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Neurocognitive Pathways in Attention-Deficit/Hyperactivity Disorder and White Matter Microstructure

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ABSTRACT

BACKGROUND: This study sought to identify attention-deficit/hyperactivity disorder (ADHD) abnormalities in relationships between brain white matter structure and individual differences in several types of impulsive behavior.

METHODS: Adolescents, n = 67 with ADHD combined subtype and n = 68 without ADHD, were given neuropsychological tests and underwent diffusion tensor imaging scans. Principal component analysis reduced test scores into factors representing different types of impulsive behavior. Tract-based spatial statistics quantified white matter integrity in relationship to components of impulsive behavior. ADHD versus non-ADHD differences in the strength and nature of linear relationships between regional white matter and three impulsivity components were examined using multiple regression.

RESULTS: Principal component analysis found three separate impulsivity-related factors that were interpreted as motor response inhibition, impulsive choice, and delay aversion. Relationships between regional fractional anisotropy and response inhibition or impulsive choice did not differ between ADHD and non-ADHD groups. There was a significant interaction between diagnostic group and delay aversion test performance relationships with regional fractional anisotropy. For youths without ADHD, greater anisotropy in numerous tracts predicted better delay aversion test performance. In contrast, anisotropy in regions including the corpus callosum, corona radiata, internal capsule, and corticospinal tracts had either a negative or no relationship with delay aversion test performance in ADHD.

CONCLUSIONS: The results provide additional support that different proposed etiological pathways to ADHD have discretely different neurobiological features. Large disorganization of white matter microstructure appears to contribute to reward-based ADHD pathways rather than motor inhibition.

Keywords: ADHD, Delay aversion, DTI, Impulsive choice, Impulsivity, Response inhibition

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Approximately 5% to 11% of American children are affected by attention-deficit/hyperactivity disorder (ADHD), a behaviorally defined disorder typically diagnosed in childhood that is characterized by inattention, hyperactivity, and impulsivity (1,2). Several neurocognitive theories of ADHD have been proposed. Some theories separate impulsive behavior into at least two domains that reflect the seminal dual-pathway model of Sonuga-Barke (3): 1) inability to withhold a behavioral response (4), linked to frontostriatal neural system dysfunction (5), and 2) intolerance for delay, thought to arise from abnormalities in the brain's reward system (3,6). These are separable constructs in non-ADHD and other clinical populations (7,8) and have distinct neuropsychological and neuroimaging abnormalities in ADHD (9,10). Commonly used paradigms to measure response inhibition include the Go/NoGo or Stop-Signal Task (SST), which quantify how well and efficiently participants can withhold a motor response (i.e., inhibition) (11). Although there are important differences between constructs of delay aversion (3) and preference for immediate reward, delay aversion often has been operationalized by performance on a delay discounting questionnaire (DDQ). The DDQ asks participants to make choices between small rewards after short delays or larger rewards after longer delays. A preference for sooner, immediate rewards has been termed impulsive choice (8). On these paradigms, adolescents and children with ADHD often make more errors of commission, are slower to inhibit responses, or fail to cancel a Go response on stop trials (disinhibition pathway) (12–14) and/or prefer smaller but more immediate rewards to larger delayed rewards (impulsive choice pathway) (15,16).

One purpose of neurocognitive models of ADHD is to link meaningful behavioral profiles to specific neurobiological influences—in this context, to explain how different forms of impulsivity could arise in ADHD. Many prior studies have asked if patients with ADHD have abnormalities in the major white matter connections among brain regions. Although nearly all prior diffusion tensor imaging (DTI) studies find ADHD deficits, a hallmark of these studies is their inconsistency. At a broad

SEE COMMENTARY ON PAGE 213

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level, ADHD deficits in white matter integrity tend to be reported most often in cingulum bundle, corona radiata, corpus callosum (CC), inferior longitudinal fasciculus, internal capsule, middle cerebellar peduncle, and superior longitudinal fasciculus [see review (17)]. Yet, positive and negative evidence for abnormality in each of these regions exists, and no specific white matter tract or region is found in every study. Associations between white matter abnormalities and inattentive and hyperactive/impulsive symptom dimensions of ADHD have likewise failed to provide consistent findings, with the most consistent association between lower white matter integrity in superior longitudinal fasciculus with inattentive symptoms (18–20).

