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Archival Report

Polygenic Risk and Neural Substrates of Attention-Deficit/Hyperactivity Disorder Symptoms in Youths With a History of Mild Traumatic Brain Injury

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ABSTRACT

BACKGROUND: Attention-deficit/hyperactivity disorder (ADHD) is a major sequela of traumatic brain injury (TBI) in youths. The objective of this study was to examine whether ADHD symptoms are differentially associated with genetic risk and brain structure in youths with and without a history of TBI.

METHODS: Medical history, ADHD symptoms, genetic data, and neuroimaging data were obtained from a community sample of youths. ADHD symptom severity was compared between those with and without TBI (TBI n = 418, no TBI n = 3193). The relationship of TBI history, genetic vulnerability, brain structure, and ADHD symptoms was examined by assessing 1) ADHD polygenic score (discovery sample ADHD n = 19,099, control sample n = 34,194), 2) basal ganglia volumes, and 3) fractional anisotropy in the corpus callosum and corona radiata.

RESULTS: Youths with TBI reported greater ADHD symptom severity compared with those without TBI. Polygenic score was positively associated with ADHD symptoms in youths without TBI but not in youths with TBI. The negative association between the caudate volume and ADHD symptoms was not moderated by a history of TBI. However, the relationship between ADHD symptoms and structure of the genu of the corpus callosum was negative in youths with TBI and positive in youths without TBI.

CONCLUSIONS: The identification of distinct ADHD etiology in youths with TBI provides neurobiological insight into the clinical heterogeneity in the disorder. Results indicate that genetic predisposition to ADHD does not increase the risk for ADHD symptoms associated with TBI. ADHD symptoms associated with TBI may be a result of a mechanical insult rather than neurodevelopmental factors.

Keywords: Attention-deficit/hyperactivity disorder, Diffusion tensor imaging, Magnetic resonance imaging, Polygenic score, Traumatic brain injury, Youths

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Traumatic brain injury (TBI) in youths is associated with cognitive, intellectual, social, and behavioral problems (1). Even in mild cases of TBI—which are by far the most common (2)—a significant proportion of children will experience persistent psychiatric symptoms associated with traumatic injury to the developing brain (3), making it an important risk factor to be addressed by treating physicians and mental health professionals. Attention problems and disinhibited behavior are common sequelae of TBI (4); as many as 50% of children develop symptoms of attention-deficit/hyperactivity disorder (ADHD) soon after TBI (5). In many cases these symptoms resolve over time; however, in some children they persist and the children are diagnosed with ADHD. Regardless of prior psychiatric history or severity of TBI (6), 14% to 21% of youths admitted to a hospital with TBI will present with a new ADHD diagnosis postinjury. (7,8). This prevalence makes ADHD the most common disorder to develop following TBI in youths. ADHD is thought to have a complex etiology; it is highly heritable (9,10) and has been associated with alterations to several neural circuits (11). While there are some established psychosocial premorbid risk factors for the development of ADHD post-TBI (7,8), to date it is not clear whether genetic risk for ADHD contributes to risk of developing ADHD following TBI and whether the neural substrates associated with ADHD symptoms are the same or different when a TBI has occurred.

ADHD is characterized by a persistent pattern of age-inappropriate levels of hyperactivity, impulsivity, and inattention (12) and is associated with a range of negative health and

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psychosocial outcomes (13). Recently, approximately 20,000 ADHD cases and 35,000 matched control subjects were analyzed in the largest ADHD genome-wide association study (GWAS) to date, which identified 12 genetic risk loci that reached genome-wide significance (14). Genes identified by GWASs are thought to act through a spectrum of biological mechanisms to contribute to ADHD pathogenesis (15), with each of these risk loci having small cumulative effects. A polygenic risk score computed from the recent GWAS data accounted for 5.5% of variance in ADHD diagnosis, and the proportion of the heritability of ADHD that can be explained by all common variants was 0.22 (14). However, GWASs have yet to fully account for the high heritability of ADHD estimated in twin studies (~75–90%) (9,10), potentially due to nonadditive genetic influences, gene–environment correlation, not examining rare variants, and genetic heterogeneity. Reduced volume and altered shape of the basal ganglia (caudate, putamen, accumbens, and globus pallidus) have been consistently implicated in the pathogenesis of ADHD and are the most replicated structural finding across neuroimaging studies to date (16–18). The basal ganglia are richly interconnected components of neuroanatomical loops that connect the cortex and thalamus. These circuits regulate many cognitive processes that are impaired in ADHD such as executive function, inhibition of behavior, and modulation of reward pathways (19).

