (1100-ms TR, 140-ms TE, 5.0-mm slices). For this sequence, a 220-mm FOV was used with a reconstructed voxel size of 0.86×0.86×5.0 mm.

Volumetric Acquisition: T1-weighted 3-D sagittal acquisition series were used for volumetric analysis. The parameters included 15-ms TR, 4.6-ms TE, 1.0-mm-thick slices with 0-mm gap, 256-mm FOV, and a voxel size of 1.0×1.0×1.0 mm.

DTI Analysis: Prior to computing FA maps with the Philips fiber tracking 4.1v3 Beta 2 software, shear and eddy current distortion and head motion artifact were corrected by using the Philips PRIDE registration tool[22]. Mean FA was used as the quantitative DTI variable. Standard thresholds were utilized (i.e., FA threshold was set to <.02 and angle threshold was < 7 degrees).[25] Quantitative tractography analysis was performed according to previously published protocols for these regions of interest[24, 26]. Linear regression analyses demonstrated no instance in which mean FA in the regions of interest was significantly associated ($p < .05$) with acquisition site when controlling for GCS score and age.

Intra- and Interrater Reliability: To ensure intrarater reliability, each region of interest for DTI data was independently analyzed twice. To examine interrater agreement, two trained raters performed an analysis of each region of interest in a sample of 10 participants randomly selected (5 TBI and 5 OI). Shrout-Fleiss intraclass correlation coefficients were

calculated and revealed satisfactory intra- (range: 0.945–1.000) and interrater (range: 0.926–0.976) reliability.

Volumetric Analysis: Volumetric segmentation was performed by the Freesurfer image analysis suite version 4.0.4 (Athinoula A. Martinos Center for Biomedical Imaging, 2005; http://surfer.nmr.mgh.harvard.edu/). Details of the procedures have been described previously and are available on the above website. Briefly, processing involves intensity normalization,[27] automated Talairach transformation, the removal of non-brain tissue, and segmentation and labeling of the subcortical WM and deep GM volumetric structures[28, 29]. Results for each subject were visually inspected to ensure accuracy of registration, skull stripping and segmentation. No editing was necessary in the automated segmentation of subcortical structures and previous studies have shown the reliability of volumes derived in this manner[9].

Cortical Thickness: FreeSurfer was also used for cortical reconstruction and segmentation[29, 30]. This method utilizes both intensity and continuity information from the entire three-dimensional MR volume to produce representations of cortical thickness. The validity of measurement of cortical thickness has been established with histological analysis[31] and manual measurements[32]. Results for each subject were visually inspected to ensure accuracy of the cortical surface reconstruction, and manual editing was performed to optimize accuracy as needed. A statistical surface map of cortical thickness between-group differences was created by computing a 2-class general linear model for the effect of the presence/absence of NPD. A cluster-wise correction for multiple comparisons was applied using a Monte Carlo simulation (vertex-wise threshold of $p<0.01$).

Lesion analysis: Areas of signal abnormality were identified and traced by a board-certified neuroradiologist using FLAIR imaging as previously described[33]; abnormalities were cross-checked using other anatomic sequences such as T1-weighted and T2-weighted fast-field echo acquisitions.

Data Analysis—The analyses conducted included comparisons between the TBI versus OI groups, NPD versus no NPD groups, and participants with versus without usable MRI data at 3 months. Fisher's exact test and χ^2 analyses, or independent sample t-tests (parametric independent sample t-tests with equal variance assumption) were used to compare the groups for dependent variables that were categorical or continuous respectively. Multivariate analysis of covariance (MANCOVA) was used in analyses of NPD and its relationship with FA (bilateral frontal and temporal lobes, bilateral uncinate fasciculi, and bilateral centrum semiovale) and volumes (cerebral GM and WM, right and left frontal WM, right and left temporal WM, corpus callosum, cerebellar GM and WM, basal ganglia, hippocampus, thalamus) controlling for group (TBI versus OI) and age. The MANCOVA for volumes also controlled for intracranial volume. To account for missing data in MANCOVAS we first multiply imputed five complete-value datasets using the method of chained equations[34]. MANCOVAs were run for all five complete value datasets and combined as described by Little and Rubin[35]. Post-hoc univariate regressions were performed if the MANCOVA was significant.

