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

Supplemental Information

Supplemental Methods

Philadelphia Neurodevelopmental Cohort

Philadelphia Neurodevelopmental Cohort subjects were drawn from a pool of approximately 50,000 subjects who had already been recruited, through a pediatric healthcare network of clinical community sites, to genetic studies at the Center for Applied Genomics at the Children's Hospital of Philadelphia. Participants from this pool who lived in the greater Philadelphia area were selected at random after stratification by sex, age, and ethnicity for enrollment in the Philadelphia Neurodevelopmental Cohort. Inclusion criteria was as follows: (a) able to provide signed informed consent; (b) English proficiency; and (c) physically and cognitively able to participate in an interview and computerized neurocognitive testing. Minimal inclusion criteria ensured that children were not screened out for any disorders (1). This study was approved by the institutional review boards of the University of Pennsylvania and the Children's Hospital of Philadelphia.

ADHD Symptom Severity Score

The ADHD symptom severity score ranged from 0 to 16 with 6 points reflecting affirmative responses to questions regarding inattentive symptoms and 3 points reflecting affirmative

responses to questions regarding hyperactive/impulsive symptoms. Inattentive symptoms that were assessed were: difficulty sustaining attention, not appearing to listen, struggling to follow through on instructions, difficulty with organization, and disliking tasks requiring sustained mental effort. Hyperactive/impulsive symptoms that were assessed were: difficulty remaining seated or fidgeting or squirming or 'always on the go', blurting answers before questions are completed or interrupting and difficulty waiting or taking turns. The remaining 7 points reflected the age of onset, environments where the difficulties occurred as well as impairment and distress associated with the symptoms as follows. One point was added if the participant met each of the following criteria: 1) Difficulties began before the age of 12, or if the first time these behaviours occurred was before 12, or if behaviours have always occurred. 2) Difficulties significantly bothered family, friends, teachers or coworkers. 3) Difficulties significantly bothered the participant. 4) Difficulties due to symptoms cause significant problems at work or school that require the participant to stay home for greater than the median number of days reported in the population. Finally, up to 3 points were added if difficulties occurred at home, at school with a teacher, and with any other adults outside of home or school.

Genetics Data Processing

Genome-wide genotyping was performed on Affymetrix (6.0 Genechip and Axiom) and Illumina (Human610, HumanHap550 v1.0, and HumanHap550 v3.0) platforms.

Quality control of genetic data was performed according to a standard protocol outlined by Anderson et al. (2). Imputation was performed for all platforms separately using PLINK (v1.90b) (3) and IMPUTE2 (v2.3.1) (4, 5) software packages, using the 1000 Genomes

Phase I integrated haplotypes (b37) reference panel. Multi-dimensional scaling was used to determine ethnicity from the genetic data (6) using HapMap3 reference populations (https://www.broadinstitute.org/medical-and-population-genetics/hapmap-3). Caucasian participants were those matched to the HapMap 3 reference populations CEU or TSI. In order to objectively identify ethnic outliers, we calculated the smallest four-dimensional distance from each subject to the centroid of each HapMap 3 reference population and labeled all subjects whose smallest distance was greater than 3 standard deviations from the sample's average smallest distance as outliers. To determine the degree of cryptic relatedness between subjects PLINK was used to calculate estimates of identity-by-descent (IBD) for every possible pair of subjects based on genotypic congruence across all SNPs. SNPs were pruned for pairwise LD (window size of 50kb, shifting 5 variants each step, removing SNPs with $r^2>0.2$), and minor allele frequency (MAF>0.01). One subject from each pair where pi-hat (P(IBD=2) + 0.5*P(IBD=1)) exceeded 0.3 (threshold chosen to exclude any second- or first-degree relatives) was chosen randomly and excluded from the analysis sample.

Polygenic Score Calculation

The Psychiatric Genetics Consortium ADHD Subgroup GWAS was the first GWAS with sufficient statistical power to identify genome-wide significant loci associated with ADHD diagnosis(7). The polygenic score for each participant was calculated genome–wide (i.e. with all available SNPs) as recommended by Wade et al 2017 (8). PLINK was used to weight the number of alleles at each SNP by the natural logarithm of its respective odds ratio and the products were summed to provide a polygenic score for each participant which was normalized with a z-score (9).

T1-weighted Image Acquisition

T1-weighted structural MRI acquisitions were obtained with the magnetization-prepared rapid gradient-echo sequence with the following parameters: field of view =180mmx240mm; matrix=192x256x160slices; TR/TE/TI=1810ms/3.5ms/1100ms; flip angle=9; 1.0mm slices (10).

