Psychiatric Disorders in Children and Adolescents in the First Six Months After Mild Traumatic Brain Injury

Jeffrey E. Max, M.B.B.Ch
Russell J. Schachar, M.D.
Julie Landis, Ph.D.
Erin D. Bigler, Ph.D.
Elisabeth A. Wilde, Ph.D.
Ann E. Saunders, M.D.
Linda Ewing-Cobbs, Ph.D.
Sandra B. Chapman, Ph.D.
Maureen Dennis, Ph.D.
Gerri Hanten, Ph.D.
Harvey S. Levin, Ph.D.

The objective was to assess the nature, rate, predictive factors, and neurocognitive correlates of novel psychiatric disorders (NPD) after mild traumatic brain injury (MTBI). Children age 5–14 years with MTBI (N=87) from consecutive admissions to five trauma centers were enrolled and studied with semistructured psychiatric interviews soon after injury (baseline), and 70 of these children were assessed again 6 months post-injury. Injury severity; lesion characteristics; pre-injury variables, including psychiatric disorder, family psychiatric history, family functioning, socioeconomic status, psychosocial adversity, and adaptive functioning; and post-injury neurocognitive and adaptive functioning measures were assessed with standardized instruments. NPD occurred in 25 of 70 participants (36%) in the first 6 months after injury. NPD at 6 months was predicted by the presence of frontal white-matter lesions on MRI at 3 months post-injury, and was associated with concurrent decrements on neurocognitive indices of processing speed, expressive language, and intellectual functioning. NPD was not predicted by other indices of severity, pre-injury psychosocial variables, estimated pre-injury academic functioning, or adaptive and executive function decrements 6 months post-injury. These findings suggest that short-term psychiatric morbidity associated with MTBI in children and adolescents may be more common than previously thought and may have readily identifiable neuroimaging and neurocognitive correlates.

(The Journal of Neuropsychiatry and Clinical Neurosciences 2013; 25:187–197)

Received January 16, 2012; revised May 15, 2012; accepted May 29, 2012. From the Dept. of Psychiatry, Rady Children's Hospital and, Univ. of California San Diego, San Diego, CA (JEM); Dept. of Psychiatry (RJS), Dept. of Psychology (MD), Hospital for Sick Children, Toronto, Ontario, Canada; Dept. of Psychology, Brigham Young Univ., Provo UT (EDB); Dept. of Physical Medicine and Rehabilitation, Baylor College of Medicine, Houston, TX (EAW, GH, HL); Dept. of Psychiatry (AS), Dept. of Pediatrics (LE-C), Univ. of Texas Health Sciences Center, Houston, TX; Center for BrainHealth, Univ. of Texas, Dallas, TX (SC). Send correspondence to Jeffrey E. Max, M.B.B.Ch; Rady Children's Hospital, San Diego, CA; e-mail: jmax@ucsd.edu

The annual incidence of children suffering traumatic brain injury in the United States is approximately 180 per 100,000, with mild traumatic brain injury (MTBI) accounting for about 90% of cases.[1,2] Even a small percentage of these children with negative outcomes would represent a major public health problem. Accurate prediction of the children with MTBI who will develop psychiatric problems is a critical and virtually unstudied goal. If prediction were possible, interventions could expediently be targeted.

Existing studies that predict which children with MTBI will develop new or novel psychiatric disorders (NPD) are scarce and limited in the range of predictive variables tested. By definition, NPD can manifest in two ways:[3] First, they could occur in a patient with no pre-injury lifetime psychiatric disorders, who then manifests a psychiatric disorder after the TBI. Second, they could occur in the case of a patient with a pre-injury lifetime psychiatric disorder, who manifests a psychiatric disorder that was not present before the TBI; for example, a patient with a pre-injury lifetime history of major depressive disorder who develops attention-deficit/hyperactivity disorder (ADHD) after the injury would receive the classification, but would not if only a new episode of major depression or a switch to mania or hypomania occurred.

There is only one study investigating the relationship of MTBI and NPD.[3] We reported that children with mild/moderate TBI and a history of psychiatric disorder before the injury were at significantly higher risk for developing NPD in the first 3 months after injury.[3] Other studies focused on specific symptom ratings, such as post-concussion symptoms (PCS), attention, and conduct, typically derived from brief parent and child interviews and/or questionnaires administered to parents, children, and teachers, rather than psychiatric disorders derived from standardized psychiatric interviews.[4–10] Similar results were obtained in an earlier study of PCS, where children with MTBI who experienced an increase in symptoms had poorer pre-injury behavioral adjustment than those who did not.[4] Other investigators found that significant ongoing behavioral difficulty 3 months post-injury was related to higher incidence of previous TBI, premorbid stressors, pre-existing psychiatric or neurological problems, and learning difficulties in children with MTBI.[5] Results from a recently-studied cohort of children with MTBI extended the findings related to PCS.[6–8,10] Results show that a high acute level of PCS was especially likely among children with MTBI whose acute clinical presentation reflected more severe injury.[10] PCS was significantly higher in the MTBI versus the orthopedic injury (OI) control group 2 weeks after injury (51% versus 30%), but not thereafter in the first year post-injury (19%−27% versus 19%−21%).[6] Findings form a birth-cohort study indicated that MTBI resulting in inpatient, rather than outpatient, treatment was associated with increased ratings of hyperactivity/inattention and conduct disorder, especially if the MTBI occurred before age 5.[9]