TBI is most frequently caused by rapid acceleration–deceleration of the head that may or may not be accompanied by head impact. In addition to focal damage, impact, torsion, tension, and compression forces initiate traumatic axonal injury, which is accompanied by myelin changes in the brain (20,21). Although traumatic axonal injury is heterogeneous and diffuse, there is a typical anatomical pattern of injuries that results from the movement of the brain relative to the skull. According to studies of postmortem axonal damage (22,23) and in vivo neuroimaging (24–26), traumatic axonal injury typically occurs in the areas of gray matter–white matter junctions of the corona radiata, the corpus callosum, and (in more severe cases) the brainstem. Recent meta-analyses have also identified alterations of the corona radiata and corpus callosum in individuals with ADHD (27–30).

Here, we characterize and contrast the etiology of ADHD symptoms in youths who have experienced a mild TBI against youths who have no history of TBI. To the best of our knowledge, we provide the first description of the contribution of genetics and brain structure to the expression of ADHD symptoms in a large community sample of youths with and without a history of mild TBI. Specifically, we tested whether having a history of mild TBI modulates the association between ADHD symptoms and 1) polygenic risk for ADHD based on the most recent Psychiatric Genetics Consortium GWAS (14), 2) volumes of ADHD-related brain structures (caudate, putamen, accumbens, and globus pallidus) from T1-weighted magnetic resonance imaging (MRI), and 3) fractional anisotropy (FA) derived from diffusion tensor imaging of white matter tracts affected by traumatic axonal injury (corpus callosum and corona radiata). Together, these analyses aimed to address whether ADHD symptoms are associated with similar or different genetic and neural substrates when there is a history of TBI, with implications for both prognosis and treatment targets.

METHODS AND MATERIALS

Sample Characterization and Analyses

Philadelphia Neurodevelopmental Cohort. Participants were subjects from the Philadelphia Neurodevelopmental Cohort, a population-based sample of children and adolescents aged 8 to 22 years (31) (see Supplemental Methods). Participants (aged 11–21 years) and parents or guardians (of those age 17 years or under) were administered a structured interview, the GOASSESS (32), which screened for psychopathology and included a comprehensive medical history. The GOASSESS is abbreviated and modified from the epidemiologic version of the National Institute of Mental Health Genetic Epidemiology Research Branch Kiddie Schedule for Affective Disorders and Schizophrenia (33). Participants also provided blood samples for genetic analysis. A subset of 1600 participants underwent multimodal neuroimaging on the same 3T Siemens TIM Trio scanner (Siemens, Erlangen, Germany) (34).

Definition of TBI. Participants were separated into two groups: those with a history of mild TBI and those with no history of TBI. The mild TBI group was composed of individuals who reported at least one TBI that was accompanied by less than 30 minutes of unconsciousness and less than 24 hours of amnesia, with no skull fracture or neurosurgical intervention associated with the injury. There were very few participants with moderate or severe TBI who were excluded from the analyses. Within the mild TBI group, participants who reported headache, loss of consciousness, or amnesia associated with the injury were classified as high risk for persistent postinjury deficits.

ADHD Symptom Severity Score. The structured interview assesses a subset of symptoms and criteria that corresponds to the diagnostic criteria for ADHD, as described in the DSM-5 (12). Positive responses to the ADHD symptom questions contributed to the score, and additional points were assigned based on the age of onset and environments where the difficulties occurred as well as impairment and distress associated with the symptoms (see Supplemental Methods).