Basal Ganglia Segmentation

Minc-bpipe-library was used to preprocess the T1 structural scans before further processing. This pipeline performs inhomogeneity correction with N4ITK using a classification estimate (11). Then affine registration to MNI ICBM 09c Symmetric space (12) is done to use the headmask to remove excess data and background in native space and to crop the scan of excess voxels. A brain mask is also estimated using the BeAST tool (13) and resampled to native space to give an estimate of total brain volume. MAGeTbrain segmentation is an extension of the multi-atlas segmentation technique, where one or more expertly segmented atlases are bootstrapped via linear and non-linear registration onto a template library constructed from a representative subset of the subject population (in this case stratified for age and sex distribution of the sample) (14, 15). The template library is then used as an expanded atlas library, linearly and non-linearly registered to each subject and the candidate labels are transformed and voted by a voxel-wise majority vote. In this work, MAGeTbrain utilized the Colin27 subcortical atlas, a single high-contrast 27-average scan of a single subject (16) that was labelled from a high resolution serial histological dataset via a novel pseudo-MRI driven deformation technique (17). When comparing

automated approaches to manual segmentation in younger populations, MAGeTbrain does better than FreeSurfer and FSL based on dice overlap measures and Bland Altman plots (18). To rule out the presence of segmentation errors, a quality control image file was visually inspected for each scan. Of the 32 scans eliminated for poor quality 9 were eliminated due to excessive movement artefacts, and 23 for other abnormalities resulting in unrepresentative labels. The participants excluded due to excessive movement in their scans did not have significantly higher ADHD symptom severity points compared to the sample included in the analysis (excluded: mean=5, SD=5; sample mean=7, SD=3; t test p=0.3).

Diffusion Weighted Image Acquisition

Diffusion weighted MRI acquisitions were obtained using a twice-refocused spin-echo single-shot EPI sequence. Acquisitions were obtained with the following parameters: 64 diffusion-weighted directions with b=1000 s/mm^2, and 7 scans with b=0s/mm^2, field of view=240mmx240 mm; matrix 128x128x70 slices; TR/TE=8100ms/82ms; flip angle=90*/180*/180*; 2.0mm slices (10).

Diffusion Imaging Quality Control

Images were evaluated for quality control using DTIPrep's automated QC parameters as follows. Images with less than 6 gradient directions, poor baseline images or b-values, or an excess of gradient directions which had to be removed due to artefacts or distortions were removed from the sample. Commonly DTI images failed quality control due to signal dropout caused by the interaction of subject motion and diffusion encoding (10). Following this step

temporal signal to noise ratio (TSNR) was calculated using an automated QA script (https://www.med.upenn.edu/cmroi/qascripts.html (19)).

White Matter Tractography

First unbiased multi-subject registration, an affine transform followed by b-spline transformation, was conducted to enable non-rigid deformations of whole brain tractography to align tracts in a common space (20). Then atlas generation was conducted on a subset of 30 randomly selected participants from the sample. Similar fibers from the participants were grouped into white matter clusters using a data-driven machine learning approach; group spectral bilateral clustering (25). These clusters were sorted into biologically relevant tracts, including the corpus callosum and corona radiata, to create a cluster atlas (21, 22). The corpus callosum was further subdivided into three regions: the genu, body and splenium (23, 24). The corona radiata was subdivided into anterior, superior and posterior subdivisions in reference to the John Hopkins University white matter atlas (25). The fibers of each subject in the dataset were then labeled by 1) aligning their tractography to atlas space and 2) assigning each tract according to the nearest atlas cluster centroid (26). Given the bilateral clustering of the atlas, the subject clusters presented fiber tracts in both hemispheres.

Statistics – Validation Analyses

Validation analyses were done to understand the underlying pattern of effect and these led to use of the statistical model presented. The results of the analyses including the ADHD severity scores of zero was not significantly different than the results without them, however

the zero inflated outcome distribution violated model assumptions and prevented us from testing the linear hypothesis. We analyzed participants with zero vs all other ADHD severity scores to test if the observed effect was due to the zeros, and since it wasn't, we excluded the large number of zeros and ended up with the model presented as it is simple, easy to interpret, and yields the same insight.

Statistics – Multiple Comparison Correction

In the neuroimaging analyses p values were considered significant based on Bonferroni correction. P values in the *Basal Ganglia Volume Analysis* were corrected for four comparisons such that they were considered significant if it was less than 0.0125(0.05/4). P values in the *White Matter Microstructure Analysis* were corrected for six comparisons such that they were considered significant if less than 0.0083 (0.05/6).