This heterogeneity raises the question of how useful tests of group-level white matter abnormalities are in our efforts to understand ADHD etiology. If most white matter abnormalities are not reliably linked to the diagnostic phenotype, are they instead nonspecific, variable phenomena that ultimately are unrelated to factors that underlie ADHD? Alternatively, perhaps abnormal white matter microstructure might not relate to the ADHD diagnostic phenotype itself, but rather to distinct proposed etiological pathways to ADHD (e.g., disinhibition, impulsive choice). This possibility has not yet been directly examined in ADHD. In recent years, DTI studies in nonclinical samples have linked performance on motor inhibition and delay discounting tasks to separate white matter tracts (21). In ADHD, an increasing number of studies have attempted to link DTI-measured white matter abnormalities to specific cognitive abilities. Such studies provide some evidence that ADHD deficits in motor inhibition might be linked to the integrity of white matter tracts that connect frontal lobe and striatal brain regions (22–24), intraparietal connections (25), or the cingulum bundle (22). Only one study has examined delay discounting associations with regional white matter in ADHD, finding a modest association with fractional anisotropy (FA) in the splenium of the corpus callosum (26). However, these approaches have been piecemeal in test selection as well as post hoc—neither testing hypotheses about expected white matter/impulsivity relationships nor statistically evaluating whether any brain/behavior associations actually differ between diagnoses. No previous study has tested whether neurocognitive markers of theoretically different ADHD etiological pathways have different white matter characteristics than found in non-ADHD.

The primary innovation of the present study was its a priori focus on abnormalities in the relationship between individual differences in DTI-measured white matter and neurocognitive markers of proposed etiological pathways in youths with ADHD. So rather than futilely seeking to identify neurocognitive or white matter deficits in the diagnostic phenotype, our goal was to target the proposed pathways by directly comparing the relationship of white matter to disinhibition-related and impulsive choice–related conceptualizations of impulsivity. We wished to learn whether any differences between ADHD and non-ADHD in these associations could be found in the same white matter tracts, different tracts for different cognitive pathways, or even essentially normal relationships with white matter microstructure in one or both proposed pathways. We included several different tasks theoretically linked to each neurocognitive pathway to produce a generalized index of the constructs that did not rely on a single test indicator. We hypothesized that these different neurocognitive profiles would have distinct white matter correlates, observable as different strength or direction of associations between regional white matter and either disinhibition or impulsive choice test performance.

METHODS AND MATERIALS

Participants

Youths with ADHD combined subtype ranging from 12 to 18 years of age and an age-, gender-, and IQ-matched group of youths without ADHD were recruited through local advertisements and physician referral at the Olin Neuropsychiatry Research Center at Hartford Hospital. Informed consent and assent were obtained from a parent or legal guardian and youths as approved by the Hartford Hospital Institutional Review Board. ADHD diagnoses were confirmed by experienced Master's- and Bachelor's-level staff who administered the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version (27) to youths and a parent or legal guardian. Diagnoses were reached by collective consensus of the research team in a supervised discussion of videotaped interview content by the second author (MCS), a licensed psychologist with 16 years of experience using the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version for ADHD research. Current comorbid oppositional defiant disorder, conduct disorder, and substance abuse (but not dependence) were allowed in youths with ADHD. Potential participants in the non-ADHD group were excluded for any current or lifetime psychiatric diagnoses. Other exclusion criteria included self-reported neurological conditions or evidence of gross brain structure abnormalities on structural magnetic resonance imaging, reported psychotic illness in a first-degree relative, and IQ estimate <80 on the two-subtest Wechsler Abbreviated Scale of Intelligence (28). The study included only unmedicated participants with ADHD or participants with ADHD who took psychostimulant medications with short half-lives ensuring full washout within 24 hours. All testing was done following psychostimulant washout. All youths were screened with a drug and pregnancy test before scanning. Several self-report and parent-report measures of behavioral, attentive, and clinical problems were collected to fully characterize the sample, including the Brown Attention-Deficit Disorder Scales for Adolescents (29), Adolescent Alcohol and Drug Involvement Scale (30), and Disruptive Behavior Rating Scale–Parent Version (31).

In all, 135 youths completed neuropsychological evaluations and quality DTI scanning (see Supplemental Methods and Materials for additional details). These youths were an average of 15.42 years old, primarily male (77.8%), and right-handed (91.9%). Youths with and without ADHD were comparable in age, gender, ethnicity/race, handedness, IQ, and alcohol and drug abuse. Youths with ADHD diagnoses evidenced greater behavioral and inattentive problems, indexed by Brown Attention-Deficit Disorder Scales for Adolescents and Disruptive Behavior Rating Scale–Parent Version (Table 1).