Summary of Analyses. Separate analyses were performed in subsets of participants determined by the availability and quality of the data and the participant inclusion criteria for each analysis as outlined below and depicted in Figure 1A. All analyses were performed in participants who had a minimum ADHD symptom severity score of 1 in order to test linear hypotheses (see Supplemental Methods) and excluded participants with moderate to severe medical conditions. Within each analysis, there was a small number of participants missing necessary variables, and these participants were excluded. Clinical data from 3611 participants were available for ADHD symptom analysis (TBI = 418, no TBI = 3193). Polygenic score analysis was performed only in participants of Caucasian ancestry in order to mitigate confounds due to ethnic differences between the current study sample and the ADHD GWAS (14) from which the polygenic score was derived. For this

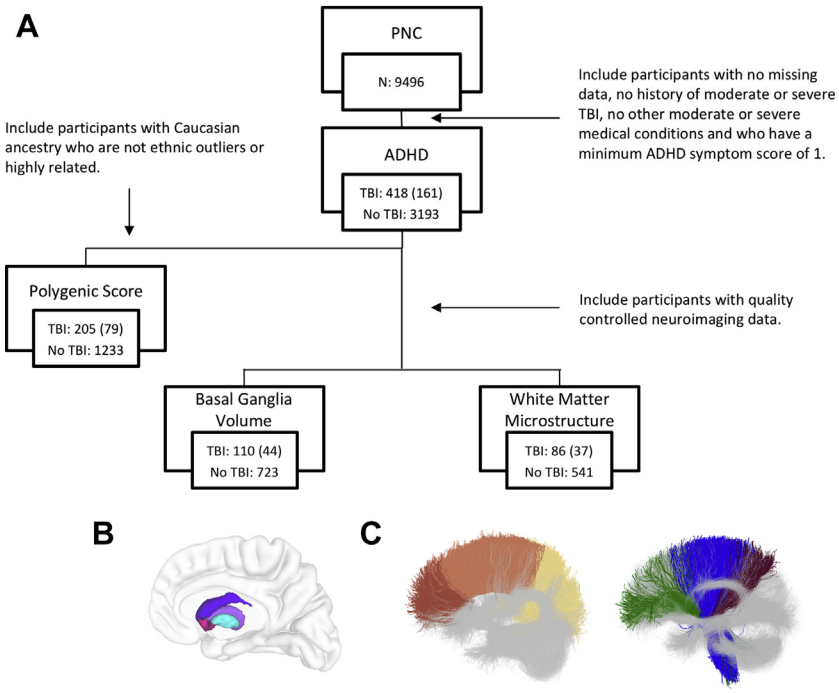

Figure 1. Summary of analyses. **(A)** Eligible participants from the Philadelphia Neurodevelopmental Cohort (PNC) were identified for each analysis from the total sample, first for attention-deficit/hyperactivity disorder (ADHD) symptom comparison between traumatic brain injury (TBI) groups, second for polygenic score analysis, third for basal ganglia volume analysis, and fourth for white matter microstructure analysis based on specific inclusion criteria summarized here and described in the Methods and Materials section. TBI indicates number of youths with a history of mild TBI who were included in that specific analysis, with the number in parentheses indicating the number of these youths who were considered high risk for persistent deficits following mild TBI. No TBI indicates the number of youths with no history of TBI included in that analysis. **(B)** Basal ganglia regions of interest for volumetric analyses are visualized in the right hemisphere embedded in a cortical surface representation for reference: caudate (purple), putamen (violet), accumbens (pink), and globus pallidus (turquoise). **(C)** White matter tract atlases show subdivisions examined in the corpus callosum (left: genu [red], body [orange], and splenium [yellow]) and corona radiata (right: anterior [green], superior [blue], and posterior [maroon]).

analysis, ethnic outliers and highly related individuals were excluded, which left 1438 individuals (TBI = 205, no TBI = 1233). Participants of all ethnic backgrounds were included in the neuroimaging analyses. After excluding individuals who did not have imaging data, 833 participants with quality-controlled T1-weighted MRI remained for basal ganglia volume analyses (TBI = 110, no TBI = 723) and 627 participants with quality-controlled diffusion tensor imaging remained for white matter microstructure analysis (TBI = 86, no TBI = 541). We also include sensitivity analyses that repeat each of these analyses in samples of participants where youths who meet criteria for ADHD diagnosis have been excluded as well as in samples of participants where youths taking medication for emotions and/or behaviors have been excluded.

Data Acquisition and Processing

Genetics Data Processing. Genome-wide genetic data were assessed for quality, and imputation was performed. Ethnicity was determined by multidimensional scaling, and ethnic outliers and related individuals were identified. Details are available in the Supplemental Methods.