RESULTS

The study involved 88 children including 44 with TBI (severe=27; moderate=7; complicated mild=10) and 44 with OI. Numbers of participants by site of recruitment (Houston, Dallas, Miami) for TBI were 14, 15, and 15, and for OI were 19, 17, and 8, respectively. All these children underwent psychiatric assessments at baseline and at 3 months post-injury to assess pre-injury psychiatric disorders and 3-month NPD respectively. In addition, they all had

usable DTI data from a research MRI conducted 3 months post-injury. This group of 88 children constituted a subset of 141 children (TBI=75; OI=66) who participated in the baseline psychiatric assessment, a subset of 118 children (TBI=65; OI=53) who participated in the 3-month psychiatric assessment, and a subset of 95 children who had usable data from the research MRI at 3 months. The children with versus without usable MRI data (n=95 versus n=46 respectively) were not significantly different with respect to age at injury, group (TBI versus OI), GCS score, gender, race, socioeconomic status, pre-injury lifetime psychiatric disorder, pre-injury adaptive function, pre-injury family psychiatric history, pre-injury family resources, pre-injury family stressors, and 3-month NPD.

Table 1 shows pre-injury characteristics of the participants. The TBI group was significantly older than the OI group (mean age [SD] 13.4 [3.0] versus 12.0 [2.6] years; t=2.45; df=86; p=.016). The groups were not significantly different in gender, race, or socioeconomic status[19]. Neither was the rate of pre-injury lifetime psychiatric disorder significantly different between TBI and OI groups (22/44 [50%] versus 24/44 [55%], respectively). This very high rate is similar to previous studies that have documented pre-injury lifetime psychiatric disorder[2, 5]. The most common pre-injury lifetime psychiatric disorders respectively in the TBI and OI groups were ADHD 15/44 (34%) versus 20/44 (46%); anxiety disorder 6/44 (14%) versus 9/44 (21%); oppositional defiant disorder (ODD) 6/44 (14%) versus 4/44 (9%); depressive disorder 4/44 (9%) versus 2/44 (5%).

Consistent with the analyses that included participants regardless of usable MRI data (Max JE, Wilde EA, Bigler ED. Psychiatric Disorders After Pediatric Traumatic Brian Injury [unpublished manuscript]. 2012.), 3-month NPD occurred significantly more frequently in the TBI group compared with the OI group (21/44 [48%] versus 6/44 [14%]; Fisher's Exact test p=.001). NPD was not associated with severity of TBI: GCS scores of TBI participants with NPD versus those without NPD were 7.1 +/− 5.0 versus 8.2 +/− 3.8; t=.81; df=42; p=.43. The most common NPDs in the TBI and OI groups respectively were personality change 14/44 (32%) versus 0/44 (0%), Fisher's Exact p<.0005; anxiety disorder 6/44 (14%) versus 4/44 (9%); ADHD 4/29 (14%) versus 1/24 (4%); ODD 3/37 (8%) versus 1/40 (3%); depressive disorder 3/41 (7%) versus 1/43 (2%); and drug abuse 0/43 (0%) versus 1/43 (2%). Denominators vary depending on eligibility to develop a specific NPD (e.g., a child with pre-injury ADHD would not be eligible to develop a novel ADHD). Table 2 charts the specific NPDs for each participant from each of the TBI and OI groups. NPD was not significantly associated with pre-injury lifetime psychiatric disorder when the entire cohort was analyzed (15/27 (56%) children with NPD had pre-injury lifetime psychiatric disorder versus 31/61 (51%) children with no NPD had pre-injury lifetime psychiatric disorder) nor when only the TBI group was considered (13/21 (62%) children with NPD had pre-injury lifetime psychiatric disorder versus 9/23 (39%) children with no NPD had pre-injury lifetime psychiatric disorder; Fisher's exact p>.22).