Although NPD is important in itself because it implies emotional and behavioral morbidity, the question of whether NPD is associated with neurocognitive deficits in an MTBI population has not been fully investigated. The anticipation of an association of NPD with neurocognitive deficits exists because brain damage, that is documented by sensitive neuroimaging methods,[11] increases the risk for both psychiatric and cognitive disturbance.[12] This knowledge lacuna is important because it is clinically necessary to know the full scope of deficits confronted by children with NPD. If NPD is often associated with cognitive deficit, in general, or specific cognitive deficit, these deficits may need to be taken into account in treatment-planning. Furthermore, there is the question of etiology. Existing knowledge of the specific neural substrates of cognition might be informative with regard to the mechanism of NPD and, by extension, psychiatric disorders that occur in the absence of MTBI. There are three studies most relevant to this area. One study found that children with MTBI whose PCS increased (8/23; 35%) versus those whose did not increase (15/23; 65%) from before injury to 3 months post-injury, performed significantly more poorly on tests of processing speed, visual memory, attention, and executive function (Stroop interference).[4] Total white-matter volume, both within a week of injury and 3 months post-injury, was significantly smaller in the group with increased symptoms, but this was interpreted as representing pre-injury status. Another study found that 17% of children with MTBI showed significant ongoing behavioral problems 3 months after injury[5] and that these children were not differentiated by their performance on verbal memory, visual memory, processing speed, attention, or executive function tests. A third study found that measures of executive function were not significantly worse in the MTBI versus the OI group in the first year after injury.[7] These findings are consistent with the authoritative reviews and

a recent study suggesting benign cognitive outcomes after MTBI.[13–15] However, MTBI was more likely to result in PCS than was OI, among children of lower, as compared with higher, cognitive ability. This was especially true for children with complicated MTBI (lesion detected on MRI).[8]

We hypothesized that in children with MTBI, NPD at 6 months post-injury would be predicted by pre-injury lifetime psychiatric disorder and frontal white-matter lesions, that is, related to diffuse axonal injury, which is the most important clinical characteristic in MTBI.[16] We further hypothesized that NPD at 6 months would be associated with significant differences in concurrent neurocognitive measures of processing speed, intellectual functioning, expressive language, and executive function, as well as significant differences in estimates of pre-injury academic functioning measured in the first weeks post-injury.

METHODS

Participants

The participants in this study consisted of 87 children and adolescents who were recruited from consecutive admissions during their initial hospitalization within 2 weeks of an MTBI at one of three academic medical centers in Texas; Rady Children's Hospital, San Diego; and The Hospital for Sick Children, in Toronto. We do not have accurate data on the number of children who were approached, the proportion who were eligible for recruitment, and participation rate among those eligible. This is in part due to the fact that our patients were not required to answer eligibility questions before making a decision regarding participation. Enrollment at the San Diego site was limited to complicated mild TBI (Glasgow Coma Scale [GCS] score $\geq$13, but with lesions seen on clinical neuroimaging).[17] Exclusion criteria included preexisting schizophrenia or autistic disorder, mental deficiency, and injury due to child abuse or penetrating missile injury. Children in San Diego were excluded only if they had attention-deficit/hyperactivity disorder (ADHD) before the injury. The parents/guardians of all children signed an informed consent, and all children signed an assent to participate in accordance with the Institutional Review Boards at each site.

Demographic details (age, gender, socio-economic status), pre-injury psychosocial variables (pre-injury lifetime psychiatric status, adaptive functioning, family functioning, family psychiatric history ratings, psychosocial adversity), and injury indices (GCS scores, depressed skull fracture incidence, mechanism of injury) are provided in Table 1. Race of participants were as follows: Caucasian: 54 (62%); African American: 13 (15%); Hispanic: 13 (15%); Asian: 3 (3%); Other: 4 (5%).

Measures

Psychiatric Assessment DSM-IV psychiatric diagnoses[18] were derived by utilizing a semistructured interview, the Schedule for Affective Disorders and Schizophrenia for school-aged children, Present and Lifetime version (K-SADS-PL).[19] The K-SADS-PL is an integrated parent–child interview that generates diagnoses based on a clinician's synthesizing data collected from parent and child separately, querying present and lifetime symptoms (at baseline assessment conducted within 2 weeks of injury) and symptoms present or past from injury to 6 months (at 6-month assessment). We also administered the Neuropsychiatric Rating Schedule (NPRS),[20] which is a semistructured interview designed to identify symptoms and subtypes of the DSM-IV diagnosis of Personality Change Due to TBI. Both parents and children served as informants in the interview that took place at baseline and at 6 months after injury.

Best-estimate psychiatric diagnoses[21] were generated by the interviewer after integrating the reports of the parent and the child from the K-SADS and NPRS interviews and, when available (56/87: 64% at baseline; 43/70: 61% at 6 months) from the Survey Diagnostic Instrument[22] completed by the teacher.

Neurological Assessments Severity of TBI classification was based on the lowest post-resuscitation score on the Glasgow Coma Scale (GCS),[17] which was recorded from clinical notes. The GCS is the standard measure of severity of acute brain injury associated with TBI. The scale measures motor, eye-opening, and verbal responsiveness. Scores range from 3 (unresponsive) to 15 (normal). Children with GCS scores of 15 were included if they had a loss of consciousness and/or posttraumatic amnesia and post-concussion symptoms.