Polygenic Score Calculation. Polygenic ADHD risk was determined by calculating an additive genome-wide polygenic score for each participant in the sample based on summary data from the Psychiatric Genetics Consortium ADHD Subgroup GWAS in subjects of Caucasian ancestry (19,099 cases and 34,194 control subjects) (14,35) (see Supplemental Methods).

Basal Ganglia Segmentation. T1-weighted image acquisition parameters have been published (34) and are described in the Supplemental Methods. The caudate, putamen, accumbens and globus pallidus volumes were automatically identified on T1-weighted images using MAGeTbrain segmentation, an extension of the multi-atlas segmentation technique (36,37) (Figure 1B). Details are provided in the Supplemental Methods. Mean volumes of the four bilateral structures were computed and used in all analyses because a previous mega-analysis of the association between subcortical volumes and ADHD diagnosis did not find evidence of laterality effects (38).

White Matter Tractography. Diffusion-weighted MRI acquisition parameters have been published (34) and are described in the Supplemental Methods. Diffusion-weighted scans were corrected for motion and eddy current distortions using DTIPrep software (39). Following quality control (see Supplemental Methods), tensors and fiber tracts were generated in 3D Slicer software (40) via the SlicerDMRI project (41) (http://dmri.slicer.org). An automated method was used for tractography segmentation (see Supplemental Methods). Mean FA was extracted from the bilateral anterior, superior, and posterior corona radiata as well as the genu, body, and splenium of the corpus callosum (Figure 1C).

Statistics

Statistical analyses were conducted using R software with multiple linear regression modeling. ADHD symptom analysis modeled the effect of TBI group on the ADHD symptoms score in order to compare the severity of ADHD symptoms reported in youths with and without mild TBI. This analysis included age, gender, and highest level of parental education as covariates. The following three analyses examined whether the relationship between the variable of interest and ADHD symptom severity differed between youths with and without a history of mild TBI

by modeling the interaction between the variable and TBI group on the ADHD symptom severity score. The variable examined in polygenic score analysis was polygenic risk score for ADHD, and the covariates included in this model were age, gender, highest level of parental education, and the top four components from multidimensional scaling analysis. Variables of interest in basal ganglia volume analysis were the volume of the caudate, putamen, accumbens, and globus pallidus, and this model included age, gender, highest level of parental education, and total brain volume as covariates. The variables examined in white matter microstructure analysis were FA of the anterior, superior, and posterior corona radiata as well as the genu, body and splenium of the corpus callosum, and this model included age, gender, highest level of parental education, and temporal signal-to-noise ratio as covariates. Significant interactions of variables with TBI group were followed up with post hoc analysis of the variable's main effects within each group separately as well as the use of the Johnson–Neyman technique to identify a region of significance that defines subgroups of participants with different ADHD symptom severity scores. When no significant interaction was detected, the model was rerun without the interaction term to examine the main effect of the variable of interest on ADHD symptom severity across groups. For all main effects, the percentage of variance explained by the key variables (polygenic score, white matter FA, and basal ganglia volume) was computed by comparing the R^2 of the model with the key variable with the R^2 of a reduced model with covariates only (ΔR^2). A linear model was also used to examine differences in these three types of variables between groups. Interaction and group difference analyses were also performed in the subsample of youths with a history of TBI who were considered high risk for persistent deficits as described in the "Definition of TBI" section above. Uncorrected p values are reported and specified as significant based on Bonferroni correction performed within analyses (polygenic score, 1 comparison, $p = .05$; basal ganglia volume, 4 comparisons, $p = .0125$; white matter microstructure, 6 comparisons, $p = .0083$).

RESULTS

Sample Characteristics

Of participants who met inclusion criteria for the ADHD symptom analysis ($n = 3611$), 11.6% ($n = 418$) reported at least one previous mild TBI, and 38.5% ($n = 161$) of these participants with mild TBI reported headache, loss of consciousness, or amnesia associated with the injury, qualifying them as high risk for persistent deficits. Injury characteristics of the TBI participants within each analysis group are summarized in Supplemental Table S1A to S1D. Within the ADHD symptom analysis sample, the mild TBI group was older and had a larger proportion of male participants compared with the group of youths with no TBI (Table 1). Age differences between TBI groups were also detected in the polygenic score, basal ganglia volume, and white matter microstructure analysis samples (Supplemental Table S2A–C).