Diffusion Tensor Imaging Analyses

The relationship between FA in regions of interest (bilateral frontal and temporal lobes, bilateral centrum semiovale, and bilateral uncinate fasciculi) and NPD and group (TBI versus OI) was analyzed by MANCOVA controlling for age (Table 3). Both variables were jointly significantly related to FA (NPD: F=2.21; df=8, 64; p=.037; and group: F=4.12; df=8, 64; p=.0005). There was a trend association between (older) age and (lower) FA (F=1.85, df=8, 64, p=.084). Further examination of the FA measures of the specific regions in *post hoc* univariate analyses revealed that bilateral frontal lobe FA, bilateral centrum semiovale FA, and bilateral uncinate fasciculi FA were significantly related to NPD, while bilateral temporal lobe FA measures were not significantly related to NPD. However, the relationship tended to significance for the right temporal lobe. An example of actual FA scores for the right frontal region as they were calculated for NPD versus no NPD were as

follows: All participants: .354 +/− .029 (n=27) versus .376 +/− .022 (n=61); t=3.97; df=86; p=.000; TBI participants only: .347 +/− .028 (n=21) versus .363 +/− .018 (n=23); t=2.33; df=42; p=.025.

To investigate whether FA was associated specifically with NPD rather than psychiatric disorders in general, we conducted the same MANCOVA except replaced NPD with lifetime pre-injury psychiatric disorder. FA was not significantly related to lifetime pre-injury psychiatric disorder (F=.99; df=8, 64; p=.47), nor to age (F=.94; df=8,64; p=.50), but was again related to group (F=5.35; df=8,64; p<.0005).

Structural Volumetric Analyses

The relationship between structural volumes in regions of interest (cerebral GM and WM, cerebellar GM and WM, right and left frontal, right and left temporal, basal ganglia, amygdala, thalamus, corpus callosum, and hippocampus) and NPD and group (TBI versus OI) was analyzed by MANCOVA controlling for age and intracranial volume. Structural volumes were not significantly related to NPD (F=1.26; df=13,58; p=.35), group (F=1.34; df=13,58; p=.36), age (F=1.67, df=13,58, p=0.12), but were related to intracranial volume (F=19.94, df=13,58; p<.00005).

Lesion Volumetric Analyses

Total lesion volume (cm^3) was not significantly different in children with NPD versus those without (16.4 ± 28.4; n=18 versus 9.8 ± 10.7; n=22; t=−1.00; df=38; p=.32). Exploratory analyses revealed that there was no significant association of lesion volume with NPD in the frontal, temporal, parietal, or occipital lobes.

Cortical Thickness Analyses

Of the subjects with MRI data, 78 had data of sufficient quality to be retained for the cortical thickness analysis (38 TBI/40 OI). No relation between cortical thickness and development of NPD was observed in any region of the cortex, after controlling for multiple comparisons.

DISCUSSION

The current study is the first to demonstrate the utility of DTI in distinguishing between brain-injured individuals who develop versus those who do not develop new-onset psychiatric disorders. Our specific finding was that even after controlling for the effect of group (TBI versus OI), FA was significantly lower in participants with versus without NPD in widely distributed WM tracts including bilateral frontal lobes, bilateral uncinate fasciculi, and bilateral centrum semiovale. Particularly notable is that FA measures are taken from normal appearing WM in the conventional MRI sequences and therefore the findings elucidate a microstructural process in the brain that is related to an overt behavioral and/or emotional disturbance that is NPD.

The second important finding was that the brain–behavior relationship of lower FA and NPD was exclusive. Sophisticated measures of WM volumes of multiple regions of interest, GM volumes of multiple regions of interest, total lesion volume, lesion volumes in regions of interest, and measures of cortical thickness did not differentiate children with or without NPD. Furthermore, FA was significantly associated specifically with NPD and not with psychiatric disorders in general, i.e., lifetime pre-injury psychiatric disorder. The latter analysis minimizes, but does not eliminate, the possibility that lower FA may be a pre-injury risk factor for NPD.

