Connectomic Disturbances in Attention-Deficit/Hyperactivity Disorder: A Whole-Brain Tractography Analysis

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Background: Few studies have sought to identify, in a regionally unbiased way, the precise cortical and subcortical regions that are affected by white matter abnormalities in attention-deficit/hyperactivity disorder (ADHD). This study aimed to derive a comprehensive, whole-brain characterization of connectomic disturbances in ADHD.

Methods: Using diffusion tensor imaging, whole-brain tractography, and an imaging connectomics approach, we characterized altered white matter connectivity in 71 children and adolescents with ADHD compared with 26 healthy control subjects. White matter differences were further delineated between patients with ($n = 40$) and without ($n = 26$) the predominantly hyperactive/impulsive subtype of ADHD.

Results: A significant network comprising 25 distinct fiber bundles linking 23 different brain regions spanning frontal, striatal, and cerebellar brain regions showed altered white matter structure in ADHD patients ($p < .05$, family-wise error-corrected). Moreover, fractional anisotropy in some of these fiber bundles correlated with attentional disturbances. Attention-deficit/hyperactivity disorder subtypes were differentiated by a right-lateralized network ($p < .05$, family-wise error-corrected) predominantly linking frontal, cingulate, and supplementary motor areas. Fractional anisotropy in this network was also correlated with continuous performance test scores.

Conclusions: Using an unbiased, whole-brain, data-driven approach, we demonstrated abnormal white matter connectivity in ADHD. The correlations observed with measures of attentional performance underscore the functional importance of these connectomic disturbances for the clinical phenotype of ADHD. A distributed pattern of white matter microstructural integrity separately involving frontal, striatal, and cerebellar brain regions, rather than direct frontostriatal connectivity, appears to be disrupted in children and adolescents with ADHD.

Key Words: ADHD, connectomics, diffusion tensor imaging, network, tractography, white matter

Attention-deficit/hyperactivity disorder (ADHD) is a highly prevalent developmental disorder among school-age children and adolescents that commonly persists into adulthood and is characterized by symptoms of inattention and/or hyperactivity/impulsivity (1). The classical understanding of the neurobiological mechanisms of ADHD posits that abnormalities of prefrontal and striatal regions play a primary role in the pathophysiology of the disorder (2), though more recent literature also suggests a role for the cerebellum (3). A large number of task-based functional magnetic resonance imaging and structural brain imaging studies have supported this model (4–6). However, the high degree of interconnectivity between many of these regions (7) suggests that no single region may be the primary source of pathology; rather, ADHD may arise from altered connectivity within and between distributed, yet anatomically connected, circuits.

Diffusion tensor imaging (DTI) has emerged as a powerful technique for investigating white matter microstructure in vivo (8). However, DTI research into ADHD has yielded somewhat inconsistent findings: while some studies lend support to the frontostriatal model (9), many studies have identified relatively diffuse white matter abnormalities that point to an alteration of numerous axonal fiber tracts (10,11). Importantly, these studies have generally focused on regional mapping of changes in water diffusion signals without taking into account which regions might be interconnected by the affected tract. This severely limits the inferences that can be drawn concerning which specific brain networks are affected in ADHD. Though some studies have conducted detailed and focused analyses of frontostriatal tracts specifically (12), their a priori focus on specific pathways neglects consideration of the potential involvement that other neural systems may have in the pathophysiology of ADHD.

Detailed and comprehensive maps of interregional brain connectivity are now obtainable by combining diffusion tractography (13) and imaging connectomics techniques (14,15). These

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analyses can be used to identify and characterize interconnected networks affected by disease (13,16) and thus provide an unbiased means for testing network-based hypotheses. Recently, Cao *et al.* (17) conducted a brain-wide test of white matter abnormalities in ADHD using DTI tractography and an imaging connectomics approach. They reported decreased structural connectivity in prefrontal-dominant circuitry and increased connectivity in orbitofrontal-striatal circuitry, which correlated with the inattention and hyperactivity/impulsivity symptoms, respectively.