Overall extracranial injury severity was documented with the Abbreviated Injury Scale (AIS), which provided an Injury Severity Score (ISS).[23] The ISS was the sum of the squares of the highest AIS score in each of the three most severely injured body regions (chest, abdominal or pelvic contents, extremities, and external), if applicable.

TABLE 1. Demographic, Psychosocial, and Injury Data of a Mild Traumatic Brain Injury (TBI) Cohort (N=87)

		N
Demographic Variables		
Age at injury, years, mean (SD)	10.02 (2.99)	87
Gender: boys, (%)	58 (66.7%)	87
Socioeconomic status,[27] mean (SD)	40.13 (11.81)	85
Psychosocial Variables		
Pre-injury lifetime psychiatric disorder number (%)	33 (37.9%)	87
Pre-injury Vineland Adaptive Behavior Composite Standard Score, mean (SD)	94.62 (15.34)	79
Pre-injury Family Functioning, mean (SD)	1.55 (0.42)	80
Family Psychiatric History, mean (SD)	1.09 (1.03)	69
Pre-injury Psychosocial Adversity, mean (SD)	0.65 (0.83)	84
Injury Variables		
Lowest post-resuscitation GCS score 13	6 (7%)	
Lowest post-resuscitation GCS score 14	20 (23%)	
Lowest post-resuscitation GCS score 15	61 (70%)	
Depressed skull fracture, N (%)	8 (9.2)	87
Mechanism of injury	N (%)	87
Auto, truck, bus passenger	17 (19.5)	
Recreational vehicle/off-road vehicle	3 (3.4)	
Bicycle	6 (6.9)	
Fall	29 (33.3)	
Hit by a falling object	3 (3.4)	
Sports or play	11 (12.6)	
Hit by motor vehicle	16 (18.4)	
Other	2 (2.3)	

SD: standard deviation; GCS: Glasgow Coma Scale.

Magnetic resonance imaging (MRI; 1.5 tesla) was conducted in most subjects 3 months after the injury, when lesions appear stable. The protocol included a T_1 volumetric spoiled gradient-recalled echo (SPGR) and fluid attenuated-inversion recovery (FLAIR) sequences, acquired in coronal and sagittal planes, according to a research protocol. Results were coded for lesion location by project neuroradiologists at each site. A total of 73 of the 87 enrolled children (84%) returned to complete their research MRI. The distribution of lesions in children who completed the research MRI is displayed on the left side of Table 2. The neuroradiologists' classification of lesions and the number of children with each pathology among children who returned for psychiatric follow up 6-months post-injury was as follows: gliosis (N=10), shearing injury (N=8), atrophy (N=7), encephalomalacia (N=4), shearing and hemorrhage (N=4), hemosiderin deposit (N=3), contusion (N=1), contusion/hematoma (N=1), contusion and encephalomalacia (N=1), atrophy and encephalomalacia (N=1), gliosis and encephalomalacia (N=1).

Psychosocial Assessments The Family History Research Diagnostic Criteria[24] interview was conducted by trained research assistants at each site. Criteria were modified to conform with DSM-IV criteria. At least one parent acted as the informant and was questioned about psychiatric disorders in each first-degree relative of the index child with TBI. Family ratings were then summarized on a 4-point scale[25] of increasing severity.

Pre-injury global family functioning at the baseline assessment was measured by using the Family Assessment Device, General Functioning scale.[26] The scale consists of 12 items in the format of a self-report questionnaire. The primary caretaker of each family responded to each item on a 4-point Likert scale ranging from 1 to 4. Lower scores represent healthier functioning.

Socioeconomic status (SES) assessment was accomplished through the Four-Factor Index.[27] Classification depends on scores derived from a formula involving both the maternal and paternal educational and occupational levels. Scores range from 8 to 66, with higher scores indicating higher educational and occupational levels and higher SES.

We used a psychosocial adversity index that was very similar to that used in an important early study of pediatric TBI.[28] Six areas were assessed; for each area that suggested adversity, a score of 1 was given, and a score of 0 was given where there was no adversity. The areas are 1) child not living with biological or adoptive parents; 2) sibship of at least 4 children, or a Person:

TABLE 2. Lesion Distribution, Based on Research MRI: Entire Cohort (N=73) and in Children With and Without Novel Psychiatric Disorder (NPD) in the First 6 Months After Injury

	All Subjects (N=73); N (%)	NPD (N=22); N (%)	No NPD (N=41); N (%)	p
Any lesion	38 (52.1)	15 (68.2)	19 (46.3)	NS
Frontal-lobe white matter	8 (11.0)	5 (22.7)	1 (2.4)	0.017
Distribution of other lesions				
Frontal lobe				
Any frontal-lobe gray matter	16 (21.9)	6 (27.3)	9 (22.0)	
Superior frontal gyrus	7 (9.6)	3 (13.6)	4 (9.8)	
Middle frontal gyrus	8 (11.0)	3 (13.6)	5 (12.2)	
Inferior frontal gyrus	6 (8.2)	3 (13.6)	3 (7.3)	
Cingulate gyrus	1 (1.4)	0	1 (2.4)	
Orbital gyrus	2 (2.7)	2 (9.1)	0	
Gyrus rectus	5 (6.8)	1 (4.5)	3 (7.3)	
Temporal lobe	7 (9.6)	2 (9.1)	5 (12.2)	
Parietal lobe	12 (16.4)	4 (18.2)	7 (17.1)	
Basal ganglia	1 (1.4)	1 (4.5)	0	
Thalamus	1 (1.4)	0	1 (2.4)	
Cerebellum hemisphere	1 (1.4)	1 (4.5)	0	

White-matter lesions were recorded specifically only in the frontal lobes.