The first two findings described above are all the more striking in the context of this cohort and its related findings. The important contextual issues are as follows. First, the study is the first controlled prospective psychiatric interview study of pediatric TBI since the original such study conducted in the late 1970s[5]. Second, this is the only such study that used brain imaging. The important related findings are as follows. First, participants with TBI developed NPD at a significantly higher rate than participants with OI. Second, there was no significant association of severity of injury and NPD in TBI participants. Third, in the first manuscript from this study (Max JE, Wilde EA, Bigler ED. Psychiatric Disorders After Pediatric Traumatic Brian Injury [unpublished manuscript]. 2012.) we demonstrated that there were no significant associations of NPD with psychosocial variables including pre-injury lifetime psychiatric disorder, pre-injury adaptive function, pre-injury family stressors, pre-injury family resources, family psychiatric history, socioeconomic status, age at injury, and gender. This may be explained, in part, by the observation in this manuscript that 14/21 cases classified as having an NPD in the TBI group were accounted for by PC which we have reported related to injury indices and not to psychosocial variables in a different cohort.[36]

The findings of this study underscore the primary importance of microstructural WM damage in the pathophysiology of NPD 3-months after TBI. The exclusivity of this finding was unexpected because previous studies have implicated psychosocial variables in the pathogenesis of NPD[1, 2]. Furthermore, although never before tested, it seemed to be a reasonable hypothesis that NPD would be related to volume reduction (atrophic) changes in WM or GM, total or regional lesion volume, and cortical thickness measurement. However, volume reductions which reflect trauma-induced atrophic brain changes, are likely much coarser indicators of brain pathology and may become more apparent later in follow-up as a consequence of decreased connectivity, whereas the DTI findings reflect a finer-grained analysis of microstructure and brain connectivity[37]. These findings support the view that it may be more important how the brain is disconnected in TBI rather than where greater focal or regional atrophy occurs[38]. Furthermore, the lesions that occur in TBI are especially heterogeneous and diverse, with minimal overlap in any TBI sample. Similarly, while focal atrophy has the potential to affect distal connections, focal damage, including localized atrophy may mostly disrupt local networks that may not extend into critical network hubs. Only when network hubs become perturbed by injury will more adverse effects of a focal injury be expressed throughout the network[39]. Measures of cortical atrophy or thinning may simply be too indirect as indicators of pathology, whereas DTI more directly assesses WM networks where damage is more closely linked to the neurobehavioral changes associated with TBI[40]. Additionally, there may be differences in the sensitivity of different advanced neuroimaging techniques to the impact of pathologies such as gliosis. For example, gliosis would not affect volumetric measures of WM, but may more substantively affect measures derived using DTI.

While the association of FA with NPD suggests systemic WM damage, this association has greater specificity in terms of WM tract involvement than the association between group (TBI versus OI) and WM tract involvement. Thus it appears that the systems implicated in the FA association with NPD specifically involve frontal WM, the uncinate fasciculi that connect the frontal and temporal poles, in particular the amygdala with basal and inferior frontal lobes, and centrum semiovale.

FA measures have previously been shown to be markers of cognitive decrements, global functional outcome in pediatric TBI, and differentiates children with TBI and OI[24]. This suggests that lower FA is not specifically associated with new onset psychiatric disorder but may be a critical microstructural correlate of a broader range of neurobehavioral and neurocognitive functioning after pediatric TBI.

A limitation of this study is that a substantial minority of participants who enrolled in the study did not have usable imaging data. This was primarily due to difficulties in the acquisition of imaging, notably metal artifact from orthodontia, and much less often related to motion-artifact, refusal to undergo imaging, or technical difficulties in the imaging acquisition in evaluating children and adolescents. However, there were no variables, including group (TBI or OI) and severity of injury, that distinguished participants with usable versus those without usable imaging data. Finally, age differed between the TBI and OI groups by just over 1 year. This difference was controlled in the statistical models.

Future manuscripts will investigate the biopsychosocial correlates of specific NPDs such as personality change due to TBI. As in previous reports, we might anticipate different specific disorders to have somewhat different biopsychosocial correlates and therefore shed light on differing mechanisms for varied injury-related psychiatric disorders[1]. We plan to investigate the nature and correlates of NPD beyond the first 3 months post-injury because it will be important to understand factors related to persistence and resolution of disorders in addition to delayed-onset disorders.

An important clinical and research implication of these findings is that treatment efforts at limiting microstructural WM damage may lead to lower rates of neuropsychiatric and neurocognitive complications after pediatric TBI. An improved understanding of the biological mechanisms involved in WM damage will be essential for this benefit to occur.

