

Novel Psychiatric Disorder 6 Months After Traumatic Brain Injury in Children and Adolescents

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Objective: To investigate the factors predictive of novel psychiatric disorders in the interval 0–6 months following traumatic brain injury (TBI).

Methods: Children ages 5–14 years consecutively hospitalized for mild to severe TBI at five hospitals were recruited. Participants were evaluated at baseline (soon after injury) for pre-injury characteristics including psychiatric disorders, socioeconomic status (SES), psychosocial adversity, family function, family psychiatric history, and adaptive function. In addition to the psychosocial variables, injury severity and lesion location detected with acquisition of a research MRI were measured to develop a biopsychosocial predictive model for development of novel psychiatric disorders. Psychiatric outcome, including occurrence of a novel psychiatric disorder, was assessed 6 months after the injury.

Results: The recruited sample numbered 177 children, and 141 children (80%) returned for the six-month assessment.

Of the 141 children, 58 (41%) developed a novel psychiatric disorder. In univariable analyses, novel psychiatric disorder was significantly associated with lower SES, higher psychosocial adversity, and lesions in frontal lobe locations, such as frontal white matter, superior frontal gyrus, inferior frontal gyrus, and orbital gyrus. Multivariable analyses found that novel psychiatric disorder was independently and significantly associated with frontal-lobe white matter, superior frontal gyrus, and orbital gyrus lesions.

Conclusion: The results demonstrate that occurrence of novel psychiatric disorders following pediatric TBI requiring hospitalization is common and has identifiable psychosocial and specific biological predictors. However, only the lesion predictors were independently related to this adverse psychiatric outcome.

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Traumatic brain injury (TBI) is a major public health concern for children and adolescents in the United States, with over 837,000 TBI-related emergency department visits, hospitalizations, and deaths occurring among children 17 and younger in 2014 alone (1). New-onset postinjury psychiatric disorders, which have been termed novel psychiatric disorders, are heterogeneous and occur frequently (2, 3). In essence, brain injury increases the risk of psychiatric disturbances in general (2, 4). They have been studied with regard to their biopsychosocial predictors or correlates only in relatively small psychiatric interview studies (N=44–65 TBI participants) (2, 5–9). The current investigation, informed by a biopsychosocial model (10), is the largest psychiatric interview prospective study of a consecutively recruited sample of children hospitalized for TBI that explores postinjury onset of novel psychiatric disorders, assessed at six-month postinjury.

Previous studies have found that novel psychiatric disorders are predicted by various pre-injury psychosocial

variables including lifetime psychiatric disorder, family function, family psychiatric history, socioeconomic status, intellectual function, and adaptive function (2, 5–7). It is also clear that in studies with a wide range of severity of injury (e.g., from mild to severe TBI), severity of injury usually predicts novel psychiatric disorders (2, 5–7). Previous studies have shown no significant relationship of novel psychiatric disorders with specific cortical lesion location correlates, lesion volume, gray matter volume, white matter volume, and cortical thickness, but a relationship with lower fractional anisotropy (FA) in bilateral frontal lobes, bilateral temporal lobes, bilateral centrum semiovale, and bilateral uncinate fasciculi has been reported (9). Biological (severity of injury and lesion location) and psychosocial predictors and correlates of specific novel psychiatric disorders (e.g., secondary attention deficit hyperactivity disorder [ADHD], personality change due to TBI, depression, anxiety, oppositional defiant disorder [ODD], and mania or hypomania) have been studied (11, 12). Results vary according to the

disorder or symptom cluster studied, with some more closely related to psychosocial (especially psychosocial adversity) or biological predictors (particularly frontal lobe lesions and severity of injury) (11–13). Since power is a potential limitation in the analyses of groups with specific novel psychiatric disorders, we elected to study predictors of the broader category of novel psychiatric disorder in the largest sample to date of children consecutively hospitalized for TBI.

Based upon a review of the existing literature, the following two hypotheses were tested: Novel psychiatric disorder is significantly predicted by psychosocial measures (socioeconomic status [SES], pre-injury psychosocial adversity, pre-injury family function, family psychiatric history, lifetime pre-injury psychiatric disorder); and novel psychiatric disorder is significantly associated with frontal lobe lesions and greater severity of injury.

METHODS

Participants

This study was conducted between 1998 and 2003. Children and adolescents were recruited from hospital-generated lists of consecutive admissions during their initial hospitalization within 2 weeks of a TBI at one of three academic medical centers in Texas (University of Texas, Houston; Baylor College of Medicine, Houston; University of Texas, Dallas); Rady Children's Hospital, San Diego; and The Hospital for Sick Children in Toronto. We do not have accurate data regarding the number of children who were approached, the proportion who were eligible for recruitment, or participation among those eligible. This is partly because we did not require our patients to answer eligibility questions before they expressed the desire to participate.

Enrollment was open to patients with mild to severe TBI as defined using the Glasgow Coma Scale (GCS) (14) at all centers except San Diego, where recruitment was limited to complicated mild (i.e., mild TBI with intracranial imaging abnormalities) to severe TBI; see Severity of TBI, below, for additional details.