Table 1. Demographic and Clinical Characteristics and Neuropsychological Performance of Adolescents With ADHD and Adolescents Without ADHD

	ADHD (n = 67)	Non-ADHD (n = 68)	Statistical Test[a]	p Value
Age, Years, Mean (SD)	15.41 (1.78)	15.43 (1.73)	$t_{133} = 0.07$	NS
Gender, Female, n (%)	12 (18)	18 (27)	$\chi^2_1 = 0.98$	NS
Race, n (%)			$\chi^2_2 = 2.06$	NS
Caucasian	52 (85)	48 (75)		
Black	6 (10)	11 (17)		
Asian/other	3 (5)	5 (8)		
Handedness, Right, n (%)	58 (87)	66 (97)	$\chi^2_1 = 3.66$	NS
Comorbid Diagnosis, n (%)	29 (43)	0	$\chi^2_1 = 34.50$	< .001
Oppositional defiant disorder	14 (21)		$\chi^2_1 = 13.48$	< .001
Conduct disorder	5 (8)		$\chi^2_1 = 3.32$	NS
Substance abuse/dependence	3 (5)		$\chi^2_1 = 1.36$	NS
Past mood/anxiety disorder	6 (9)		$\chi^2_1 = 4.36$	.04
Current Medications, n (%)	42 (64)	0	$\chi^2_1 = 60.11$	< .001
Dextroamphetamine	11 (17)		$\chi^2_1 = 10.23$	< .001
Methylphenidate	20 (30)		$\chi^2_1 = 21.89$	< .001
Lisdexamfetamine	4 (6)		$\chi^2_1 = 2.41$	NS
Dexmethylphenidate	5 (8)		$\chi^2_1 = 3.45$	NS
BADDS-Parent, Mean (SD)	69.08 (23.67)	17.07 (19.39)	$t_{116} = 12.94$	< .001
BADDS-Child, Mean (SD)	57.82 (24.52)	29.87 (20.76)	$t_{130} = 7.08$	< .001
DBRS-PV Inattention, Mean (SD)	19.41 (5.80)	3.16 (4.04)	$t_{111} = 17.94$[b]	< .001
DBRS-PV Hyperactive/Impulsive, Mean (SD)	15.76 (5.84)	1.37 (2.88)	$t_{93} = 17.37$[b]	< .001
WASI 2–Subscale IQ, Mean (SD)	105.28 (12.06)	108.05 (9.25)	$t_{124} = 1.49$[b]	NS
AADIS Total Score, Mean (SD)	11.52 (16.93)	9.41 (14.52)	$t_{127} = 0.76$	NS
Neuropsychological Performance, Mean (SD)				
Conners CPT-II, commission errors	21.96 (7.86)	21.28 (6.16)	$t_{125} = -0.54$	NS
Stop-signal reaction time	294.57 (72.18)	286.30 (71.86)	$t_{118} = -0.63$	NS
Delayed memory test, commission error percentage	0.52 (0.18)	0.43 (0.18)	$t_{131} = -2.90$	.004
Single Key Impulsivity Paradigm, average IRT	7.37 (17.95)	15.03 (25.54)	$t_{110} = 1.92$[b]	.06
Experiential Discounting Task, AUC	0.61 (0.15)	0.62 (0.15)	$t_{116} = 0.29$	NS
Delay Discounting Questionnaire, AUC	0.34 (0.22)	0.41 (0.31)	$t_{108} = 1.47$[b]	NS

AADIS, Adolescent Alcohol and Drug Involvement Scale; ADHD, attention-deficit/hyperactivity disorder; AUC, area under the curve; BADDS, Brown Attention-Deficit Disorder Scales for Adolescents; CPT, continuous performance test; DBRS, Disruptive Behavior Rating Scale–Parent Version; NS, not significant; IRT, interresponse time interval; WASI, Wechsler Abbreviated Scale of Intelligence.

[a]All χ^2 tests use a continuity correction if a 2 × 2 variable table (e.g., χ^2_1).

[b]Owing to significantly different variances determined by Levene test, ADHD and non-ADHD groups were compared using an equality of variances degrees of freedom adjustment.

Group comparison of impulsivity-related raw test scores also are presented in Table 1.

Neuropsychological Assessments and Data Preparation

A fixed-order battery of computerized tests assessed impulsive behavior in all participants. Tests selected to measure the proposed disinhibition factor included the Conners Continuous Performance Test II (CPT-II), SST, and Immediate and Delayed Memory Task (IMT/DMT). The CPT-II is a 14-minute computerized task with 360 trials over a total of 18 blocks (32,33). Participants press a key when any letter except "X" appears on the screen (10%). The dependent measure from this task was number of responses to a nontarget (commissions). CPT-II inhibition failures typically are interpreted as deficits in the ability to withhold a prepotent response. The SST is similar with the exception that auditory stop signals are presented shortly after Go signals on 25% of trials, requiring participants to withhold prepotent responses that have already started (34). Stop-signal delays were adjusted until responses were correctly inhibited on approximately 50% of trials. Elapsed time from Go presentation to stop signal determines the stop-signal reaction time, or the amount of time participants require to correctly inhibit half of their Go responses. Task duration varied across participants but was never longer than 12.1 minutes. Stop-signal reaction time is typically interpreted as one's efficiency in countermanding active responses. The IMT/DMT is another CPT-II variant that assesses impulsive responding with or without cognitive demands (35–37). Sequential 5-digit stimuli are presented, and participants are tasked to respond to identical stimuli consecutively (IMT) or three trials later (DMT). Using default settings, stimuli have variable presentation rates and intertrial intervals, lasting a total of 21.5 minutes. The dependent measure from this task was percent of commission errors to catch stimuli on the DMT,

which differ in 1 digit from target sequences and require longer than other nontargets to accurately process. This measure differs from other inhibition tests by adding greater information processing demands to capture inhibition failures that might not occur in simpler contexts.