Room ratio exceeding 1; 3) admission of the child into the care of the local authority because of family difficulties; 4) maternal "malaise inventory" score of ≥7; 5) paternal criminality; and 6) father or mother with an unskilled or semiskilled job.

Pre-injury adaptive functioning was retrospectively assessed shortly after the injury, and adaptive functioning at 6 months post-injury was assessed with the Vineland Adaptive Behavior Scale interview.[29] This involved a semistructured interview conducted with the primary caretaker by a trained research assistant.

Neurocognitive Assessments The parents/guardians of participants were asked to withdraw stimulant medication for 24–48 hours before testing because stimulants could attenuate the cognitive deficits.

Estimates of Pre-Injury Cognitive Functioning Woodcock-Johnson Revised Calculation and Letter–Word Identification subtests were conducted at baseline (within 2 weeks of injury).[30] The Calculation subtest is an untimed test measuring accuracy of completing math problems. A standard score was analyzed based upon total problems correct. The Letter–Word Identification measures accuracy of reading aloud letters and words. A standard score was analyzed reflecting the total number of items read correctly. There is evidence that the baseline post-injury assessment of these academic function domains estimates pre-injury functioning, especially in children with mild TBI,[31] although pre-injury academic functioning also depends on other factors.

Concurrent Neurocognitive Function (6 months post-injury) Processing speed was measured with the Wechsler Intelligence Scale for Children–III (WISC–III) Coding and Symbol Search subtests.[32,33] On the Coding subtest, children transcribed the correct geometric designs below numbers by use of a key. Number of symbols correctly transcribed in 2 minutes was measured. In the Symbol Search subtest, the child was presented with target stimuli and asked to check a Yes or No box as fast as possible, indicating whether or not the target(s) appeared among an array of stimuli (45 total trials). The score was the number of correct responses minus the number of errors completed in 120 seconds. A scaled score was obtained and averaged for both subtests.

Intellectual functioning was measured with the Wechsler Abbreviated Scale of Intelligence (WASI).[34] Full-Scale IQ was assessed by means of the Vocabulary, Similarities, Block Design, and Matrix Reasoning subtests.

Expressive language was assessed with the Clinical Evaluation of Language Fundamentals–3rd Edition (CELF−3) Formulated Sentence subtest.[35] Children were asked to formulate one sentence in response to a visual picture that also contained a target word or phrase. This 22-item subtest measured expressive language ability at the sentence level. Scaled scores were used in the analyses.

The Stroop Color–Word Interference Task[36] was used to measure the interference inherent in naming the color of the print of color words presented in colors that are semantically incongruent (e.g., the word "red" printed in blue letters), involving suppression of the

more strongly-established response of reading the color word ("red"). Conditions were 1) oral reading six words in black print; 2) naming three common colors presented individually as rectangles; 3) naming the color of print (red, green, and blue) of three words (dog, cat, bed) that did not denote color; 4) naming the color of print of three color names (red, green, blue) which were presented under a congruent condition (e.g., red print for the word "red") or incongruent condition (e.g., green print for the word "red"). Raw scores adjusted for age for the incongruent condition were used in the analyses.

The Stop Signal Reaction Time Task (SSRT)[37,38] was used as a measure of motor-response inhibition. A visual-choice reaction time task (use left index finger to press one button when an X appears on the screen and the right index finger to press a different button when an O is presented) and a stop task in which the child was instructed to cease the response when a tone was presented after the Go signal (X or O) were given concurrently to the child, with stop trials occurring unpredictably on 25% of the trials. After failed stop-trials, the delay between the Go signal and the Stop signal was shortened (allowing more time for child to abort response) by a computer algorithm, whereas the delay was increased (i.e., the Stop signal sounded at a later stage of the child's response, thus increasing the difficulty in stopping) after successful stop-trials. This tracking algorithm converges on the delay between presentation of the Go and the Stop signals at which the participant can inhibit their responses half the time. The difference between mean Go reaction-time on Go trials (i.e., trials without a Stop signal) and the mean delay on the Stop-signal trials, known as stop-signal reaction-time, provides an estimate of the latency of the motor-response inhibition process, which is considered a measure of executive function. Eight blocks of 40 trials were presented. Raw scores with adjustment for age were used in the analyses.

Data Analysis

The association of 6-month post-injury NPD with the hypothesized predictive variables of pre-injury lifetime psychiatric disorder and neuroimaging abnormalities, specifically the presence of any lesion, and the presence of frontal lobe white-matter lesions, was tested by χ^2 analyses or Fisher's exact test, as appropriate. Furthermore, we analyzed the relationship of NPD with baseline academic testing scores (WJ-R Calculation and Letter–Word ID scales) as well as concurrent neurocognitive functioning 6 months post-injury for specific domains hypothesized to be sensitive to disruption related to behavioral disturbance after MTBI (WISC–III Processing Speed, WASI Full-Scale IQ, CELF−3 Formulated Sentences, Stroop, Stop Signal reaction-time). Other exploratory analyses regarding variables potentially associated with NPD included demographics (age at injury, gender, SES, race), pre-injury psychosocial (pre-injury lifetime psychiatric status, adaptive functioning, family functioning scores, family psychiatric history ratings, psychosocial adversity), and injury (GCS scores, CT scan abnormality, depressed skull fracture, extracranial Injury Severity Score) variables. Because the inclusion/exclusion criteria in San Diego were different in some respects from the other sites, all analyses were repeated without these participants, but the results were essentially unchanged and are therefore not reported here. Statistical tests were independent-sample *t*-tests or χ^2 and effect size analyses as appropriate. Alpha levels were set at 0.05.