Exclusion criteria, ascertained by medical chart review and a screening recruitment interview with the parent or guardian, included pre-existing schizophrenia or autistic disorder, intellectual deficiency, pre-existing neurologic disorder associated with cerebral dysfunction (e.g., cerebral palsy, epilepsy), previous hospitalization for head injury, injury due to child abuse or penetrating missile injury, Abbreviated Injury Scale (15) score ≥ 4 for body parts other than head in mild and moderate TBI patients, and child who was a non-English speaker. Children in San Diego were excluded if they had ADHD before the injury, as assessed with the screening recruitment interview. Medical diagnoses including sleep disorders, bone fractures, migraines, and chronic pain did not constitute grounds for exclusion. One child whose autism spectrum disorder was missed on the screening recruitment interview was excluded after

enrollment and administration of the standardized psychiatric assessment. The parents or guardians of all children signed an informed consent form, and all children signed an assent to participate in accordance with the institutional review board at each site.

Measures

Psychiatric assessments. *DSM-IV* (16) psychiatric diagnoses derived during the first year of recruitment were converted to *DSM-IV-TR* (17) diagnoses when the latter version became available in 2000; *DSM-IV-TR* diagnoses were derived for the remainder of the study. The psychiatric diagnoses were derived using a semistructured interview, the Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present and Lifetime version (K-SADS-PL) (18). The K-SADS-PL is an integrated parent-child interview that produces diagnoses based on a clinician's synthesis of data collected from parent and child separately, inquiring about 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). The Neuropsychiatric Rating Schedule (NPRS) (19), a semistructured interview designed to identify symptoms and subtypes of the *DSM-IV-TR* formal categorical diagnosis of personality change due to TBI, which is not captured with the K-SADS-PL, was also administered. Parents and children served as informants at both the baseline and 6-month post injury interviews. We waived the 1-year duration of symptomatology criterion to permit us to monitor the course of the disorder for the first 6 months after injury. The diagnosis of personality change due to TBI is the most common and important new-onset psychiatric disorder, especially in the early months post-TBI in youths hospitalized for TBI (8, 20–22).

Best-estimate psychiatric diagnoses (23) were generated by the interviewer after integrating the reports of the parent and the child from the NPRS and the K-SADS-PL interviews and, when available (120/177: 68% at baseline; 101/141: 72% at 6-month), from the Survey Diagnostic Instrument (24) completed by the teacher at baseline and 6-months.

The psychiatric assessment yielded data on pre-injury lifetime psychiatric disorder as a category (present or absent), specific pre-injury lifetime psychiatric disorders, clusters of pre-injury lifetime psychiatric disorders (e.g., internalizing disorder, externalizing disorder), postinjury new-onset psychiatric disorder (called in the literature novel psychiatric disorder) as a category (present or absent), specific novel psychiatric disorder(s), and clusters of novel psychiatric disorders (e.g., internalizing disorder, externalizing disorder). The outcome variable for this investigation was novel psychiatric disorder as a category (present or absent).

The pre-injury lifetime psychiatric disorders were identified retrospectively at the baseline assessment. The designation of novel psychiatric disorder was applied according to the literature in one of two conditions. First, this could

manifest in a participant with no lifetime psychiatric disorders as of the baseline assessment who then develops a psychiatric disorder within the injury to 6-month postinjury assessment interval. Second, novel psychiatric disorder could occur in the case of a participant with a lifetime psychiatric disorder who, within the injury to 6-month postinjury assessment interval, manifests a psychiatric disorder that was not present before the TBI. For example, a participant with a lifetime history of major depressive disorder who develops ODD after the TBI would receive the classification but not if only a new episode of major depressive disorder or a transformation to mania or hypomania occurred. Historically (3, 7, 25–27), the term novel was used to avoid confusion with the findings of an early and seminal study of pediatric TBI (2), which focused on “new” psychiatric disorders that corresponded only with the first condition of our definition of novel psychiatric disorder.

Family psychiatric history assessment. The Family History Research Diagnostic Criteria (28) interview was conducted at each site by trained research assistants. Criteria were modified to conform with *DSM-IV-TR* criteria. At least one parent, acting as the informant, was questioned regarding presence of psychiatric disorders in each first-degree relative of the index child with TBI. Family ratings were then summarized on a four-point scale (0–3) (3) of increasing severity.

Family function assessment. The Family Assessment Device, General Functioning Scale (29) was used at the baseline assessment to measure pre-injury global family functioning. The scale is a self-report questionnaire consisting of 12 items. Each item was responded to on a four-point Likert scale ranging from 1 to 4. Lower scores represent healthier functioning. The primary caretaker of each family responded to each item. Scores in families of medical, psychiatric, and nonclinical probands were 1.89 (0.45), 2.27 (0.51), and 1.89 (0.43), respectively (30).

Socioeconomic status assessment. SES was assessed using the Four Factor Index (31). Participants were classified depending on scores derived from a formula involving both the maternal and paternal educational and occupational levels. Scores ranged from 8 to 66; higher scores indicate higher educational and occupational levels and higher SES.