ADHD Symptom Analysis

Youths with mild TBI had a higher ADHD symptom severity score compared with those without TBI (no TBI: mean = 6.8, SD = 3.4; TBI: mean = 7.1, SD = 3.4; $t_{3604} = 3.0$, $\Delta R^2 = .002$, $p = .002$). This difference did not reach our threshold for statistical significance when examining only youths with mild TBI at high risk for persistent deficits (TBI high risk: mean = 6.9, SD = 3.5; $t_{3347} = 2.0$; $\Delta R^2 = .001$; $p = .06$).

Polygenic Score Analysis

There was a significant interaction between polygenic score and TBI group ($t_{1427} = -2.1$, $p = .04$), indicating that the relationship between polygenic score and symptom severity score differed with respect to TBI history. Polygenic score showed a strong positive association with ADHD symptom score in youths without TBI ($t_{1224} = 3.5$, $\Delta R^2 = .009$, $p = .004$) and no association with ADHD symptom score in those with mild TBI ($t_{196} = -0.4$, $\Delta R^2 = -.004$, $p = .70$) (Figure 2). Assessing a region of significance indicated that low genetic risk (polygenic score < 0.26) is protective against ADHD symptoms in youths without TBI but not in those with mild TBI. This interaction did not reach significance when examining only mild TBI participants at high risk for persistent deficits ($t_{1301} = -1.3$, $p = .20$). There was no difference in mean polygenic score between youths with and without mild TBI (TBI: mean = 0.04, SD = 1.0, no TBI: mean = −0.006, SD = 1.0; $t_{1429} = 0.7$, $p = .50$), as was the case when examining only high-risk mild TBI participants (TBI high risk: mean = 0.03, SD = −0.002; $t_{1303} = 0.5$, $p = .60$).

Basal Ganglia Volume Analysis

No significant interactions between structure volume and TBI group on ADHD symptom score were detected in the caudate, putamen, accumbens, or globus pallidus when including either all mild TBI participants or only those considered high risk. However, a negative association between caudate volume and ADHD symptom score was found in the overall group ($t_{809} = -2.58$, $p = .01$, $\Delta R^2 = .007$) (Table 2). In addition, putamen volume was larger in high-risk mild TBI youths compared with those with no TBI ($t_{744} = 2.6$, $p = .01$) (Supplemental Table S3).

White Matter Microstructure Analysis

A significant interaction between FA in the genu of the corpus callosum and TBI group on ADHD symptom score was detected when examining participants with mild TBI at high risk for persistent deficits ($t_{570} = -2.83$, $p = .005$). FA in the genu of the corpus callosum showed a positive association with ADHD symptom score in youths without TBI ($t_{535} = 2.52$, $\Delta R^2 = .01$, $p = .012$) but showed a negative association with ADHD symptom score in youths with TBI ($t_{31} = -3.43$, $\Delta R^2 = .25$, $p = .0017$) (Supplemental Figure S1). Assessing a region of significance indicated that high FA in this tract (>0.49) is associated with lower levels of ADHD symptom severity in youths with mild TBI than in those without TBI. No significant interactions or main effects were detected in the corpus callosum body, splenium, or corona radiata (Table 3). There were no significant differences in tract FA between TBI groups (Supplemental Table S4).

Sensitivity Analyses

All results remained highly similar when these analyses were rerun in samples of participants where youths who met criteria for ADHD diagnosis were excluded (Supplemental Results and Supplemental Table S5A and S5B) as well as in samples of

Table 1. Participant Characteristics in the Symptom Analysis Sample

	No TBI	Mild TBI	High Risk Mild TBI	*p* Value TBI	*p* Value High Risk Mild TBI
Age, Years, Mean (SD)	13.6 (3.5)	14.4 (3.4)	15.4 (3.1)	1.5×10^{-6}	4.0×10^{-12}
Gender, *n*	1592 M, 1595 F, 6 U/O	254 M, 163 F, 1 U/O	89 M, 71 F, 1 U/O	8.9×10^{-6}	6.2×10^{-5}
Education, Years, Mean (SD)	15.0 (2.5)	15.1 (2.3)	15.3 (2.5)	.15	.09
Medication, *n*	378	63	27	.07	.07
ADHD, *n*	629	93	30	.20	.86
Anxiety Disorder, *n*	560	77	33	.61	.19
Behavior Disorder, *n*	727	104	39	.36	.55
Mood Disorder, *n*	424	82	33	5.8×10^{-4}	.01