RESULTS

In all, 70 of the original 87 children (80.5%) returned for the 6-month psychiatric assessment. The returning group was not significantly different from the children who did not return with respect to distribution of GCS scores, age, gender, race, SES, psychosocial adversity, pre-injury lifetime psychiatric disorder, or pre-injury adaptive function. Ten of the children with missing 6-month psychiatric data had a research MRI. Lesion presence and specific location on the research MRI did not differ in those with psychiatric follow-up versus those without.

Pre-Injury and Novel Psychiatric Disorders

Lifetime pre-injury psychiatric disorders were present in 33/87 (38%) of enrolled children. Specifically, these disorders included ADHD (N=20), simple phobia (N=8, including 2 in remission), separation anxiety disorder (N=5, including 2 in remission), oppositional defiant disorder (N=3, including 1 in remission), obsessive-compulsive disorder (N=2), generalized anxiety disorder (N=2), encopresis (N=1), disruptive behavior disorder, not otherwise specified (N=1), eating disorder, not otherwise specified (N=1), social phobia (N=1), chronic

TABLE 3. Pre-Injury and Injury Correlates of Novel Psychiatric Disorder (NPD) in the 6 Months After Mild TBI

	NPD (N=25)	No NPD (N=45)	*t*	df
Demographic variables				
Age at injury, years	9.8 (3.3)	10.4 (2.9)	0.73	68
Gender: boys (%)	17 (68%)	30 (67%)		1
Socioeconomic status	37.7 (11.2) N=24	41.9 (12.1)	1.42	67
Race				4
White	13	31		
African American	4	5		
Hispanic	5	6		
Asian	2	1		
Other	1	2		
Psychosocial variables				
Pre-injury lifetime psychiatric disorder, number (%)	10 (40%)	18 (40%)		1
Pre-injury Vineland Adaptive Behavior Composite	94.2 (16.0) N=23	95.2 (16.0) N=43	–0.25	64
Pre-injury Family Functioning	1.53 (0.42) N=24	1.56 (0.43) N=44	–0.06	66
Family Psychiatric History	1.1 (0.9) N=23	1.1 (1.1) N=39	0.15	60
Pre-injury Psychosocial Adversity	0.9 (0.9) N=23	0.6 (0.9)	–1.22	66
Injury variables				
Lowest post-resuscitation GCS score				2
Number of participants with GCS 13	3	3		
Number of participants with GCS 14	7	11		
Number of participants with GCS 15	15	31		
Abnormal CT scan	11/21 (52%)	15/42 (36%)		
Depressed skull fracture	3/25 (12%)	4/45 (9%)		
Abbreviated Injury Scale: Injury Severity Score	3.2 (6.8)	1.4 (3.2)	–1.31	30.2

None of the analyses reached statistical significance. Values are expressed as mean (standard deviation) except where indicated.
GCS: Glasgow Coma Scale.

motor tic disorder (N=1), and major depressive disorder (N=1, in remission).

NPD occurred in 25/70 children (36%) who returned for the 6-month assessment. The specific NPDs were ADHD (N=7), personality change due to TBI (N=7), oppositional defiant disorder (N=5), adjustment disorder (N=4, including 2 in remission), posttraumatic stress disorder (N=3), major depressive disorder (N=3, including 1 in remission), generalized anxiety disorder (N=2), specific phobia (N=2), separation anxiety disorder (N=2), and substance abuse (N=1).

Table 3 presents data on the variables tested as potential predictors of the development of NPD during the first 6 months after TBI. Our hypothesis that pre-injury lifetime psychiatric disorder would predict NPD at 6 months was not supported. The remainder of Table 3 lists exploratory comparisons of other psychosocial variables according to the presence or absence of NPD at 6 months. None of the other demographic or psychosocial variables, including age at injury, gender, socioeconomic status, race, pre-injury adaptive functioning, pre-injury family functioning, family psychiatric history, or pre-injury psychosocial adversity discriminated between groups. Similarly, injury variables, including the lowest post-resuscitation GCS score, CT scan documented lesions, proportion of depressed skull fractures, and AIS extracranial injury severity scores, did not discriminate between those who did versus those who did not develop NPD.

Lesion Correlates of NPD

The hypothesis that the presence versus absence of a lesion on the research MRI would predict NPD was not supported (15/22 children with NPD had a lesion; 19/41 children with no NPD had a lesion; Table 2). However, NPD was significantly associated with lesions within the frontal white matter: 5/22 children with NPD had a frontal white-matter lesion; 1/41 children with no NPD had a frontal white-matter lesion (Fisher's exact test; p=0.017). Additional details regarding lesion distribution are shown in Table 2.

NPD at 6-Month Assessment: Neurocognitive Predictors at Baseline Post-Injury

The groups with and without NPD were not significantly different with respect to performance in the first weeks after injury on the Woodcock-Johnson Revised Calculation and Letter–Word ID subtests, although the NPD group tended to have lower scores (p=0.083) on the latter subtest (Table 4).