Psychosocial adversity assessment. The psychosocial adversity index used was very similar to the one used in an important earlier study of pediatric TBI (2). Six areas were assessed; if an area suggested adversity, a score of 1 was given, and if an area showed no adversity, a score of 0 was given. The areas assessed are as follows: child not living with biological or adoptive parents; sibship of at least four children, or a person:room ratio exceeding 1; admission of the child into the care of the local authority because of family difficulties; maternal malaise inventory score ≥ 7 ; paternal

criminality; and father or mother with an unskilled or semiskilled job.

Adaptive function assessment. Pre-injury adaptive functioning was assessed retrospectively soon after the injury using the Vineland Adaptive Behavior Scale interview (32). This was conducted with the primary caretaker and involved a semistructured interview by a trained research assistant.

Assessment of TBI severity. Severity of TBI was classified based on the lowest postresuscitation score on the GCS (14), which was recorded from emergency services and hospital 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, with scores ranging from 3 (unresponsive) to 15 (normal). Mild, moderate, and severe TBI are defined respectively as lowest postresuscitation GCS scores of 13–15, 9–12, and 3–8. Participants with GCS scores of 15 were included if they experienced a loss of consciousness, posttraumatic amnesia, or both, and postconcussion symptoms.

Brain lesion assessment. MRI (1.5 tesla) was administered to most participants 3 months after the injury, when lesions appeared stable. The protocol included a T1-weighted volumetric spoiled gradient-recalled echo and fluid attenuated-inversion recovery 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 151 of the 177 children enrolled (85%) completed their research MRI.

Medications. Medications taken by participants at the 6-month assessment were recorded. A protocol was in place encouraging parents to coordinate with the child's physician to have a 24- to 48-hour washout period for stimulant medication because these medications could attenuate the cognitive and behavioral deficits under investigation. Ethical and medical issues surrounding the need to continue medications that are given for weeks to be effective or would be dangerous to discontinue supervened with regard to antidepressant and anticonvulsant medication. Participants were compensated for their time.

Data Analyses

To test the relationship of 6-month novel psychiatric disorder with the hypothesized continuous and categorical psychosocial and severity of injury and frontal lobe lesion predictors, logistic regression single-predictor analyses were conducted. To shed light on the relative importance of hypothesized variables significantly associated with novel psychiatric disorder, a multipredictor logistic regression analysis was performed with novel psychiatric disorder as the dependent variable. The independent baseline predictors with $p < 0.15$ in single-predictor analyses were included in the initial model and backward model selection was used

TABLE 1. Demographic and psychosocial data of traumatic brain injury cohort (N=177)^a

Variable	Mean or N	SD or %
Demographic		
Mean age at injury (years)	10.13	2.77
Male	125	71
Race		
White	100	56.5
Hispanic	32	18.1
Black	31	17.5
Asian	5	2.8
Other	9	5.1
Psychosocial		
Pre-injury lifetime psychiatric disorder	56	31.6
Vineland adaptive behavior composite mean score (N=165)	94.37	15.43
Family Assessment Device global functioning scale mean score (N=160)	1.62	0.47
Family history research diagnostic criteria (N=135)	1.16	1.07
Socioeconomic status (N=173)	37.01	12.90
Psychosocial adversity (N=165)	0.82	0.95
Injury variables		
Lowest postresuscitation GCS score	10.85	4.20
Mild TBI (GCS 13–15)	87	49
Moderate TBI (GCS 9–12)	26	15
Severe TBI (GCS 3–8)	64	36
Depressed skull fracture	17	9.6
Mechanism of injury		
Hit by motor vehicle	49	27.7
Fall	41	23.2
Auto, truck, bus passenger	40	22.6
Sports or play	15	8.5
Recreational vehicle/off-road vehicle	10	5.6
Bicycle	9	5.1
Motorcycle-moped	5	2.8
Hit by a falling object	5	2.8
Other	3	1.7

^a TBI, traumatic brain injury; GCS, Glasgow Coma Scale.

with a $p < 0.15$ threshold based on the likelihood ratio test. The p values and 95% confidence intervals (CI) for the odds ratio of 6-month novel psychiatric disorder are based on the likelihood ratio test. In addition, exploratory analyses using single-predictor logistic regression investigated the association of novel psychiatric disorder with additional demographic predictors (age, sex, race).

Exploratory predictor analyses of the association of extrafrontal lesions with presence of novel psychiatric disorder were performed with logistic regression. Furthermore, at the suggestion of the reviewers, additional predictor analyses were conducted to define the relationships between novel psychiatric disorder, injury severity, and presence of

any lesion on MRI. These used logistic regression. For the injury severity variable (mild, moderate, severe TBI) p and CI were Bonferroni corrected.

Statistical significance was considered at $\alpha = 0.05$. All tests were two-sided. The analysis was conducted in SPSS.