Tests of impulsive choice were the DDQ, Experiential Discounting Task (EDT), and Single Key Impulsivity Paradigm (SKIP). The DDQ randomly presents questions in which participants are asked to choose between a varying amount of hypothetical money now or after a varying delay (38). Hyperbolic equations were fitted to each participant's indifference point. The area under the curve from the hyperbolic model was used as the primary measure. The EDT is a behaviorally based measure of temporal discounting that requires participants to experience choice consequences (waiting) during the task itself (39). It is similar to the DDQ but presents participants with immediate consequences of their decisions, which has shown differing performance from hypothetical versions of the paradigm (40). Similar to DDQ, the area under the curve was used as the primary measure. The SKIP measures the ability to endure long delays between reward-directed responses in a free operant procedure (37). In a 20-minute session, participants clicked a button whenever desired to add monetary reward to a counter, briefly displayed to enable participants to detect a delay contingency (41,42). The average interresponse time was used as the primary measure. Although the SKIP was constructed based on free operant conditioning principles, average interresponse time behaviorally operationalizes one's preference for immediate reward instead of relying on self-report or forced-choice methods.

Confirmatory factor analyses examined if test choices fit our proposed two-factor model of disinhibition and impulsive choice. These analyses were conducted in R Version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria), using the lavaan package and maximum likelihood estimation with the first dependent variable as the standard indicator. Inhibition was indicated by CPT-II, SST, and DMT; reward was indicated by EDT, DDQ, and SKIP. However, poor representation of the data instead led to using exploratory principal component analysis (PCA) with varimax rotation to depict more than two orthogonal impulsivity components. Eigenvalues and scree plots were used to determine number of components (see Supplemental Methods and Materials for details).

Diffusion Tensor Imaging

Diffusion data were acquired on a Siemens Allegra (Siemens Healthcare, Erlangen, Germany) 3T head-only scanner at the Olin Neuropsychiatry Research Center. The pulse sequence was a single-shot spin echo echo-planar imaging sequence (repetition time = 6300 ms, echo time = ms, field of view = 220 mm, matrix 100, diffusion-sensitizing orientations = 32, b = 0 and 1000 s/mm^2) that covered the whole brain in 45 slices with 1.7 × 1.7 × 3.0 mm^3 resolution. Three sequences were acquired for a total scanning lasting approximately 11 minutes. Visual inspection ensured that all DTI data were artifact-free (see Supplemental Methods and Materials for details). Diffusion-weighted images were distortion-corrected using gradient echo fieldmaps and then registered to a common non–diffusion-weighted image using a mutual information cost function as employed in the FSL FLIRT toolbox (43,44) with eddy current corrections (45). To avoid possible signal contamination related to head movement, any image with a scan-to-scan displacement >2 mm was discarded. The remaining images were concatenated and tensor calculated. A sample-specific mean FA image was calculated from all datasets, then tract-based spatial statistics (46) calculated the scalar FA measures for subject-specific skeletons. Data were spatially normalized to a common Montreal Neurological Institute space template using FNIRT toolbox (47).

Association of Performance With White Matter Integrity

Three multivariate general linear models using FSL's randomise program (48) examined the interaction of diagnostic study group by each impulsivity component on FA across the whole brain. Age, gender, and IQ were included in the model as nuisance covariates (49,50). Statistical significance was evaluated using nonparametric permutation-based inference (5000 samples) and thresholded for contiguous voxels surpassing threshold-free cluster enhancement, $p_{corrected} < .05$ (51). Tract labels were applied from the John Hopkins University atlas within FSL combined with visual inspection in reference to published stereotactic atlases (52). Individual FA values were extracted to depict these interaction patterns at the locations of peak effect for each distinct region as determined by visual inspection. Cohen's d effect sizes were computed for these peak values for added comprehension of effect magnitude (53). To clarify the nature of the basic associations identified by general linear model, simple SPSS Version 24 (IBM Corp., Armonk, NY) Pearson correlations determined direction and magnitude of interaction patterns. Supplemental analyses were also performed to test group-level whole-brain differences in FA while covarying for age, gender, and IQ, using the same thresholds for statistical significance (see Supplemental Results).