Supplemental Results

Sensitivity Analyses

Sensitivity Analyses were performed with 1) participants with ADHD diagnosis excluded and 2) patients taking medication because of emotions and/or behaviours excluded. Consistent with the primary analysis ADHD symptom severity remained higher in participants with a history of mild TBI with ADHD diagnosed participants excluded (No TBI: mean=5.9, SD=2.8; TBI: mean=6.1, SD=2.8; $t_{(2884)}$=1.9; ΔR^2=0.001; p=0.05), as well as when participants taking medication were excluded (No TBI: mean=6.4, SD=3.4; TBI: mean=6.8, SD=3.2; $t_{(3101)}$=3.0; ΔR^2=0.002; p=0.003). Similar patterns of results were also observed in the polygenic score

analyses. In the analysis with participants with ADHD diagnosis excluded, there was a interaction between polygenic score and TBI group ($t_{(1427)}$=-1.8; p=0.07) that did not meet our threshold for significance but was driven by a positive association with ADHD symptom score in youth without a history of TBI ($t_{(1004)}$=2.3; ΔR^2=0.004; p=0.02), and no association with ADHD symptom score in those with history of mild TBI ($t_{(146)}$=-0.86; ΔR^2=-0.002; p=0.39). Similarly, in the analyses with participants taking medication excluded the interaction did not meet significance ($t_{(1173)}$=-1.8; p=0.08), but was driven by a positive association with ADHD symptom score in youth without a history of TBI ($t_{(1010)}$=2.7; ΔR^2=0.006; p=0.008), and no association with ADHD symptom score in those with history of mild TBI ($t_{(156)}$=-0.48; ΔR^2=-0.005; p=0.64). Results of the basal ganglia volume analysis and white matter microstructure analysis in ADHD excluded (Supplemental Tables S5A and S5B) and medication excluded (Supplemental Tables S6A and S6B) samples also showed similar patterns of results as the primary analysis, though the relationships did not remain significant following Bonferroni correction.

Post hoc Power Analyses

Post hoc power sensitivity analyses revealed that with 90% power and taking into account the different levels of alpha required to meet multiple comparison correction, each analysis would be sensitive enough to detect small interaction effects (minimum Cohen's f^2: genetics =0.007; basal ganglia volume =0.018; white matter microstructure=0.025).

Supplemental Tables

Supplemental Table S1A – TBI characteristics in ADHD symptom analysis sample

	Symptoms		
TBI group size	418		
Number of TBI (mean)	1.3 (0.6)		
LOC	YES	NO	UNKNOWN
	106	296	16
LOC (mean min)	1.9 (2.5)	--	--
Amnesia	YES	NO	UNKNOWN
	13	394	11
Amnesia (mean min)	160 (400)	--	--
Headaches post TBI	YES	NO	UNKNOWN
	75	322	21

Mean values of continuous variables are reported with standard deviations in brackets.
LOC: loss of consciousness.

Supplemental Table S1B – TBI characteristics in polygenic score analysis sample

	Polygenic Score		
TBI group size	205		
Number of TBI (mean)	1.3 (0.6)		
LOC	YES	NO	UNKNOWN
	53	144	8
LOC (min)	1.7 (2.0)	--	--
Amnesia	YES	NO	UNKNOWN
	4	196	4
Amnesia (min)	91 (180)	--	--
Headaches post TBI	YES	NO	UNKNOWN
	32	168	5

Mean values of continuous variables are reported with standard deviations in brackets.
LOC: loss of consciousness

Supplemental Table S1C – TBI characteristics in the basal ganglia volume analysis sample

	Basal Ganglia Volume		
TBI group size	110		
Number of TBI (mean)	1.5 (1.1)		
LOC	YES	NO	UNKNOWN
	26	84	0
LOC (min)	1.5 (1.3)	--	--
Amnesia	YES	NO	UNKNOWN
	11	95	4
Amnesia (min)	190 (432)	--	--
Headaches post TBI	YES	NO	UNKNOWN
	23	82	5

Mean values of continuous variables are reported with standard deviations in brackets.
LOC: loss of consciousness.