The *p* values reflect differences between the specified mild TBI group and no TBI group calculated with Student *t* test for continuous variables and with chi-square test for categorical variables. Education refers to the highest level of parental education. Medication refers to the number of participants who were taking medication because of emotions and/or behaviors. Diagnosed anxiety disorders include agoraphobia, generalized anxiety disorder, panic disorder, and separation anxiety disorder. Diagnosed behavior disorders include oppositional defiant disorder and conduct disorder. Mood disorders include major depressive disorder and mania.

ADHD, attention-deficit/hyperactivity disorder; F, female; M, male; TBI, traumatic brain injury; U/O, unknown/other.

participants where youths taking medication for emotions and/or behaviors have been excluded (Supplemental Results and Supplemental Table S6A and S6B).

DISCUSSION

Here, we examined genetic and brain structural correlates of ADHD symptoms in a community sample of youths with and without a history of mild TBI. Youths with mild TBI reported increased ADHD symptom severity, consistent with previous studies (7,8). Assessment of the relationship between polygenic risk and ADHD symptoms revealed that, as expected, polygenic score was associated with increased ADHD symptom severity, although this relationship was driven by youths with no TBI. Caudate volume was negatively associated with number of ADHD symptoms regardless of TBI history. In contrast, the volumes of the putamen, accumbens, and globus pallidus were not associated with number of ADHD symptoms. Intriguingly, an interaction between FA in the genu of the corpus callosum and TBI group on ADHD symptoms indicated that the direction of association between FA and ADHD symptoms was dependent on whether or not participants had a history of TBI. Overall, the results of this study suggest that when ADHD symptoms occur in conjunction with mild TBI, established genetic risk for ADHD might not be an important risk factor. In addition, they point to common brain structures associated with ADHD symptoms with a potentially different underlying cellular-level disruption in the genu of the corpus callosum contributing to symptoms manifestation.

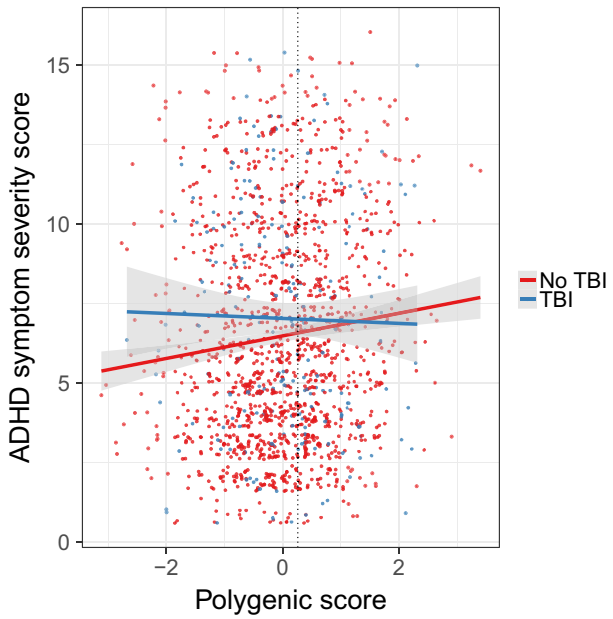

Figure 2. Polygenic score is differentially associated with attention-deficit/hyperactivity disorder (ADHD) symptoms in youths with a history of traumatic brain injury (TBI). A significant interaction between polygenic score and TBI history on ADHD symptom severity is driven by a strong positive relationship in youths without a history of TBI (red) and no association in youths with a history of TBI (blue). Regression lines for those with and without a history of TBI are plotted with shaded 95% confidence intervals. Youths with mild TBI and polygenic scores to the left of the dotted vertical line have higher ADHD symptom severity scores than those with no history of TBI.