Our primary aim in the present study was to investigate whether a large, clinical sample of children and adolescents diagnosed with ADHD could be differentiated from age-matched healthy control subjects based on their connectome. Secondly, we examined the functional effects of disturbed connectivity in any putative ADHD-related networks by correlating measures of white matter microstructure in these systems with performance on neuropsychological indices of attention. Finally, we compared patients diagnosed with the disorder's combined subtype with those with the inattentive subtype to examine whether differences in the clinical expression of ADHD mapped onto changes in brain connectivity. Our comprehensive, regionally unbiased approach allowed us to assess the whole brain for interregional white matter connectivity abnormalities and in doing so conduct a stringent test of the frontostriatal model of ADHD.

Methods and Materials

Participants

Children and adolescents with ADHD were recruited from the Seoul National University Hospital in Korea. A total of 81 ADHD participants and 27 healthy control subjects were initially recruited. Attention-deficit/hyperactivity disorder patients with an IQ below 70; a past or an ongoing history of either tic disorder, obsessive-compulsive disorder, language disorder, learning disorder, convulsive disorder, pervasive developmental disorder, schizophrenia, bipolar disorder, or brain damage; a past history of taking stimulants or atomoxetine longer than 6 months; or a recent history of taking stimulants or atomoxetine over the last 4 weeks were excluded from the study. The exclusion criteria for the control group were the same as above, except for additionally excluding those with a past or an ongoing history of ADHD. The study protocol was approved by the institutional review board for human subjects at the Seoul National University Hospital. Detailed information about the study was given to parents and children, and written informed consent was obtained before study entry.

Diagnostic and Clinical Evaluations

We assessed the presence of ADHD and other psychiatric diagnoses using a semi-structured diagnostic interview, the Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (K-SADS-PL). The validity and reliability of the original and the Korean versions of the K-SADS-PL have been established (18,19). The diagnostic interview using the K-SADS-PL was carried out by certified child and adolescent psychiatrists (i.e., S.-B.H., S.P., Y.-H.Y., M.-H.P.). Level of attention and response inhibition were assessed in both groups using a standardized visual version of the computerized continuous performance test (CPT) (20). The CPT was standardized for age among Korean children and adolescents, and its reliability and validity as a diagnostic instrument for ADHD have been established (21). In this study, we used three major variables: omission errors (a measure of inattention), commission errors (a measure of impulsivity), and response time variability (a measure of consistency of attention) (22).

Image Acquisition and Processing

The image acquisition and processing implemented herein, including whole-brain tractography, was based on standard protocols and methods utilized in previous work (13) with a few modifications and is described in detail in Supplement 1. In brief, for each individual, we seeded deterministic streamlines throughout all of white matter and reconstructed the connectome using a variety of cortical and subcortical parcellations. The connectivity between each pair of regions was quantified by the number of interconnecting streamlines, as well as the average fractional anisotropy (FA) over the volume delineated by these streamlines.

Data Analyses

Diffusion tensor imaging data from one control subject and nine patients were excluded due to acquisition artifact or poor quality data. A further patient was excluded due to excess head motion, leaving a total of 71 patients (age range 6.0–15.7 years, 56 male and 15 female patients) and 26 control subjects (age range 6.3–15.9 years, 13 male and 13 female subjects) for analysis. These two groups did not differ in mean head translation or rotation along any of the three (x, y, z) axes (Table S1 in Supplement 1). Neither the volume of the mask used for tractography (ADHD: 1488 $\pm$ 134 cm^3; control group: 1489 $\pm$ 138 cm^3) nor the number of streamlines generated per individual (ADHD: 1,903,274 $\pm$ 199,054; control group: 1,906,354 $\pm$ 210,177) differed between groups ($p < .05$).

The network-based statistic (23,24) (http://www.nitrc.org/projects/nbs/) was used to identify regional brain networks showing a significant between-group difference in interregional connectivity strength. Specifically, a t test was performed to test for a between-group difference in the streamline count at each of the $N(N-1)/2 = 6670$ unique regional pairings. Interconnected networks, formally known as graph components, were then identified among the connections with a t statistic exceeding a predefined t threshold of 2. A graph component represents a set of connections for which the null hypothesis can be rejected at a significance that is not corrected for multiple comparisons. The basis of the network-based statistic is to correct for multiple comparisons by testing for evidence against the null at the level of graph components, rather than at the level of individual connections. To this end, a family-wise error (FWE)-corrected p value was calculated for the size of each graph component using permutation testing (10,000 permutations) (25). A FWE-corrected p value was estimated for each component as the proportion of permutations that yielded a larger component or one of equal size. The reported network was adjusted for demographic and clinical variables that were noted with significant between-group differences.