RESULTS

One-hundred-seventy-seven children and adolescents participated in this study. Demographic details (age, sex, race), pre-injury psychosocial variables (pre-injury lifetime psychiatric status, adaptive functioning, family functioning, family psychiatric history ratings, SES, psychosocial adversity), and injury indices (GCS scores (14), depressed skull fracture incidence, mechanism of injury) are provided in Table 1. Racial characteristics of participants were as follows: White: 100 (56.5%); African American: 31 (17.5%); Hispanic: 32 (18.1%); Asian: 5 (2.8%); other: 9 (5.1%).

Lesion distribution in children who completed both the research MRI and the 6-month psychiatric follow-up assessment (N=131) can be seen in the left two columns of Table 2. Among children who returned 6 months postinjury for psychiatric follow-up, the neuroradiologists' classification of lesions and the number of children with each pathology was as follows: gliosis (N=30), shearing injury (N=20), atrophy (N=16), encephalomalacia (N=17), shearing and hemorrhage (N=16), hemosiderin deposit (N=25), contusion (N=3), contusion/hematoma (N=5), contusion and encephalomalacia (N=2), atrophy and encephalomalacia (N=3), gliosis and encephalomalacia (N=5). Participants who had lesions could have more than one lesion, lesion location, or type of lesion pathology.

Of the original 177 participants, 141 (80%) returned for the 6-month psychiatric assessment. The children who did not return were not significantly different from the children who did with respect to distribution of GCS scores, age, sex, race, SES, psychosocial adversity, pre-injury lifetime psychiatric disorder, and pre-injury adaptive function. Lesion location detected by the research MRI did not differ in those with psychiatric follow-up (N=131) versus those without (N=20).

The distribution of medications prescribed for neuropsychiatric indications in those who returned for the 6-month assessment were stimulants in 12 children, antidepressants in seven children, anticonvulsants in four children, and desmopressin in two children. Of particular interest, the children receiving antidepressants included one child with new-onset social phobia and panic disorder, one child with new-onset post-traumatic stress disorder (PTSD), one child with TBI-related headache (on amitriptyline), one child with new-onset major depressive disorder, one child with persisting pre-injury obsessive compulsive disorder, one child with persisting pre-injury enuresis, and two children with new-onset personality change due to TBI. We are unable to access data on the prevalence of suicidal ideation. However, of the 141 children who returned for the 6-month

TABLE 2. Lesion distribution of entire cohort and by novel psychiatric disorder (NPD) status

Lesion position	All subjects (N=131)		NPD (N=54)		No NPD (N=77)		OR	95% profile likelihood CI	p
	N	%	N	%	N	%			
Frontal lobe lesions									
Frontal-lobe white matter	28	21.4	18	33.3	10	13.0	3.35	1.43–8.28	0.005
Superior frontal gyrus	26	19.8	17	31.5	9	11.7	3.47	1.44–8.88	0.005
Middle frontal gyrus	19	14.5	9	16.7	10	13.0	1.34	0.50–3.58	0.558
Inferior frontal gyrus	27	20.6	18	33.3	9	11.7	3.78	1.58–9.63	0.003
Cingulate gyrus	1	0.8	0	0	1	1.3	0	na	0.301
Orbital gyrus	7	5.3	6	11.1	1	1.3	9.50	1.56–182.28	0.012
Gyrus rectus	15	11.5	7	13.0	8	10.4	1.29	0.42–3.82	0.650
Extrafrontal lesions									
Temporal lobe	31	23.7	13	24.1	18	23.4	1.04	0.45–2.34	0.926
Temporal pole	7	5.3	3	5.6	4	5.2	1.07	0.20–5.07	0.928
Parietal lobe	26	19.8	11	20.4	15	19.5	1.06	0.44–2.51	0.900
Occipital lobe	11	8.4	8	14.8	3	3.9	4.29	1.18–20.35	0.027
Basal ganglia	6	4.6	4	7.4	2	2.6	3.00	0.56–22.22	0.198
Anterior corpus callosum	2	1.5	2	3.7	0	0	>10 ⁹	na	0.058
Mid corpus callosum	5	3.8	4	7.4	1	1.3	6.08	0.87–120.72	0.070
Posterior corpus callosum	8	6.1	6	11.1	2	2.6	4.69	1.03–32.89	0.045
Thalamus	3	2.3	1	1.9	2	2.6	0.71	0.03–7.57	0.776
Cerebral peduncles	1	0.8	0	0	1	1.3	0	na	0.301
Midbrain	1	0.8	1	1.9	0	0	>10 ⁹	na	0.182
Medulla	1	0.8	0	0	1	1.3	0	na	0.301
Cerebellum hemisphere	5	3.8	3	5.6	2	2.6	2.21	0.35–17.19	0.389
Internal capsule	4	3.1	2	3.7	2	2.6	1.44	0.17–12.33	0.719
External capsule	1	0.8	1	1.9	0	0	>10 ⁹	na	0.182
Any lesion	94	71.8	46	85.2	48	62.3	3.47	1.49–8.87	0.003

postinjury assessment, only five children had ongoing major depressive disorder (including one child with persisting pre-injury major depressive disorder), one child had already resolved major depressive disorder (i.e., definitely not suicidal), and one child had new-onset depressive disorder not otherwise specified. Only one of these seven children with a depressive disorder was receiving an antidepressant medication.