Supplemental Table S1D – TBI characteristics in the white matter microstructure analysis sample

	White Matter Microstructure		
TBI group size	86		
Number of TBI (mean)	1.5 (1.1)		
LOC	YES	NO	UNKNOWN
	21	65	0
LOC (min)	1.5 (1.5)	--	--
Amnesia	YES	NO	UNKNOWN
	9	74	3
Amnesia (min)	228 (473)	--	--
Headaches post TBI	YES	NO	UNKNOWN
	19	62	5

Mean values of continuous variables are reported with standard deviations in brackets.
LOC: loss of consciousness.

Supplemental Tables S2A – Participant characteristics in the polygenic score analysis sample

	Polygenic Score				
	No TBI	TBI	TBI high risk	p value TBI	p value TBI high risk
Age (mean years)	13.8 (3.7)	14.7 (3.5)	16.1 (2.9)	4.1e-4	8.9e-10
Sex	644M 589F	119M 85F	37M 42F	0.12	0.45
Education (mean years)	15.7 (2.4)	15.7 (2.1)	16.2 (2.4)	0.83	0.09
Medication	185	36	18	0.42	0.08
ADHD	220	50	18	0.03	0.38
Anxiety Disorder	170	31	14	0.62	0.23
Behavior Disorder	190	43	16	0.05	0.24
Mood Disorder	157	42	17	0.004	0.04

Mean values of continuous variables reported with standard deviations in brackets. P values reflect differences between specified mild TBI group and no TBI group calculated with Students t test for continuous variables and chi squared test for categorical variables. M: male, F: female. Education: highest level of parental education. Medication: 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.

Supplemental Tables S2B – Participant characteristics in the basal ganglia volume analysis sample

	Basal Ganglia Volume				
	No TBI	TBI	TBI high risk	p value TBI	p value TBI high risk
Age (mean years)	14.1 (3.3)	15.0 (3.3)	15.9 (3.1)	0.02	6.3e-4
Sex	355M 368F	64M 46F	23M 21F	0.09	0.80
Education (mean years)	14.7 (2.5)	15.1 (2.3)	15.6 (2.6)	0.17	0.03
Total brain volume (mean cm^3)	1306 (135)	1320 (124)	1336 (131)	0.26	0.14
Medication	87	20	10	0.09	0.04
ADHD	151	16	4	0.15	0.07
Anxiety Disorder	145	20	7	0.92	1.0
Behavior Disorder	185	23	8	0.48	0.65
Mood Disorder	127	29	12	0.03	0.11

Mean values of continuous variables reported with standard deviations in brackets. P values reflect differences between specified mild TBI group and no TBI group calculated with Students t test for continuous variables and chi squared test for categorical variables. M: male, F: female. Education: highest level of parental education. Medication: 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.

Supplemental Tables S2C – Participant characteristics in the white matter microstructure analysis sample

	White Matter Microstructure				
	No TBI	TBI	TBI high risk	p value TBI	p value TBI high risk
Age (mean years)	14.6 (3.1)	15.4 (3.1)	16.2 (3.0)	0.02	0.003
Sex	257M 284F	45M 41F	17M 17F	0.47	0.78
Education (mean years)	14.8 (2.5)	15.3 (2.3)	15.8 (2.7)	0.07	0.03
TSNR	7.1 (0.6)	7.2 (0.6)	7.1 (0.6)	0.29	0.93
Medication	63	15	6	0.16	0.47
ADHD	104	11	3	0.17	0.13
Anxiety Disorder	109	18	6	0.87	1.0
Behavior Disorder	128	18	7	0.80	0.98
Mood Disorder	101	23	8	0.10	0.77

Mean values of continuous variables reported with standard deviations in brackets. P values reflect differences between specified mild TBI group and no TBI group calculated with Students t test for continuous variables and chi squared test for categorical variables. M: male, F: female. Education: highest level of parental education. TSNR: temporal signal to noise ratio. Medication: 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.

Supplemental Table S3 – Basal ganglia volume differences between groups

ROI	NoTBI		mTBI		mTBI high risk		NoTBI mTBI		NoTBI mTBI high risk	
	mean	SD	mean	SD	mean	SD	t	p	t	p
Caudate	7.76	0.97	7.81	1.14	7.95	0.95	-0.37	0.71	0.55	0.58
Putamen	**10.21**	**1.14**	10.47	1.05	**10.68**	**1.05**	1.60	0.11	**2.58**	**0.01**
Accumbens	2.35	0.29	2.38	0.29	2.44	0.30	0.52	0.6	1.80	0.07
Globus Pallidus	2.85	0.30	2.89	0.31	2.94	0.27	0.82	0.41	1.90	0.06

Mean values and standard deviations of structure volumes reported. Group difference p value and t value reflects basal ganglia structure volume (cm^3) differences between TBI groups. Differences assessed with a linear model that included age, sex, highest level of parental education, medication use and total brain volume as covariates.