RESULTS

Neuropsychological Measures Data Reduction

Confirmatory factor analysis found evidence contrary to our two-factor disinhibition and impulsive choice model. Although model fit was adequate (Tucker Lewis index = 1.37), DDQ scores loaded opposite to other reward-test indicators on the impulsive choice factor, there was poor latent variable consistency (Cronbach's α = .47 and .15), and variance between DMT and SKIP was not well accounted for. Exploratory PCA helped to clarify that a three-factor model best fit the data (Table 2), explaining 61% of test variance. All six tests showed significant communalities with all extractions >0.4, indicating good model fit. Loading profiles for two factors offered straightforward interpretations. As expected, three tests of motor inhibition (CPT-II, stop-signal reaction time, and DMT) loaded significantly on the first component (eigenvalue = 1.50; 25% of the variance) comprising the ability to accurately withhold a response to nontarget stimuli (disinhibition). Also as expected, two tests (DDQ and EDT) loaded significantly on another component (eigenvalue = 1.02; 17% of the variance), reflecting planned willful choices about waiting for rewards

Table 2. Factor Loadings of Neuropsychological Measures Using Principal Component Analysis With Varimax Rotation and Group Differences on These Factors

	Disinhibition	Delay Aversion	Impulsive Choice
Neuropsychological Test			
Conners CPT-II, commission errors	0.73[a]	0.06	−0.01
Stop-signal reaction time	0.71[a]	0.28	−0.12
Delayed memory test, commission error percentage	0.64[a]	−0.49[a]	0.17
Single Key Impulsivity Paradigm, average IRT	0.12	0.80[a]	0.08
Experiential Discounting Task, AUC	0.11	0.37[a]	0.52[a]
Delay Discounting Questionnaire, AUC	−0.12	−0.10	0.86[a]
Group Characteristics, Mean (SD)			
ADHD	−0.16 (0.94)	−0.03 (0.89)	−0.17 (0.82)
Non-ADHD	0.16 (1.04)	0.03 (1.11)	0.17 (1.13)
t test *(df)*	1.90 (133)	0.31 (133)	2.03 (133)[b]

ADHD, attention-deficit/hyperactivity disorder; AUC, area under the curve; CPT, continuous performance task; IRT, interresponse time.
[a]Factor loadings > .30.
[b]$p < .05$.

(impulsive choice). In addition, EDT, SKIP, and DMT scores loaded on a final component (eigenvalue = 1.13; 19% of the variance), thus labeled delay aversion, in part to differentiate it from impulsive choice, which has been well established in prior published reports to reflect DDQ scores (54). It also represented the clearest behavioral manifestation of a characteristic aversion to waiting rather than a planned willful choice. Although EDT loaded onto both this factor and impulsive choice, the factor structure indicates a clear dissociation between neuropsychological measures in real-world performance-based contexts (SKIP and EDT) versus measures emphasizing decision making (DDQ and EDT). DMT commission error percentage negatively loaded onto delay aversion, and positively loaded onto disinhibition along with CPT-II commission errors. Given the additional separation of DMT from CPT-II commission errors, it is possible that ADHD behavioral manifestations of delay aversion may somehow be linked to relative weaknesses holding pertinent information in mind to direct behavior, although other interpretations also are possible.

Relationships Between Impulsivity and White Matter Tracts in ADHD and Non-ADHD

No significant interaction between ADHD and non-ADHD groups was found between disinhibition or impulsive choice components and white matter integrity at threshold-free cluster enhancement–corrected significance levels. However, numerous widespread tracts, including CC, bilateral anterior and posterior corona radiata, right superior and left inferior longitudinal fasciculus, bilateral internal capsules, left external capsule, and corticospinal tracts, were associated with a differing relationship between ADHD and non-ADHD groups in performance on delay aversion measures, showing a range of small to medium effects. Table 3 lists tracts, peak *t* coordinates, threshold-free cluster enhancement–corrected significance levels, and Cohen's *d* effect size for all findings; Figure 1 depicts these findings. Pearson correlations for significant tracts within ADHD and non-ADHD groups are reported and presented in Supplemental Figure S1. In general, associations at the location of peak effects indicate that youths without ADHD have a significant positive relationship between FA and delay aversion performance. Across different tracts, youths with ADHD showed either a negative or an insignificant relationship between FA and performance on delay aversion measures.