TABLE 4. Neurocognitive Correlates of Novel Psychiatric Disorders (NPD) in the 6 Months After Mild Traumatic Brain Injury (MTBI)

	NPD (N=25)	No NPD (N=45)	t	df	p	Effect Size
Estimates of pre-injury cognitive functioning (conducted after the injury)						
WJ-R Calculation standard score	103.2 (15.4)	108.4 (15.3); N=44	1.37	67	NS	0.34
WJ-R Letter Word ID standard score (SD)	99.9 (16.6)	107.5 (17.7)	1.76	68	<0.1	0.44
Neurocognitive correlates 6 months post-injury						
WISC–III Processing Speed standard score	104.5 (17.1); N=23	117.1 (16.4); N=43	2.93	64	<0.005	0.75
WASI Full-Scale IQ standard score	96.0 (13.6); N=22	110.3 (14.3); N=40	3.85	60	<0.000	1.02
CELF–3 Formulated Sentences scaled score	8.6 (1.9); N=23	11.3 (3.0); N=43	3.85	64	<0.000	1.08
Stroop Color and Word Test reaction time (SD)	1,106.8 (243.5); N=19	1,092.8 (241.3); N=36	–0.20	53	NS	0.06
Stop Signal reaction time (SD)	342.4 (254.4) N=17	324.2 (215.1) N=37	–0.27	52	NS	0.08
Adaptive Functioning 6 months post-injury						
Vineland ABC Standard Score (SD)	91.1 (16.6) N=24	95.1 (14.4)	1.04	67	NS	0.26

Values are expressed as mean (standard deviation).
ABC: Adaptive Behavior Composite; CELF: Clinical Evaluation of Language Fundamentals; NS: not significant; WASI: Wechsler Abbreviated Scale of Intelligence; WISC: Wechsler Intelligence Scale for Children; WJ–R: Woodcock-Johnson–Revised.

NPD at 6-Month Assessment: Neurocognitive and Adaptive Function Correlates at 6 Months

The group with NPD had significantly lower WISC–III processing speed (p=0.005), WASI FIQ ($p < 0.0005$), and CELF−3 Formulated Sentences ($p < 0.0005$) scores than the group with no NPD (Table 4). However, the groups were not significantly different with regard to Stroop Color and Word Test reaction time or Stop Signal reaction time. Adaptive function measured by the Vineland Adaptive Behavior composite was not significantly different across groups. It is unlikely that concurrent psychotropic medication affected the results because only one participant was taking an anticonvulsant; one was taking a selective serotonin reuptake inhibitor; and one, a tricyclic antidepressant.

DISCUSSION

The main findings of this study are that the rate of NPD 6 months after MTBI in children was high, that frontal white-matter lesions significantly predicted NPD, which was, in turn, significantly correlated with neurocognitive decrements in processing speed, intellectual functioning, and expressive language.

NPD was relatively common after mild TBI, occurring in 25 of 70 children (36%) from consecutive MTBI admissions in the first 6 months after injury. This rate was higher than rates of NPD in children with mild/moderate TBI reported in an earlier, similarly designed study (3-month outcome: 8/27 (30%); 6-month outcome: 3/30 (10%).[39] If the high rate of NPD found in this study were to be replicated in a larger sample with injured controls, the public health implications would be substantial because of the high incidence of MTBI.[1,2] The NPDs were heterogeneous, as found in other studies of pediatric TBI.[25,28] This suggests that studies of mild TBI that rely on measuring "post-concussive" symptoms will underestimate new behavioral morbidity, because such symptoms correspond most closely with Personality Change Due to TBI, and not with the other heterogeneous disorders.[4]

The specific presence of frontal white-matter lesions, rather than a nonspecific lesion detected on MRI or even other indices of injury severity, such as the lowest post-resuscitation GCS, depressed skull fracture, or abnormal CT scan, predicted NPD. This specificity emphasizes that frontal white-matter is important in cortical networks and that diffuse injury results in a less connected and relatively less efficient complex of neural systems.[40] This type of white-matter damage may lead to many adverse outcomes in childhood disorders of brain and behavior.[41]

NPD at 6 months post-injury was associated with concurrent deficits in processing speed, intellectual functioning, and expressive language, but not with measures of executive function. It may not be that these robust findings are related to differences that pre-dated the injury because the groups with NPD versus no-NPD were similar in multiple pre-injury demographic and psychosocial variables that may influence these neurocognitive domains. The presumed mechanism of the association of NPD with neurocognitive deficits is that brain damage increases the risk for both psychiatric and cognitive disturbances.[12] Our findings are in partial agreement with the two relevant previous studies of

markers of post-MTBI behavioral change with neurocognitive deficits.[4,5] One study found no association of behavioral change with processing speed or executive function tests,[5] whereas the other found an association with tests in both these neurocognitive domains.[4] Conversely, it is possible that if the groups differed in pre-injury cognitive functioning, they could have been more vulnerable to developing NPD.