The identified networks comprised axonal fiber bundles that were traversed by a different number of streamlines in the ADHD group compared with healthy control subjects. A tract-averaged FA value was extracted for each fiber bundle by averaging the FA values over all voxels intersected by at least one streamline. Pearson's correlation coefficient was used to evaluate any potential association between FA and the CPT scores. Fractional anisotropy is a continuous measure of white matter integrity, whereas the streamline counts are integer values. Thus, FA was

Table 1. Demographic and Clinical Characteristics of the Participants

	All Participants ($n = 97$)					ADHD Participants				
	ADHD ($n = 71$)		Control Subjects ($n = 26$)		p	Combined ($n = 39$)		Inattentive ($n = 26$)		p
Age (Years), Mean (SD)	9.39	(2.59)	10.04	(2.47)	.27	9.30	(2.47)	9.78	(2.81)	.47
Gender (Female), *n* (%)	15	(21.1)	13	(50.0)	.00	6	(15.4)	6	(23.1)	.52
IQ, Mean (SD)	106.06	(12.47)	117.27	(10.39)	.00	105.38	(12.71)	108.31	(11.87)	.35
Handedness (Right), *n* (%)	63	(88.7)	24	(92.3)	.60	33	(84.6)	24	(92.3)	.46
CPT, Mean (SD)										
Omission errors	67.34	(20.90)	50.73	(6.73)	.00	68.41	(20.10)	63.88	(20.91)	.38
Commission errors	64.32	(17.19)	57.92	(14.13)	.09	67.46	(18.59)	60.00	(14.98)	.09
Response time variability	65.18	(17.89)	52.73	(10.26)	.00	66.69	(17.06)	61.19	(18.77)	.22
Social Variables										
Paternal education (Years), Mean (SD)	15.00	(1.83)	15.69	(1.08)	.02	14.84	(1.99)	15.36	(1.49)	.24
Maternal education (Years), Mean (SD)	15.00	(1.74)	15.20	(1.63)	.62	14.78	(1.86)	15.30	(1.55)	.24
Familial SES, *n* (%)					.43					.89
High (very or moderately)	15	(22.4)	2	(7.7)		9	(24.3)	5	(20.0)	
Middle class	39	(58.2)	18	(69.2)		21	(56.8)	15	(60.0)	
Low (very or moderately)	13	(19.4)	6	(23.1)		7	(18.9)	5	(20.0)	
Obstetric Variables, Mean (SD)										
Maternal age at pregnancy (years)	29.54	(3.67)	28.92	(3.24)	.45	29.66	(3.98)	29.29	(3.43)	.70
Child's birth weight (kg)	3.28	(.44)	3.40	(.43)	.26	3.26	(.38)	3.33	(.51)	.55
ADHD Types, *n* (%)										
Combined	39	(54.9)								
Inattentive	26	(36.6)								
Hyperactive-impulsive	1	(1.4)								
Not otherwise specified	5	(7.1)								
Comorbid Disorders, *n* (%)										
Oppositional defiant disorder	14	(19.7)				10	(25.6)	4	(15.4)	.32
Anxiety disorder	2	(2.8)				2	(5.1)	0	(.0)	.51

Different number of total respondents for paternal education ($n = 93$), maternal education ($n = 89$), familial SES ($n = 93$), maternal age at pregnancy ($n = 90$), and child's birth weight ($n = 88$).

ADHD, attention-deficit/hyperactivity disorder; CPT, continuous performance test; IQ, intelligence quotient; SD, standard deviation; SES, socioeconomic status.

used in the post hoc correlation analysis to avoid potential binning artifacts associated with an integer scale. To avoid making normality assumptions, bootstrapped p values and 95% confidence intervals were obtained with 10,000 samples. Statistical tests were performed using SPSS 20.0 (SPSS Inc., Chicago, Illinois) and results are reported with a significance threshold of $p < .05$ (two-tailed). Additionally, false discovery rate correction was applied to correct for multiple comparisons. As we intended to perform a post hoc analysis to assess the clinical significance of the connectome pathology identified in the ADHD group, we only tested for clinical associations at connections for which a significant between-group difference was identified. The same statistical analysis was applied to identify possible white matter differences between distinct ADHD subtypes.