DISCUSSION

This study's primary question was not whether ADHD white matter itself is abnormal, but rather if the relationship between white matter microstructure and cognitive ability was different in youths with ADHD than what is typically found in youths without ADHD. On the neurocognitive level, we replicated two well-established domains of impulsivity—motor response inhibition and preference for smaller, immediate rewards over later, larger rewards. However, the relationship between white matter microstructure and those specific ADHD neurocognitive pathway markers did not differ in our sample of youths with and without ADHD. Hypotheses were supported by different white matter/neurocognitive pathway associations for a component that reflected a behavioral index of ADHD delay aversion. Youths without ADHD evidenced a positive relationship between delay aversion performance and FA in CC, bilateral corona radiata, internal capsules, and corticospinal tracts, suggesting that typical development of these tracts, whether increased myelination, increased collinearity of fibers, or pruning of neuronal branches (55–59), or another specific microstructural feature linked to FA, reflects a greater ability to tolerate delayed reward delivery. In contrast, youths with ADHD demonstrated either a negative or no relationship in different tracts. This clearly does not reflect a simple explanation such as diminished normal associations. Instead, it most likely reflects disorganization of brain/behavior relationships; however, the possibility that these abnormal associations arise because of atypical development or even compensation for deficits cannot be ruled out. Importantly, these results statistically controlled for known influences on test performance and white matter from differences in participant maturation, intelligence, or gender. Similar tracts to these have been implicated in ADHD broadly in prior meta-analyses and even our supplemental group analysis (e.g., right anterior corona radiata, genu splenium and tapetum of the CC, bilateral internal capsules, and left inferior fronto-occipital fasciculus) (17,60). The specific findings here—abnormal association between white matter and specific neurocognitive test performance—are consistent with the idea that different neurocognitive pathways have unique neural correlates. These results suggest that ADHD white matter microstructure may be linked to the delay aversion proposed pathway (61) rather than microstructural differences in the diagnosis of ADHD more broadly. Future studies that attempt to replicate this delay aversion/white matter relationship and possibly extend it to

Table 3. White Matter Regions From Tract-Based Spatial Statistics Analysis Where Fractional Anisotropy Was Significantly Differently Related to Delay Aversion in Adolescents With ADHD Compared With Adolescents Without ADHD

	Interaction Effect				Pearson Correlation	
Location Description	MNI x, y, z	*t*	TFCE *p*	Cohen's *d*	ADHD	Non-ADHD
Frontal						
Body of corpus callosum	11, 19, 21	1.63	.047	0.29	−0.09	0.12
Genu of corpus callosum (forceps minor)	14, 31, 11	3.00	.042	0.53	−0.29[a]	0.07
Left anterior corona radiata	−25, 12, 19	2.41	.015	0.42	−0.08	0.24
Right anterior corona radiata	26, 20, 13	3.46	.019	0.61	−0.30[a]	0.21
Right anterior corona radiata (forceps minor)	17, 35, 7	2.55	.043	0.45	−0.12	0.31[a]
Right tapetum	33, −43, 10	2.51	.027	0.44	−0.16	0.24[a]
Occipital						
Splenium of corpus callosum (forceps major)	28, −59, 11	3.05	.028	0.54	−0.13	0.34[a]
Temporal						
Left inferior longitudinal fasciculus	−27, −19, −4	2.98	.027	0.52	−0.16	0.33[a]
Left uncinate fasciculus/inferior fronto-occipital fasciculus	−37, −7, −15	2.69	.030	0.47	−0.21	0.26[a]
Right superior longitudinal fasciculus	42, −52, 4	2.15	.030	0.38	−0.19	0.15
Parietal						
Left posterior corona radiata (corticospinal tract)	−26, −28, 22	2.46	.016	0.43	−0.13	0.26[a]
Right posterior corona radiata	26, −39, 26	2.64	.027	0.46	−0.10	0.23
Left superior corona radiata	−26, 7, 22	3.43	.013	0.60	−0.25[a]	0.27[a]
Subcortical						
Left anterior limb of internal capsule (anterior thalamic radiation)	−19, 16, 6	2.66	.018	0.47	−0.21	0.15
Right anterior limb of internal capsule (anterior thalamic radiation)	17, 4, 10	2.45	.020	0.43	−0.24	0.05
Left posterior limb of internal capsule (corticospinal tract)	−20, −16, −4	2.85	.015	0.50	−0.28[a]	0.15
Right posterior limb of internal capsule (corticospinal tract)	21, −16, −4	3.92	.017	0.69	−0.34[a]	0.25[a]
Left retrolenticular part of internal capsule	−27, −24, −2	2.86	.015	0.50	−0.10	0.40[a]
Right retrolenticular part of internal capsule	26, −20, 1	3.36	.019	0.59	−0.30[a]	0.23
Right posterior thalamic radiation	35, −55, 15	1.94	.028	0.34	−0.08	0.20
Left external capsule	−27, 14, 10	2.00	.020	0.35	−0.13	0.17
Brainstem						
Left cerebral peduncle (corticospinal tract)	−17, −14, −9	2.02	.017	0.35	−0.22	0.08
Right cerebral peduncle (corticospinal tract)	18, −17, −9	2.41	.019	0.42	−0.20	0.17
Left superior cerebellar peduncle	−5, −39, −20	2.27	.020	0.40	−0.12	0.18
Left corticospinal tract	−9, −27, −28	3.41	.019	0.60	−0.20	0.31[a]
Left medial lemniscus	−5, −36, −29	2.49	.020	0.44	−0.24[a]	0.08

All locations represent distinct peak regions within three clusters found after statistical corrections for searching the tract-based spatial statistics–derived white matter skeleton using TFCE, $p_{corrected} < .05$.