Acknowledgments

This research has been supported by the National Institute of Mental Health grant K-08 MH01800 (J.E.M.) and the National Institute of Neurological Disorders and Stroke (NINDS) grant NS-21889 (H.S.L.).

Dr. Thompson served as the statistical expert for this research.

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Table 1

Demographics and Injury Characteristics

	Traumatic Brain Injury (n=44)	Orthopedic Injury (n=44)	t	df	significance
Age at Injury, mean (SD)	13.4 (3.0)	12.0 (2.6)	2.45	86	.016
Male, n (%)	30 (68)	32 (73)			ns
Race, n					ns
Black	4	12			
Caucasian	19	16			
Hispanic	19	13			
American Indian	1	0			
Asian	0	1			
Biracial	1	2			
Socioeconomic Status					
Composite z-score of the Socioeconomic Index	−.0418 (.833)	.1825 (.847)	−1.25	86	ns
Mechanism of injury, n				8	.000
Auto, truck, bus (driver/passenger)	17	1			
Motorcycle/moped	6	4			
RV/off-road	4	1			
Bicycle	3	3			
Fall	8	9			
Falling Object	0	1			
Sports/play	1	23			
Hit by motor vehicle (pedestrian)	4	1			
Other	1	1			

Note: ns = not significant.

Table 2

Novel Psychiatric Disorder 3 Months After Traumatic Brain Injury (TBI) and Orthopedic Injury (OI)

TBI	OI
1 Personality Change due to TBI	1 Major Depressive Disorder
2 Personality Change due to TBI	2 Attention-Deficit/Hyperactivity Disorder, Inattentive type
3 Separation Anxiety Disorder Anxiety Disorder, not otherwise specified (PTSD symptoms)	3 Specific Phobia Oppositional Defiant Disorder
4 Personality Change due to TBI	4 Acute Stress Disorder Substance Abuse
5 Personality Change due to TBI	5 Post-Traumatic Stress Disorder
6 Personality Change due to TBI Attention-Deficit/Hyperactivity Disorders, Combined Type	6 Post-Traumatic Stress Disorder
7 Personality Change due to TBI	
8 Personality Change due to TBI Major Depressive Disorder Post-Traumatic Stress Disorder	
9 Personality Change due to TBI Anxiety Disorders, Not Otherwise Specified	
10 Personality Change due to TBI Major Depressive Disorder	
11 Personality Change due to TBI	
12 Personality Change due to TBI	
13 Personality Change due to TBI	
14 Personality Change due to TBI Oppositional Defiant Disorder Generalized Anxiety Disorder Separation Anxiety Disorder Post-Traumatic Stress Disorder	
15 Attention-Deficit/Hyperactivity Disorder, inattentive type	
16 Adjustment Disorder with Depressed Mood	
17 Post-Traumatic Stress Disorder Adjustment Disorder with Mixed Anxiety and Depressed mood	
18 Oppositional Defiant Disorder	
19 Anxiety Disorder, Not Otherwise Specified	
20 Attention-Deficit/Hyperactivity Disorder, Not Otherwise Specified	
21 Personality Change due to TBI Attention-Deficit/Hyperactivity Disorder, Inattentive type Depressive Disorder, Not Otherwise Specified Oppositional Defiant Disorder	

Note: PTSD = post-traumatic stress disorder.

Table 3

Relationship of Novel Psychiatric Disorder at 3 Months Post-injury, Functional Anisotropy, and Group.

Multivariate Analysis of Covariance:			
	F	**df**	**Sig**
Novel Psychiatric Disorder	2.21	8,64	.0372
Group	4.12	8,64	.0005
Age	1.85	8,64	.0843
Logistic Regression:			
Functional Anisotropy in Specific Regions (controlling for group and age) and Novel Psychiatric Disorder			
Right frontal	14.3	1	.0003
Left frontal	10.1	1	.0022
Right uncinate fasciculus	13.5	1	.0004
Left uncinate fasciculus	8.8	1	.0040
Right centrum semiovale	6.2	1	.0147
Left centrum semiovale	6.8	1	.0108
Right temporal	3.5	1	.0662
Left temporal	2.2	1	.1437