Supplemental Table S4 – White Matter Imaging Results: Tract FA differences between groups

ROI	No TBI		mTBI		mTBI high risk		No TBI mTBI		NoTBI mTBI high risk	
	mean	SD	mean	SD	mean	SD	t	p	t	p
CC genu	0.48	0.03	0.48	0.02	0.47	0.02	-1.22	0.23	-1.63	0.10
CC body	1.51	0.07	1.52	0.06	1.52	0.06	0.08	0.94	-1.04	0.30
CC splenium	0.53	0.02	0.53	0.02	0.53	0.02	-0.20	0.84	-1.13	0.26
CR anterior	0.78	0.04	0.79	0.04	0.79	0.04	-0.69	0.49	-1.24	0.22
CR superior	0.94	0.04	0.95	0.03	0.94	0.03	-0.84	0.40	-1.62	0.11
CR posterior	0.87	0.06	0.87	0.05	0.86	0.05	-0.80	0.42	-2.18	0.03

Mean values of FA and standard deviations reported. Group differnce t and p values reflects white matter tract FA differences between TBI groups. Differences were assessed with a linear model that included age, sex, highest level of parental education, medication use and signal to noise ratio as covariates.

Supplemental Table S5A – Associations between basal ganglia volumes and ADHD symptoms – Participants with ADHD diagnosis excluded

	Interaction – TBI		Interaction – TBI high risk		Main Effect		
	t value	p value	t value	p value	t value	ΔR^2	p value
Caudate	0.99	0.32	0.83	0.41	**-2.20**	**0.006**	**0.03**
Putamen	0.11	0.91	0.62	0.54	-1.48	0.002	0.14
Accumbens	0.78	0.43	0.60	0.55	-1.32	0.001	0.19
Globus Pallidus	-0.26	0.80	-0.31	0.76	-1.65	0.003	0.10

Supplemental Table S5B – Associations between white matter microstructure and ADHD symptoms – Participants with ADHD diagnosis excluded

	Interaction - TBI		Interaction - TBI high risk		Main Effect		
	t value	p value	t value	p value	t value	ΔR^2	p value
Corpus Callosum Genu	-1.54	0.13	**-1.91**	**0.05**			
Corpus Callosum Body	-0.32	0.75	-0.67	0.50	0.56	-0.001	0.58
Corpus Callosum Splenium	-1.22	0.22	-1.53	0.13	0.18	-0.002	0.85
Anterior Corona Radiata	-0.24	0.81	-0.17	0.86	-0.15	-0.002	0.88
Superior Corona Radiata	-0.47	0.64	-1.07	0.28	-0.68	-0.001	0.50
Posterior Corona Radiata	-0.49	0.62	-0.32	0.75	0.95	-0.0002	0.34