ADHD, attention-deficit/hyperactivity disorder; MNI, Montreal Neurological Institute; TFCE, threshold-free cluster enhancement.

[a]Relationship with delay aversion significant, $p < .05$.

other putative etiological pathways might ultimately explain inconsistencies seen across prior ADHD studies of white matter [e.g., (17)].

Delay aversion has been conceptualized as a motivational style thought to result from mesolimbic reward circuit dysfunction (3). The current findings link white matter microstructure in projection fibers connecting thalamus and putamen with widespread prefrontal cortex (corticospinal tracts, corona radiata, thalamic radiation, and internal capsule) to delay aversion tendencies in ADHD. In addition, brain/behavior relationships in ADHD differed in projection fibers passing through thalamus, basal ganglia, and medulla to spinal cord (e.g., left superior cerebellar peduncle, corticospinal tracts); commissural fibers connecting cerebellar hemispheres (e.g., CC); and a few long association fibers connecting distal portions of the cortex (e.g., superior and inferior longitudinal fasciculus). These findings not only implicate mesolimbic circuitry and its integration with higher-order cognition in ADHD delay aversion behavior but also implicate dopamine-sensitive sensorimotor circuits that have been linked to ADHD pathology (62). For instance, previous studies have demonstrated a relationship between motor control, reward performance, and specific white matter tracts. Faster delay discounting reaction times were associated with left inferior longitudinal fasciculus microstructure in adolescents at risk for alcoholism (63), steeper delay discounting with splenium of the CC in adults with ADHD (26), and steeper delay discounting with frontostriatal tracts in healthy adults (64). Considerable literature has also begun to expand on the role of faulty time estimation in impulsiveness (65–67) and ADHD dysfunction (61) and its

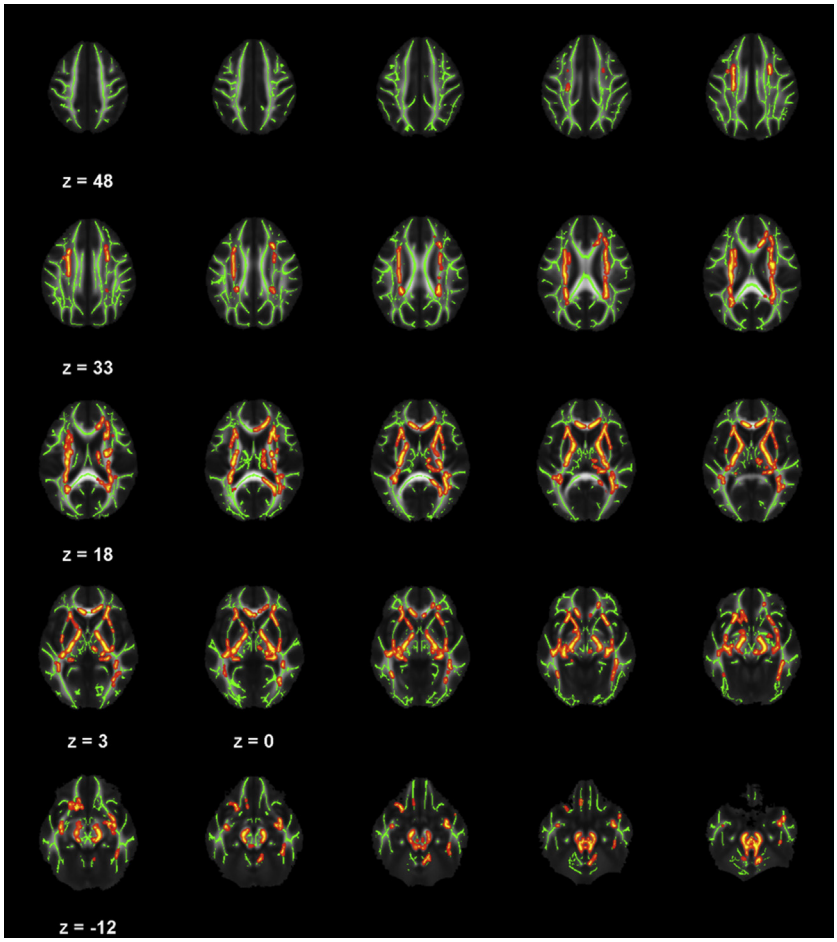

Figure 1. White matter regions from tract-based spatial statistics analysis where fractional anisotropy was significantly differently related to delay aversion in adolescents with attention-deficit/hyperactivity disorder compared with adolescents without attention-deficit/hyperactivity disorder, as indicated in red-yellow ($p < .05$, corrected for searching the tract-based spatial statistics–derived white matter skeleton using threshold-free cluster enhancement).

potential mediating role in the relationship between ADHD and reward sensitivity (68–70). Further research disentangling potential effects of time estimation difficulties, behavioral delay aversion, and other forms of impulsivity is needed to differentiate and determine the relationship of these tracts to these cognitive constructs.