Pre-Injury and Novel Psychiatric Disorders

Table 3 shows the distribution of pre-injury lifetime psychiatric disorders. Any pre-injury lifetime psychiatric disorder was present in 42/141 (30%) of children who participated in the 6-month follow-up. The specific pre-injury lifetime disorders included ADHD (N=26; 18%), ODD/disruptive behavior disorder not otherwise specified (DBD NOS)/conduct disorder (CD) (N=7; 5%), externalizing disorder (ADHD, ODD/DBD NOS/CD; N=30; 21%), depressive disorder (major depressive disorder/dysthymia/depressive disorder not otherwise specified) (N=3; 2%), anxiety disorder (simple phobia, social phobia, panic disorder, obsessive compulsive disorder, separation anxiety disorder, PTSD; N=19; 14%), and internalizing disorder (depressive disorder, anxiety disorder; N=21; 15%).

Table 3 also shows that novel psychiatric disorder, the analyzed outcome variable of interest, occurred in 58/141 (41%) of children who returned for the 6-month assessment. The specific novel psychiatric disorders were personality change due to TBI (N=31/141; 22%), ADHD (N=18/115;

16%), ODD/DBD NOS/CD (N=11/134; 8%), externalizing disorder (N=23/138; 17%), depressive disorder (N=6/138; 4%), anxiety disorder (N=12/141; 9%), and internalizing disorder (N=15/141; 11%). Where the denominator was less than 141, it reflected that the individual already had the corresponding pre-injury disorder and was therefore ineligible to develop the corresponding novel disorder. Co-occurring novel psychiatric disorders in individual participants account for the sum of the novel psychiatric disorders in each of the above-noted categories of disorders being greater than count of children categorized as having a novel psychiatric disorder (N=58) versus no novel psychiatric disorder (N=83).

Psychosocial Predictors of Novel Psychiatric Disorder

Table 4 shows data on variables tested as potential predictors for the development of novel psychiatric disorder in the first six months after TBI. Both SES (OR=0.97; 95% CI [0.95, 1.0]; p=0.039) and psychosocial adversity (OR=1.46; 95% CI [1.03, 2.11]; p=0.036) were significantly associated with novel psychiatric disorder. The mean (SD) SES scores among children who developed novel psychiatric disorder versus those who did not were 35.16 (12.72) and 39.62 (12.33), respectively, with lower scores indicating worse status. In terms of psychosocial adversity, the mean (SD) scores for children with novel psychiatric disorder versus those without novel psychiatric disorder were 1.04 (0.98) and 0.68 (0.96), respectively, with higher scores indicating greater adversity. None of the other psychosocial variables,

TABLE 3. Pre-injury lifetime psychiatric disorders and 6-month novel psychiatric disorders^a

Disorder	Pre-injury lifetime disorder		Novel psychiatric disorder	
	N	%	N	%
Any pre-injury lifetime disorder	42/141	30	na	
Any novel psychiatric disorder	na		58/141	41
ADHD	26/141	18	18/115	16
ODD/CD/Disruptive behavior disorder not otherwise specified	7/141	5	11/134	8
Externalizing disorder	30/141	21	23/138	17
Personality change due to TBI	0/141		31/141	22
Depressive disorder	3/141	2	6/138	4
Anxiety disorder	19/141	14	12/141	9
Internalizing disorder	21/141	15	15/141	11

^a ADHD, attention deficit/hyperactivity disorder; ODD, oppositional defiant disorder; CD, conduct disorder; TBI, traumatic brain injury. When the denominator is less than 141, it reflects that the individual already had the corresponding pre-injury disorder and was therefore ineligible to develop the corresponding novel disorder. Total number of children with externalizing disorder is lower than the sum of children with ADHD and children with ODD/CD/disruptive behavior disorder because some children have both diagnoses. Similarly, the total number of children with internalizing disorder is lower than the sum of children with depressive disorder and anxiety disorder because of comorbidity. Disruptive behavior disorder not otherwise specified corresponded to the *DSM-5* diagnosis of "other specified disruptive, impulse-control, and conduct disorder."

including pre-injury family function, family psychiatric history, pre-injury adaptive function, and pre-injury lifetime, predicted novel psychiatric disorder.

Table 4 also includes exploratory comparisons of other variables according to the presence or absence of novel psychiatric disorder at 6-month follow-up. None of these variables, including age at injury, sex, and race, discriminated between groups.