Polygenic risk for ADHD was strongly associated with ADHD symptoms in youths with no TBI and showed no association with ADHD symptoms in those with mild TBI. This suggests that in individuals who experience TBI, the physical insult to the brain and resulting alterations in structure and function may be influential contributors to the presentation of post-TBI ADHD symptoms, whereas additive genetic predisposition contributes to developmentally acquired ADHD. These results oppose the idea that those with higher polygenic scores may be more vulnerable to developing ADHD symptoms following brain injury but are consistent with a recent study of soldiers with TBI finding that the genetic predisposition to persistent postconcussion symptoms following TBI does not have substantial overlap with genetic predisposition to neurodegenerative and psychiatric diseases (42).

We found that TBI history did not influence the relationship between basal ganglia volumes and ADHD symptoms. A large body of research has demonstrated reduced striatum and globus pallidus volumes associated with ADHD diagnosis and symptoms (16–18). Recently, a large mega-analysis confirmed the relationship between decreased volumes in the caudate,

Table 2. Associations Between Basal Ganglia Volumes and ADHD Symptoms

	Interaction–Mild TBI		Interaction–High Risk Mild TBI		Main Effect		
	t Value	*p* Value	*t* Value	*p* Value	*t* Value	ΔR^2	*p* Value
Caudate	0.96	.34	1.23	.22	−2.58[a]	.007	.01[a]
Putamen	−0.12	.90	0.71	.48	−1.09	.0002	.27
Accumbens	0.99	.33	0.91	.37	−1.17	.0004	.24
Globus Pallidus	−0.78	.44	−0.60	.55	−1.41	.001	.16

Interaction refers to the interaction between structure volume and traumatic brain injury (TBI) group on attention-deficit/hyperactivity disorder (ADHD) symptom severity score when examining all participants with mild TBI as well as the subset at high risk for persistent deficits (high risk mild TBI). No significant interactions were detected, and the model was rerun without the interaction term to assess main effects of structure volume on symptom severity (main effect). Raw *p* values are reported.

[a]Effect significant at a Bonferroni-corrected $p < .05$.

putamen, and accumbens and ADHD but did not find any differences in the volumes of the globus pallidus in individuals with ADHD (38). Here, we detected a weak negative relationship in the caudate, demonstrating that reduced caudate volume is associated with ADHD symptom severity score, but not in the putamen, accumbens, and globus pallidus. The major difference between the cited studies and this one is that here we examined a dimensional variable, ADHD symptom severity score, in a community sample rather than ADHD diagnosis in a clinical sample. In addition, the psychiatric assessment used in this study to create the ADHD severity score is an abbreviated version of the full Kiddie Schedule for Affective Disorders and Schizophrenia that is used for diagnosis of ADHD (32). That half of the symptoms of ADHD were sampled here may also contribute to the discrepancy in findings related to the putamen and accumbens.

There was a differential direction of association between FA and ADHD symptoms in the genu of the corpus callosum in youths with and without a history of TBI. This suggests that different means of disruption that correspond to different types of white matter pathology in this tract may contribute to ADHD symptoms in each TBI group. Decreases in FA in the genu of the corpus callosum associated with ADHD symptoms in youths with mild TBI may reflect damaged axons, reduced myelination, inflammation, edema, or a combination of these factors (43,44). However, the interpretation of the pathophysiology that is driving the opposing direction of association in youths with no history of TBI is less straightforward. Many previous studies that used a categorical approach have demonstrated decreased white matter FA in participants with ADHD diagnosis compared with healthy control subjects (27,45). Conversely, using a dimensional approach, the literature in children and adolescents indicates a significant amount of support for positive associations between FA and ADHD symptom load in widespread brain regions, including the genu of the corpus callosum (28,46). One possible interpretation is that it reflects compensatory accelerated development of the corpus callosum that is associated with ADHD symptoms. In general, these results are consistent with a roll for circuits that contain the genu of the corpus callosum in attention processes and ADHD (27,28,30,47) and a particular vulnerability of the genu of the corpus callosum to axonal injury (22–26).