In the dual-pathway ADHD conceptual model of Sonuga-Barke (3), delay aversion arises as a secondary consequence of deficits in dopaminergic reward system inefficiencies producing impulsive drive to immediate reward, frequent conflict with others, frustration, and ultimately a tendency to escape from delay when possible. Although the current study links delay aversion to differing brain/behavior relationships, it is unclear if they reflect the proposed ADHD primary deficit or the proposed behavioral consequence. It seems less likely that widespread differences in brain/behavior relationships would be associated with what is believed to be an acquired behavioral tendency. The latter cannot be ruled out, as evidence exists for experience-dependent change in DTI-measured white matter (71,72). Because we statistically controlled for maturational differences that typically approach adult levels by mid- to late adolescence for both behavioral performance and white matter, we likely have observed a differing relationship not bound to one period of development. However, children with ADHD have shown a delay in myelin development in tracts involved in limbic system function, such as the internal capsule (17,19,72). Thus, additional research is needed to ascertain exactly when in adolescent maturation this relationship between delay aversion tendencies and white matter is first observable, when the relationship is most different in adolescents with ADHD relative to peers without ADHD, and whether or not this difference eventually resolves if white matter microstructural differences catch up (73). Both cross-sectional and longitudinal comparisons of brain/behavior relationships in younger youths with an ADHD diagnosis will be needed to tease out these possibilities.

In contrast to the findings with delay aversion, brain/behavior relationship differences were not found between ADHD and non-ADHD groups for the other impulsivity-related components. These other neurocognitive pathways may not involve white matter differences, might have smaller effects requiring even larger sample sizes for detection, or might be more prominent in other clinical presentations of ADHD (e.g., inattentive subtype). Our lack of findings with response inhibition may also be due to specific examination of this construct rather than executive functioning more broadly, as some other

studies show a negative relationship between executive functioning and FA (74,75). Despite this, the current findings are consistent with theories of multiple neurocognitive pathways in ADHD. They highlight the significance of behavioral manifestations of delay aversion in white matter integrity (76).

The current study has several limitations to take into consideration. First, DTI methodology cannot determine the underlying mechanism of reduced FA, which can be lower myelination, loss of axons, cell-packing density, gliosis, edema and/or hydration, or fiber orientation (55–58). If future research determines the current findings ultimately reflect differences in FA development during adolescence, the mechanism of reduced FA might be myelination or axonal diameter growth (59,77). While it remains unclear owing to underexamination whether ADHD psychostimulants have long-term effects on brain structure, such effects may exist and should be considered in future experiments and meta-analyses. Importantly, the current study did not find ADHD differences in white matter, several cognitive tasks, and PCA-derived disinhibition and delay aversion. Whereas these findings raise questions about diagnostic certainty or test selection, these issues were carefully addressed. Instead, the lack of simple case-control differences at rigorous thresholds likely reflects heterogeneity of ADHD neuropathophysiology. We previously have demonstrated neurocognitive differences on these tests in the larger sample from which these ADHD cases are drawn (78). Here, although the DTI × cognition interaction effects were strong enough to survive rigorous statistical control, study group association *r* values between DTI and test performance were modest. This suggests that these white matter characteristics might be but one of several influences on ADHD delay aversion behavior. Indeed, we also recently reported strong evidence for nonoverlapping brain dysfunction as measured by functional magnetic resonance imaging in subgroups identified using similar methods (78). The current study employed an exploratory PCA data reduction approach, which found a component of impulsivity that could be variously interpreted. Finally, some prior research has suggested important differences between temporal estimation and/or discounting and other forms of reward-related impulsivity (61). Our common factor analysis and PCA results support this distinction, but future studies will need to confirm this latent structure of reward-related impulsivity both in ADHD and in non-ADHD groups of adolescents.

In conclusion, this study found differing widespread corticospinal FA in relationship to delay aversion performance across youths with and without ADHD, suggesting that this brain/behavior relationship may be one multifactorial pathway (of many) to observed ADHD behavioral outcomes. A concerted effort from large-scale studies using careful case-control approaches could confirm relationships between these proposed etiological pathways and various forms of neurobiological dysfunction in ADHD.

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