Severity of Injury and Lesion Correlates of Novel Psychiatric Disorder

GCS score tended toward significance (OR=0.94; 95% CI [0.86, 1.01]; $p=0.099$), with the mean (SD) scores for children with novel psychiatric disorder versus no novel psychiatric disorder being 10.12 (4.41) and 11.30 (3.99), respectively, with lower scores indicating greater injury severity (Table 4). Table 2 shows lesion distribution according to novel psychiatric disorder status. Novel psychiatric disorder was significantly associated with lesions within the frontal white matter (18/54 children with novel psychiatric disorder; 10/77 children with no novel psychiatric disorder; OR=3.35; 95% CI [1.42, 8.28]; $p=0.005$); the superior frontal gyrus (17/54 children with novel psychiatric disorder; 9/77 children with no novel psychiatric disorder; OR=3.47; 95% CI [1.44, 8.88]; $p=0.005$); the inferior frontal gyrus (18/54 children with novel psychiatric disorder; 9/77 with no novel psychiatric disorder; OR=3.78; 95% CI [1.58, 9.63]; $p=0.003$); the orbital gyrus (6/54 children with novel psychiatric disorder; 1/77 with no novel psychiatric disorder; OR=9.50; 95% CI [1.56, 182.28]; $p=0.012$).

As planned, a backward stepwise likelihood ratio logistic regression was conducted with novel psychiatric disorder as the dependent variable and the independent variables comprised from baseline assessment measures that were

associated with novel psychiatric disorder in single-predictor analyses at the $p<0.15$ level (SES, psychosocial adversity score, GCS, and lesions to the frontal-lobe white matter, superior frontal gyrus, inferior frontal gyrus, orbital gyrus). The regression produced a significant final model (likelihood ratio $\chi^2=25.23$; $df=5$; $p<0.001$) that included lesions to the frontal-lobe white matter (likelihood ratio $\chi^2=3.908$; $df=1$; $p=0.048$), OR=2.61; 95% CI (1.01, 6.93), the superior frontal gyrus (likelihood ratio $\chi^2=4.524$; $df=1$; $p=0.033$), OR=2.93; 95% CI (1.09, 8.18), orbital gyrus (likelihood ratio $\chi^2=6.046$;

$df=1$; $p=0.014$), OR=11.28; 95% CI (1.58, 229.31), SES (likelihood ratio $\chi^2=3.78$; $df=1$; $p=0.052$), OR=0.97; 95% CI (0.94, 1.00), and inferior frontal gyrus (likelihood ratio $\chi^2=2.82$; $df=1$; $p=0.093$), OR=2.35; 95% CI (0.87, 6.58) (see Table 5).

Exploratory Analyses Concerning Novel Psychiatric Disorder, Injury Severity, and Lesions

Exploratory analyses of extrafrontal lesions revealed that novel psychiatric disorder was significantly associated with occipital lobe lesions (8/54 children with novel psychiatric disorder; 3/77 children with no novel psychiatric disorder; OR=4.29; 95% CI [1.18, 20.35]; $p=0.027$). Similarly, novel psychiatric disorder was significantly associated with lesions within the posterior corpus callosum (6/54 children with novel psychiatric disorder; 2/77 with no novel psychiatric disorder; OR=4.69; 95% CI [1.03, 32.89]; $p=0.045$).

Additional predictor analyses related to novel psychiatric disorder, injury severity, and lesions are presented at the suggestion of the reviewers: Novel psychiatric disorder was not significantly associated with severity of injury category. The rates of novel psychiatric disorder in children with mild, moderate, and severe TBI were 25/70 (35.7%), 7/17 (41.2%), and 26/54 (48.2%), respectively; they did not differ significantly from each other ($p=0.378$). The presence of any lesion on the research MRI was significantly associated with injury severity (in children with mild, moderate, and severe TBI; any lesion was present in 34/63 children with mild TBI; 12/17 children with moderate TBI; 48/51 children with severe TBI; severe TBI vs. mild TBI, OR=13.65; 95% CI [3.53, 89.87] $p=0.0002$; severe TBI vs. moderate TBI, OR=6.67; 95% CI [1.03, 55.70]; $p=0.050$); moderate TBI versus mild TBI, OR=2.05; 95% CI [0.53, 9.54] $p=0.672$, all Bonferroni corrected. Novel psychiatric disorder was significantly associated with any lesion (46/54 children with novel

TABLE 4. Novel psychiatric disorders at 6 months postinjury in relation to psychosocial, demographic, and severity of injury variables

Variable	Novel psychiatric disorder (N=58)		No novel psychiatric disorder (N=83)		OR	95% profile likelihood CI	p
	N	%	N	%			
Socioeconomic status (mean, SD)	35.16	12.72	39.62	12.33	0.972	0.95–1.00	0.039
Family psychiatric history (mean, SD)	1.36	1.00	1.08	1.11	1.268	0.90, 1.81	0.179
Pre-injury psychosocial adversity score (mean, SD)	1.04	0.98	0.68	0.96	1.458	1.03–2.11	0.036
Family function (mean, SD)	1.68	0.56	1.59	0.43	1.032	0.97–1.10	0.298
Vineland adaptive behavior composite standard score (mean, SD)	95.57	13.48	95.54	15.32	1.000	0.98–1.02	0.991
Pre-injury lifetime psychiatric disorder	17	29.3	25	30.1	0.96	0.46–2.00	0.918
Age at injury (mean, SD)	10.19	2.90	10.20	2.80	1.00	0.89–1.13	0.980
Sex, female	16	27.6	28	33.7	0.75	0.35–1.55	0.436
Race							0.833
Asian	2	3.4	2	2.4	1.58	0.18–13.73	
Black	12	20.7	12	14.5	1.58	0.63–3.99	
Hispanic	10	17.2	17	20.5	0.93	0.37–2.23	
Other	3	5.2	3	3.6	1.58	0.28–9.02	
White	31	53.4	49	59.0	1.00		
Glasgow Coma Scale score (mean, SD)	10.12	4.41	11.30	3.99	0.94	0.86–1.01	0.099