A recent review concluded that "there is a paucity of evidence available to definitively guide management of attention problems after pediatric TBI" (48). Because attention is a prerequisite for behavioral and neurocognitive functioning, attention deficits have been shown to relate to daily life problems after pediatric TBI (4). This study suggests that the etiology of developmental versus acquired ADHD may be distinct, providing a description of divergent genetic risk and distinct as well as nondistinct neural substrates. This indicates that fundamental differences exist between acquired and developmental ADHD despite similarities in behavioral features and are in line with previous evidence of distinct neuropsychological impairments (49,50) and response to treatment (51,52). Population-based estimates in adolescent samples for

Table 3. Associations Between White Matter Tract FA and ADHD Symptoms

	Interaction–Mild TBI		Interaction–High Risk Mild TBI		Main Effect		
	t Value	*p* Value	*t* Value	*p* Value	*t* Value	ΔR^2	*p* Value
Corpus Callosum Genu	−1.38	.17	−2.83[a]	.005[a]			
Corpus Callosum Body	−0.04	.97	−1.43	.15	0.98	−.0005	.33
Corpus Callosum Splenium	−1.14	.25	−1.98	.05	1.12	.0004	.26
Anterior Corona Radiata	0.67	.50	0.36	.72	0.46	−.001	.64
Superior Corona Radiata	0.16	.87	−1.08	.28	0.05	−.002	.96
Posterior Corona Radiata	−0.52	.61	−0.56	.58	1.56	.002	.12

Interaction refers to the interaction between tract fractional anisotropy (FA) and traumatic brain injury (TBI) group on attention-deficit/hyperactivity disorder (ADHD) symptom severity score when examining all participants with mild TBI as well as the subset at high risk for persistent deficits (high risk mild TBI). Where significant interactions were observed, the relationship between tract FA and symptoms was assessed in separate groups with and without a history of TBI. When the interaction was not significant, the model was rerun without the interaction term to assess effect of tract FA on ADHD symptoms (main effect). Raw *p* values are reported.

[a]Effect significant at a Bonferroni-corrected $p < .05$.

self-report lifetime concussion are approximately 20% (53,54), higher than the 11% of youths who reported a previous mild TBI in this cohort. Conversely, population estimates of ADHD in youths range from 5% to 9% (33,55,56), lower than the 18% of participants who met diagnostic criteria in this cohort (32). Irrespective of the exact numbers, it stands that a significant number of ADHD cases in the general population have co-occurring ADHD and mild TBI, with approximately half of these ADHD cases acquired post-TBI (7). Consequently, TBI history should be evaluated by treating clinicians. The identification of children at highest risk for ADHD following TBI may be facilitated by in vivo neuroimaging that evaluates damage to the corpus callosum in conjunction with other known predisposing factors such as preinjury adaptive functioning, psychosocial adversity, and socioeconomic status (7,8).

There are several important limitations to this study. First, ADHD is a risk factor for and major sequela of TBI in youths. In this retrospective analysis, we cannot distinguish pre- and postinjury ADHD and must assume that the participants with a history of TBI are reporting symptoms that manifest both before and after injury. Previous studies indicate that of the children who have experienced TBI, half of ADHD cases were present prior to the injury and half developed after the injury (7). Nonetheless, we were able to identify differences in associations with symptom severity scores between injury and noninjury groups. Future work will need to examine these associations in a prospective manner. Second, we used a polygenic score based on common risk variants to assess genetic risk for ADHD symptoms, which does not take into account all genetic risk. Third, each set of analyses examined different samples dependent on the availability of that type of data and specific exclusion criteria. Because the sample sizes differed between analyses, the analyses were powered to detect different effect sizes (see Supplemental Results). Fourth, in line with using a dimensional approach (57), we generated the ADHD severity score from the GOASESS structured interview, although we acknowledge that this continuous score has not been validated. Future work would benefit from using the Strengths and Weaknesses of ADHD Symptoms and Normal Behavior rating scale, which, unlike the scale used here, is bidirectional and can capture the full spectrum of the population distribution for ADHD symptoms (58). Lastly, replication of these results in a comparable dataset will be an important next step.

Medical history that includes a mild TBI is common in this large community sample of youths and is associated with no elevated genetic risk for ADHD as well as distinct and nondistinct neural substrates associated with ADHD. The identification of characteristic ADHD etiology in youths with a history of TBI is a first step toward understanding neurobiological and clinical heterogeneity, which will ideally pave the way for the development of tailored interventions that may differ among youths with ADHD, informed by presence or absence of TBI history.

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