Results

Participant Characteristics

No significant difference was found in age and handedness between ADHD and control groups (Table 1). A significant male predominance was found in ADHD participants, reflecting the gender ratio of this population (1). IQ was higher in healthy control subjects (26), and no significant difference was found between the two groups in social and obstetric variables, except higher paternal education level in healthy control subjects. Sixty-one ADHD patients (85.9%) were drug-naïve and 10 ADHD patients (14.1%) had a past history of taking stimulants or atomoxetine, which were no longer than 6 months in duration and not within the last 4 weeks. As expected, the CPT omission errors and response time variability were significantly higher in the ADHD group, with a trend-level difference in CPT commission errors. Participants with either of the two most prevalent ADHD subtypes, namely the combined and the inattentive subtypes, were not significantly different regarding any of the demographic and clinical variables.

Differences between ADHD and Healthy Control Subjects

A single network showing significantly ($p < .05$, FWE-corrected) decreased connectivity in children and adolescents with ADHD compared with healthy control subjects was identified. The network comprised 25 links, involving 23 different brain regions (Figure 1A; Table S2 in Supplement 1). This result remained significant after controlling for gender and IQ. Figure 1A was visualized with the BrainNet Viewer (27) (http://www.nitrc.org/projects/bnv/). We did not identify any network with significantly increased connectivity in the ADHD group.

The subsequent correlation analysis was performed in ADHD patients. Multiple significant negative associations were found between FA and the CPT scores (Table 2). The correlations with the CPT omission errors that were significant after false discovery rate correction for multiple comparisons are illustrated in Figure 1B–G. No significant positive correlation was found between FA and the CPT scores.

Given the wide age range of the sample, the original between-group analysis was repeated controlling for age as well as