psychiatric disorder; 48/77 children with no novel psychiatric disorder; OR=3.47; 95% CI [1.49, 8.87]; $p=0.003$) (Table 2).

DISCUSSION

The study's two hypotheses were largely supported: novel psychiatric disorder is significantly predicted by psychosocial measures, and novel psychiatric disorder is significantly associated with biological variables, including frontal lobe lesions. Novel psychiatric disorder occurs at a high frequency in the first 6 months after TBI in children and adolescents. The biopsychosocial clinical correlates for the most part coincide with but also expand findings from the few related previous studies. Specifically, novel psychiatric disorder at 6 months postinjury occurred in 41% of children aged 5–14 years at the time of injury and was significantly associated in univariable analyses with pre-injury psychosocial risk factors (lower SES, higher psychosocial adversity) and lesions to the frontal-lobe white matter, superior frontal gyrus, inferior frontal gyrus, and the orbital gyrus. Multivariable analyses showed that only lesions of the frontal-lobe white matter, superior frontal gyrus, and orbital gyrus independently were significantly associated with novel psychiatric disorder, suggesting that biological variables were relatively more important than psychosocial variables in relation to this adverse psychiatric outcome.

The association of 6-month novel psychiatric disorder with any cortical lesion demonstrated on MRI is a new finding. In contrast, a relationship of novel psychiatric disorder and white matter FA (in a cohort of complicated mild

to severe TBI participants) (9) and frontal white matter lesions (in a mild TBI subsample of the current cohort) were reported previously (33). Particularly striking is that novel psychiatric disorder was independently associated with varied lesion location including frontal-lobe white matter, superior frontal gyrus, and orbital gyrus. These findings may be understood within the context of previous 6-month postinjury analyses of the current cohort separately examining lesion correlates for specific novel psychiatric disorders, including personality change due to TBI, ADHD, depressive disorders, and anxiety disorders (20, 34–36). For example, personality change due to TBI, which was the most frequently occurring novel psychiatric disorder (22%), was significantly associated with superior frontal gyrus lesions (20). With regard to novel ADHD, which was the second most common novel psychiatric disorder (16%), the orbital gyrus was the significant lesion correlate (36). Furthermore, novel definite/subclinical anxiety disorder was significantly associated with superior frontal gyrus lesions (34). Additionally, novel definite/subclinical depressive disorder was

TABLE 5. Multipredictor model of novel psychiatric disorders at 6 months postinjury^a

Variable	OR	95% CI	p
Frontal lobe white matter lesion	2.61	1.09–6.93	0.048
Superior frontal gyrus lesion	2.93	1.09–8.18	0.033
Orbital gyrus lesion	11.28	1.58–229.31	0.014
Socioeconomic status	0.97	0.94–1.00	0.052
Inferior frontal gyrus lesion	2.35	0.87–6.58	0.093

^a 95% CI and p values from the likelihood ratio test.

significantly associated with left inferior frontal gyrus and right frontal white matter lesions (35). Subclinical anxiety disorder and depressive disorder designations were made in situations where there was no clear functional impairment, even though participants met or were one symptom short of meeting criteria for a specific anxiety disorder or depressive disorder, respectively (34, 35). However, there were no significant lesion associations for novel ODD/DBD NOS/CD, despite significant comorbidity with personality change due to TBI as well as novel ADHD (20, 36, 37).

The phenomenological link between personality change due to TBI and novel definite/subclinical anxiety disorder, both of which are significantly associated with superior frontal gyrus lesions (20, 34), is acquired disturbance in affective dysregulation (i.e., predominantly irritability with personality change due to TBI and anxiety with novel definite/subclinical anxiety disorder). Consideration of the dorsal neural frontal system and the ventral neural system informs our understanding of the relationship of disorders of affective regulation and superior frontal gyrus lesions (38). The dorsal frontal neural system (dorsolateral prefrontal cortex, dorsomedial prefrontal cortex including the superior frontal gyrus, dorsal anterior cingulate gyrus, and hippocampus) is important for effortful regulation of affective states generated from the activity of the ventral neural system. The ventral neural system (insula, amygdala, orbitofrontal cortex, ventrolateral prefrontal cortex, ventral anterior cingulate gyrus, ventral striatum, thalamus, brainstem nuclei) is needed for the identification of the emotional importance of environmental stimuli and the production of emotional states, including irritability (39). The ventral neural system is also a significant contributor to automatic regulation and mediation of autonomic responses to emotional stimuli and contexts that accompany the elaboration of affective states. Dorsal prefrontal injury may disturb this balance such that affective states produced by the ventral system cannot be sufficiently regulated in the proposed effortful process resulting in increased irritability and anxiety after TBI.