It is particularly striking that the group with NPD was not significantly different in any of the carefully studied pre-injury psychosocial factors measuring personal psychiatric history, adaptive functioning, family functioning, or family psychiatric history, as well as psychosocial adversity and SES. These findings ran counter to those of previous MTBI-related studies.[3,4]

The 38% rate of lifetime pre-injury psychiatric disorder is consistent with the other studies of consecutively hospitalized children with TBI.[3,28] This is a high rate, as compared with norms from epidemiological studies, where the rate is approximately 20%.[42] It is likely that pre-injury psychiatric disorder is a risk factor for TBI, in part related to impulsivity of ADHD.[43]

The findings of this study must be considered within its limitations. Our MTBI sample was limited to hospitalized children. There is a growing trend for children with MTBI to be discharged from emergency rooms,[44] and therefore our sample may differ from the broader group of children with MTBI. Our sample may reflect adverse injury factors or psychosocial factors that would influence the decision to hospitalize. The rate of NPD may be elevated in this higher-risk subgroup, but it is not clear how or whether predictors or correlates of NPD would be affected. Interrater reliability assessments for the diagnosis of NPD were not directly tested based on videotaped interviews. However, the child psychiatrists or psychologists at each site closely supervised the assessments. Furthermore, 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. Attrition, in terms of participation of children, was almost 20%. However, there were no demographic, psychosocial, or injury variables upon which the children with missed assessments differed from those who returned. Although the image analysis did not use volumetric measurements that might have more clearly delineated lesion correlates of NPD, the images themselves were of research quality required for such volumetric assessments that allowed project neuroradiologists to document even the smallest of lesions. Whereas our hypotheses did not call for an orthopedic injury comparison group, such a group could control for NPD in children predisposed to and exposed to injuries. There was some heterogeneity within our sample, in that the San Diego cohort excluded children with pre-injury ADHD and children with uncomplicated MTBI. However, the San Diego cohort accounted for only 6 of 70 cases (9%) of those assessed at 6 months.

The strengths of this study should also be appreciated. This is the largest psychiatric interview study of a consecutively-admitted, non-referred population of pediatric MTBI assessed shortly after injury and studied prospectively thereafter. The breadth and depth of assessments were extensive and included interview assessments of psychopathology, adaptive functioning, and family psychiatric history, in addition to rating scales encompassing injury and other psychosocial risk factors for new-onset psychiatric disorder. Furthermore, lesion analysis was based on readings by expert neuroradiologists.

The current findings have specific clinical and research implications. Children with MTBI should be screened for the development of NPD in the first few months after injury. Individuals with evidence of frontal white-matter injury, deficits in language, or processing speed should be monitored particularly carefully. There is an urgent need for a large psychiatric study, such as we are now conducting, of consecutively-treated inpatients and outpatients with MTBI and age, gender, and SES-matched injured control patients, to determine the extent of the morbidity related to this extremely common type of TBI. Future studies might also address the relationship between specific neuropsychological deficits and neuropsychiatrically-identified NPD status after MTBI.

This work was completed at the Dept. of Psychiatry, University of California, San Diego, and Rady Children's Hospital, San Diego, CA.

This study was supported by National institute of Mental health (NIMH) Grant K-08 MH01800 (Dr. Max) and National Institute of Neurological Disorders and Stroke (NINDS) Grant NS-21889 (Dr. Levin).

Disclosures: Dr. Schachar is a consultant for Eli Lilly Corporation and Purdue Pharma (Canada). None of the other authors has financial disclosures to make relative to for-profit enterprises.