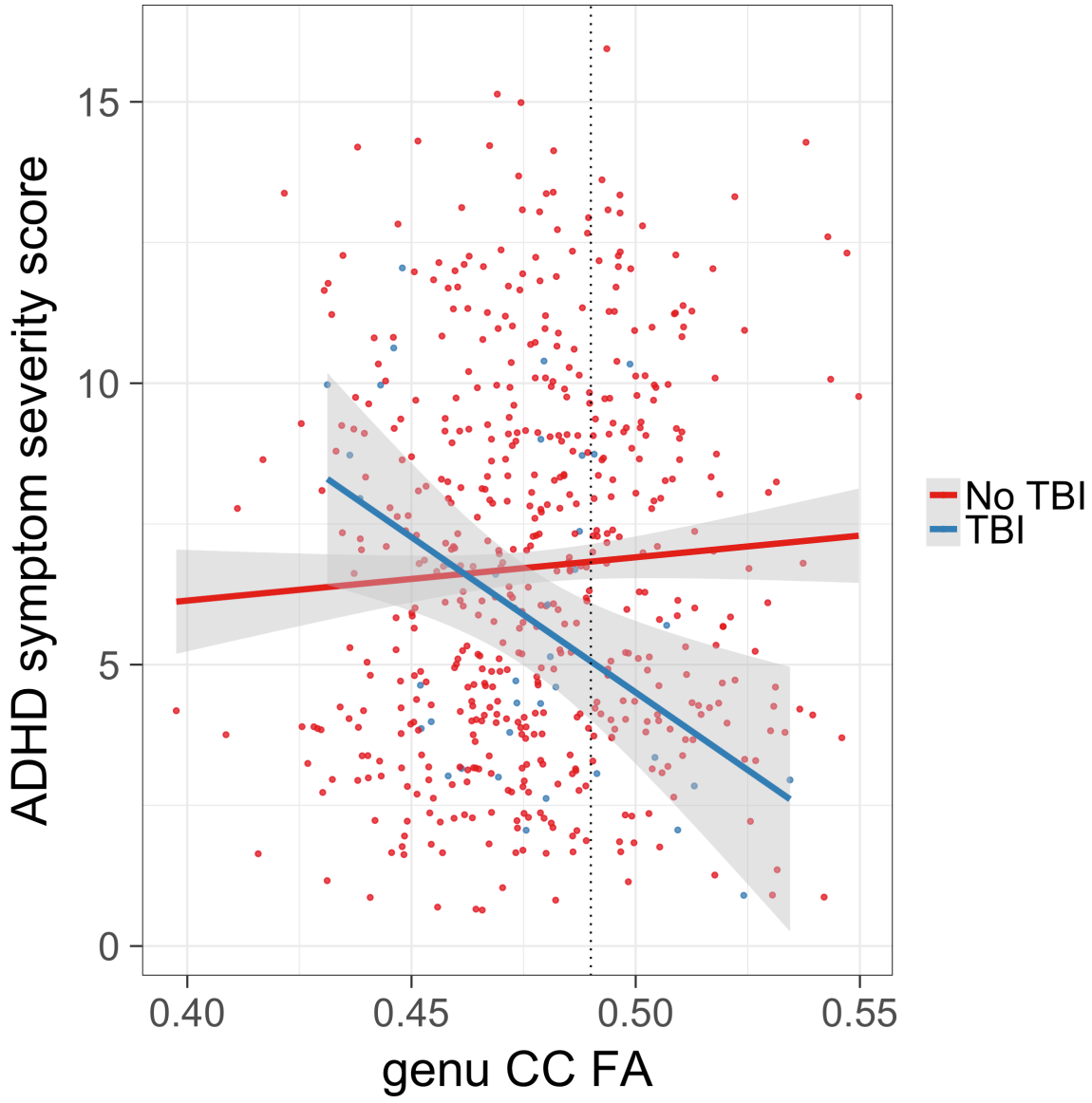
Supplemental Table S6A – Associations between basal ganglia volumes and ADHD symptoms – Participants taking medication excluded

	Interaction – TBI		Interaction – TBI high risk		Main Effect		
	t value	p value	t value	p value	t value	ΔR^2	p value
Caudate	1.04	0.30	1.21	0.23	**-2.26**	**0.006**	**0.02**
Putamen	0.63	0.53	0.95	0.35	-0.78	-0.005	0.44
Accumbens	0.92	0.36	0.53	0.60	-1.12	0.0004	0.26
Globus Pallidus	-0.05	0.96	-0.47	0.63	-0.85	-0.004	0.39

Supplemental Table S6B – Associations between white matter microstructure and ADHD symptoms – Participants taking medication excluded

	Interaction - TBI		Interaction - TBI high risk		Main Effect		
	t value	p value	t value	p value	t value	ΔR^2	p value
Corpus Callosum Genu	-1.35	0.18	**-2.34**	**0.02**			
Corpus Callosum Body	-0.16	0.87	-1.04	0.30	1.26	0.001	0.21
Corpus Callosum Splenium	-0.91	0.36	-1.59	0.11	0.90	-0.0003	0.37
Anterior Corona Radiata	0.86	0.39	0.91	0.36	0.12	-0.002	0.91
Superior Corona Radiata	0.20	0.84	-1.11	0.27	-0.32	-0.002	0.75
Posterior Corona Radiata	-0.23	0.82	-0.30	0.76	1.94	0.005	0.05

Supplemental Figure



Supplemental Figure S1. FA in the genu of the corpus callosum is differentially associated with ADHD symptoms in youth with a history of TBI. A significant interaction between FA in the genu of the corpus callosum and TBI history on ADHD symptom severity is driven by a positive relationship in youth without a history of TBI (red) and a strong negative relationship in youth with a history of TBI (blue). Regression lines for those with and without a history of TBI are plotted with shaded 95% confidence intervals. Youth with mild TBI and FA values to the right of the dotted vertical line have lower ADHD symptom severity scores than those with no history of TBI.

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