The independent relationship of novel psychiatric disorder with orbital gyrus lesions was not surprising given that the second most common novel psychiatric disorder (i.e., novel ADHD) was associated with damage to this region (36). Additional lesion studies provide further evidence of an association of orbitofrontal damage and ADHD and ADHD-like behavior. For example, studies in adults have reported that disinhibited, poorly regulated, impulsive, disorganized, distractible, and inattentive behavior, as well as poor planning, were associated with ventromedial cortical lesions that include the orbitofrontal cortex (40). Furthermore, an orbitofrontal and mesial frontal lesion complex caused by stroke in children was significantly associated with ADHD symptomatology (41).

Our findings underscore the importance of frontal lobe network damage in addition to cortical lesions in understanding novel psychiatric disorder, including depression

(35). Diffuse frontal-lobe white matter injury results in a relatively less efficient and less connected network of neural systems (42) that may lead to psychiatric dysfunction. Diffusion tensor imaging-derived FA values are more sensitive measures of white matter microstructural integrity than gross lesions visualized by study radiologists (43) and may further elucidate the relationship of white matter injury and neurobehavioral outcome after TBI (44). For example, in a nonoverlapping cohort, the networks that were involved in the association of FA with novel psychiatric disorder implicated frontal white matter, uncinate fasciculi which connect the frontal and temporal poles, specifically the amygdala with basal and inferior frontal lobes, and centrum semiovale (9).

Novel psychiatric disorder was found to be significantly associated with lower pre-injury SES and lower pre-injury psychosocial adversity in univariable analyses; however, no pre-injury psychosocial variables were significant in the multivariable analyses. The association of novel psychiatric disorder and lower pre-injury SES was just short of significance in the latter analyses. It would be premature to conclude that novel psychiatric disorder is not associated with pre-injury psychosocial variables, because other studies have implicated SES and intellectual function, family function, family psychiatric history, adaptive function, and lifetime psychiatric disorder (2, 5–7). Clearly, additional studies are necessary to answer this question in the context of neuroimaging findings and other biological variables.

There were several limitations in study methodology that are important to acknowledge. First, there was an absence of a non-brain-related-injury control group to compare with the TBI group. This hindered our ability to establish a causal pathway between TBI and the development of novel psychiatric disorder. Second, we did not test interrater reliability for psychiatric diagnoses. However, specific quality control and training procedures sought to mitigate this issue. Third, image analyses did not include diffusion tensor imaging, tissue segmentation, or volumetric measurements; although lesions were localized in general regions, there was heterogeneity in the size, precise location, and underlying etiology of lesion. Fourth, *DSM-IV-TR* rather than *DSM-5* diagnostic criteria were used because of the timing of the study. Fifth, attrition was approximately 20%. However, those lost to follow-up were not significantly different from participants at 6 months postinjury with respect to distribution of lesion location, GCS scores, age, sex, race, SES, psychosocial adversity, pre-injury lifetime psychiatric disorder, and pre-injury adaptive function. Sixth, we did not test interrater reliability for recording of lesions by study neuroradiologists. Seventh, we were unable to access data on the prevalence of suicidal ideation, which was likely to be uncommon given the data presented on depressive disorder. Eighth, the multisite sample was not homogeneous, and there may have been site-specific skews to the results.

There are several notable strengths of this study. This was the largest prospective psychiatric interview study that

examined novel psychiatric disorder, with a sample that reflected the racial and ethnic diversity of the regions from which participants were recruited. The breadth and depth of assessments were extensive and included interview assessments of psychiatric disorders, family psychiatric history, and adaptive function, in addition to rating scales encompassing other psychosocial and injury risk factors for novel psychiatric disorder. Psychiatric and behavioral assessment depended on multiple informants for the majority of the participants because of teachers' behavioral data reports. Lesion analysis was based on location and pathology characterizations provided by expert neuroradiologists.

The current findings have specific clinical and research implications. Children who have been hospitalized for TBI should be screened for the common development of novel psychiatric disorder in the first few months after injury. The most frequently occurring novel psychiatric disorder is personality change due to TBI, the presentation of which is dominated by affective dysregulation, notably irritability (21). The diagnosis may be unfamiliar to clinicians who do not typically treat patients with TBI. Clinicians should monitor for other disorders including ADHD and other externalizing disorders, as well as anxiety and depressive disorders. Individuals with frontal white matter, superior frontal gyrus, and orbital gyrus injury, and possibly lower SES, should be monitored particularly carefully, because these appear to potentially increase risk for novel psychiatric disorder. Future reports from this cohort will shed light on phenomenology and risk factors for novel psychiatric disorder in longer term follow-up and address the relationship between specific neuropsychological characteristics and novel psychiatric disorder status after TBI.

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