References

1. Kraus JF: Epidemiological features of brain injury in children: occurrence, children at risk, causes, and manner of injury, severity, and outcomes, in Traumatic Head Injury in Children. Edited by Broman SH, Michel ME. New York, Oxford University Press, 1995, pp 22–39
2. Kraus JF, Nourjah P: The epidemiology of mild, uncomplicated brain injury. J Trauma 1988; 28:1637–1643
3. Max JE, Smith WL Jr, Sato Y, et al: Traumatic brain injury in children and adolescents: psychiatric disorders in the first three months. J Am Acad Child Adolesc Psychiatry 1997; 36:94–102
4. Yeates KO, Luria J, Bartkowski H, et al: Post-concussive symptoms in children with mild, closed head injuries. J Head Trauma Rehabil 1999; 14:337–350
5. Ponsford J, Willmott C, Rothwell A, et al: Cognitive and behavioral outcome following mild traumatic head injury in children. J Head Trauma Rehabil 1999; 14:360–372
6. Hajek CA, Yeates KO, Gerry Taylor H, et al: Relationships among post-concussive symptoms and symptoms of PTSD in children following mild traumatic brain injury. Brain Inj 2010; 24:100–109
7. Maillard-Wermelinger A, Yeates KO, Gerry Taylor H, et al: Mild traumatic brain injury and executive functions in school-aged children. Dev Neurorehabil 2009; 12:330–341
8. Fay TB, Yeates KO, Taylor HG, et al: Cognitive reserve as a moderator of post-concussive symptoms in children with complicated and uncomplicated mild traumatic brain injury. J Int Neuropsychol Soc 2010; 16:94–105
9. McKinlay A, Dalrymple-Alford JC, Horwood LJ, et al: Long term psychosocial outcomes after mild head injury in early childhood. J Neurol Neurosurg Psychiatry 2002; 73:281–288
10. Taylor HG, Dietrich A, Nuss K, et al: Post-concussive symptoms in children with mild traumatic brain injury. Neuropsychology 2010; 24:148–159
11. Kou Z, Wu Z, Tong KA, et al: The role of advanced MR imaging findings as biomarkers of traumatic brain injury. J Head Trauma Rehabil 2010; 25:267–282
12. Max JE, Roberts MA, Koele SL, et al: Cognitive outcome in children and adolescents following severe traumatic brain injury: influence of psychosocial, psychiatric, and injury-related variables. J Int Neuropsychol Soc 1999; 5:58–68
13. Carroll LJ, Cassidy JD, Peloso PM, et al; WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury: Prognosis for Mild Traumatic Brain Injury: Results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med 2004; (43; Suppl)84–105
14. Satz P, Zaucha K, McCleary C, et al: Mild head injury in children and adolescents: a review of studies (1970–1995). Psychol Bull 1997; 122:107–131
15. Babikian T, Satz P, Zaucha K, et al: The UCLA longitudinal study of neurocognitive outcomes following mild pediatric traumatic brain injury. J Int Neuropsychol Soc 2011; 17:886–895
16. Bigler ED, Abildskov TJ, Wilde EA, et al: Diffuse damage in pediatric traumatic brain injury: a comparison of automated versus operator-controlled quantification methods. Neuroimage 2010; 50:1017–1026
17. Teasdale G, Jennett B: Assessment of coma and impaired consciousness: a practical scale. Lancet 1974; 2:81–84
18. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Washington, DC, American Psychiatric Press, 1994
19. Kaufman J, Birmaher B, Brent D, et al: Schedule for Affective Disorders and Schizophrenia for School-Age Children: Present and Lifetime Version (K-SADS–PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 1997; 36:980–988
20. Max JE, Castillo CS, Lindgren SD, et al: The Neuropsychiatric Rating Schedule: reliability and validity. J Am Acad Child Adolesc Psychiatry 1998; 37:297–304
21. Leckman JF, Sholomskas D, Thompson WD, et al: Best estimate of lifetime psychiatric diagnosis: a methodological study. Arch Gen Psychiatry 1982; 39:879–883
22. Boyle MH, Offord DR, Racine Y, et al: Identifying thresholds for classifying childhood psychiatric disorder: issues and prospects. J Am Acad Child Adolesc Psychiatry 1996; 35:1440–1448
23. Association for the Advancement of Automotive Medicine: Abbreviated Injury Scale, 1990 Revision. Des Plaines, IL, Association for the Advancement of Automotive Medicine, 1990
24. Andreasen NC, Endicott J, Spitzer RL, et al: The family-history method using diagnostic criteria. reliability and validity. Arch Gen Psychiatry 1977; 34:1229–1235
25. Max JE, Robin DA, Lindgren SD, et al: Traumatic brain injury in children and adolescents: psychiatric disorders at two years. J Am Acad Child Adolesc Psychiatry 1997; 36:1278–1285
26. Miller IW, Epstein NB, Bishop DS, et al: The McMaster Family Assessment Device: reliability and validity. J Marital Fam Ther 1985; 11:345–356
27. Hollingshead A: Four-Factor Index of Social Status Yale University, Department of Sociology, 1975
28. Brown G, Chadwick O, Shaffer D, et al: A prospective study of children with head injuries, III: psychiatric sequelae. Psychol Med 1981; 11:63–78
29. Sparrow S, Balla D, Cicchetti D: The Vineland Adaptive Behavior Scales. Circle Pines, MN, American Guidance Services, 1984
30. Woodcock R, Mather N: Woodcock-Johnson Tests of Cognitive Ability, 3rd Edition, Manual. DLM Teaching Resources, Allen, TX, 1989
31. Yeates KO, Taylor HG: Predicting premorbid neuropsychological functioning following pediatric traumatic brain injury. J Clin Exp Neuropsychol 1997; 19:825–837
32. Wechsler D: Wechsler Intelligence Scale for Children, 3rd Edition. New York, Pychological Corporation, 1991
33. Wechsler D: WISC–III Manual. San Antonio, TX, The Psychological Corporation, 1991
34. Wechsler D: Weschler Abbreviated Scale of Intelligence Manual. San Antonio, TX, The Psychological Corporation, 1999
35. Semel E, Wiig EH, Secord WA: Clinical Evaluation of Language Fundamentals, 3rd Edition (CELF–3). San Antonio, TX, The Psychological Corporation, 1995
36. Stroop JR: Studies of interference in serial verbal reactions. J Exp Psychol 1935; 18:643–662
37. Logan GD: On the ability to inhibit thought and action: a users' guide to the Stop Signal Paradigm, in Inhibitory

Processes in Attention, Memory, and Language. Edited by Dagenbach D, Carr TH. San Diego, Academic Press, 1994, pp 189–239
38. Leblanc N, Chen S, Swank PR, et al: Response inhibition after traumatic brain injury (TBI) in children: impairment and recovery. Dev Neuropsychol 2005; 28:829–848
39. Max JE, Lindgren SD, Robin DA, et al: Traumatic brain injury in children and adolescents: psychiatric disorders in the second three months. J Nerv Ment Dis 1997; 185:394–401
40. Sharp DJ, Beckmann CF, Greenwood R, et al: Default mode network functional and structural connectivity after traumatic brain injury. Brain 2011; 134:2233–2247
41. Max JE, Levin HS, Schachar RJ, et al: Predictors of personality change due to traumatic brain injury in children and adolescents six to twenty-four months after injury. J Neuropsychiatry Clin Neurosci 2006; 18:21–32
42. Costello EJ, Angold A, Burns BJ, et al: The Great Smoky Mountains Study of Youth: functional impairment and serious emotional disturbance. Arch Gen Psychiatry 1996; 53:1137–1143
43. Gerring JP, Brady KD, Chen A, et al: Premorbid prevalence of ADHD and development of secondary ADHD after closed head injury. J Am Acad Child Adolesc Psychiatry 1998; 37:647–654
44. Thurman D, Guerrero J: Trends in hospitalization associated with traumatic brain injury. JAMA 1999; 282:954–957