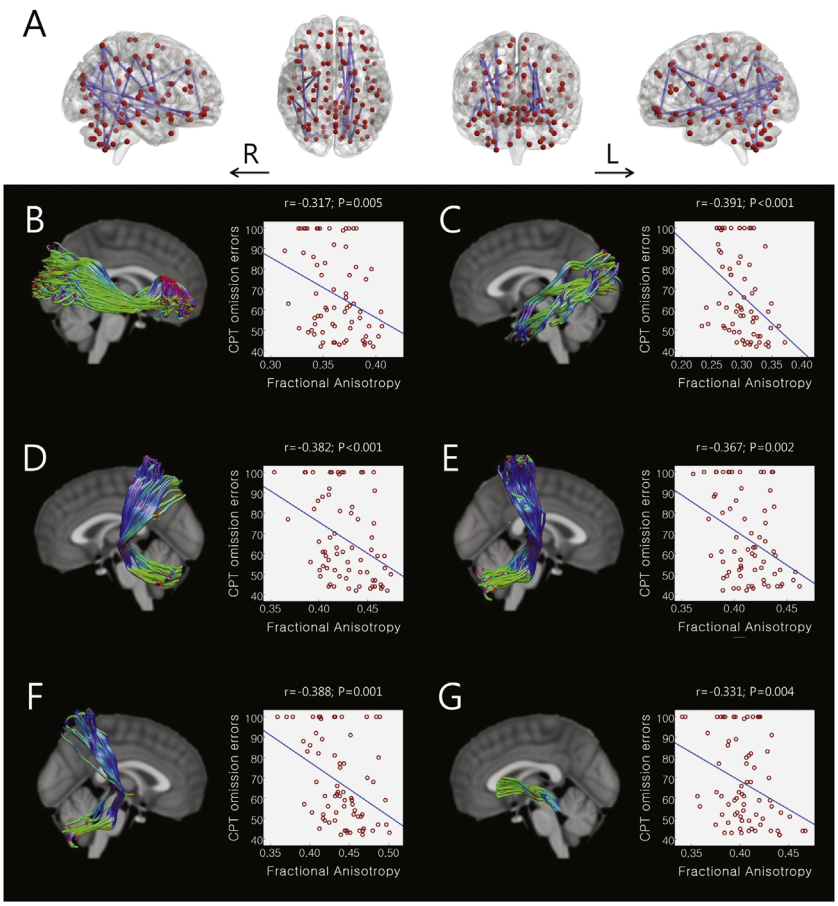

Figure 1. Significantly decreased white matter connectivity in children and adolescents with attention-deficit/hyperactivity disorder compared with healthy control subjects. A single abnormal network was identified (t = 2.2) **(A)**. The correlations between the tract-averaged fractional anisotropy value and the continuous performance test (CPT) omission errors that were significant after false discovery rate correction for multiple comparisons are illustrated **(B–G)**. L, left; R, right.

gender and IQ. Controlling for all three nuisance covariates did not substantially alter the original result, with 23 of the original 25 links still showing significant evidence of disruption. The links between left amygdala and left pallidum and between right postcentral gyrus and right pallidum were no longer significant.

To examine a clearer phenotype of ADHD, those with comorbid oppositional defiant disorder or anxiety disorder were

Table 2. Significant Correlations between the Tract-Averaged FA Value and the CPT Scores Within the Altered White Matter Network Differentiating Children and Adolescents with ADHD from Healthy Control Subjects

ADHD Participants (n = 71)	r	p	95% CI
CPT Omission Errors			
Inferior frontal gyrus (orbital part), right ↔ middle occipital gyrus, right	−.317	.005[a]	−.487 to −.138
Superior occipital gyrus, left ↔ fusiform gyrus, left	−.391	<.001[a]	−.554 to −.237
Superior parietal gyrus, right ↔ pallidum, right	−.306	.010	−.526 to −.079
Precuneus, left ↔ cerebellar hemisphere (crus I), left	−.382	<.001[a]	−.561 to −.178
Postcentral gyrus, right ↔ cerebellar hemisphere (lobule VIII), right	−.367	.002[a]	−.553 to −.148
Superior parietal gyrus, right ↔ cerebellar hemisphere (lobule VIII), right	−.388	.001[a]	−.583 to −.161
Putamen, left ↔ cerebellar vermis (lobule I, II)	−.331	.004[a]	−.503 to −.158
CPT Commission Errors			
Superior occipital gyrus, left ↔ precuneus, left	−.311	.002[a]	−.493 to −.123
Precuneus, left ↔ cerebellar hemisphere (crus I), left	−.269	.043	−.506 to −.003
CPT Response Time Variability			
Superior occipital gyrus, left ↔ fusiform gyrus, left	−.255	.023	−.459 to −.052
Postcentral gyrus, right ↔ pallidum, right	−.246	.041	−.447 to −.038
Superior parietal gyrus, right ↔ pallidum, right	−.298	.014	−.498 to −.088
Precuneus, left ↔ cerebellar hemisphere (crus I), left	−.237	.028	−.434 to −.039
Postcentral gyrus, right ↔ cerebellar hemisphere (lobule VIII), right	−.325	.009	−.532 to −.103
Superior parietal gyrus, right ↔ cerebellar hemisphere (lobule VIII), right	−.339	.004[a]	−.523 to −.141

ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; CPT, continuous performance test; FA, fractional anisotropy.
[a]Significant after false discovery rate correction for 75 multiple comparisons (i.e., 25 links × 3 CPT variables).

excluded in a subsequent analysis (Figure S1 in Supplement 1). Next, only drug-naïve ADHD participants were compared with the control group (Figure S2 in Supplement 1). Lastly, only male patients and male control subjects were included in another set of analyses (Figure S3 in Supplement 1). As a result, significantly altered white matter networks with similar configurations were identified throughout the analyses ($p < .05$, FWE-corrected), with a distributed pattern of abnormalities separately involving frontal, striatal, and cerebellar brain regions rather than abnormalities of direct frontostriatal connectivity.

Differences between Combined and Inattentive Subtypes

Among ADHD participants, 39 were diagnosed with the combined subtype (age range 6.0–14.8 years, 33 male and 6 female participants), 26 with the inattentive subtype (age range 6.3–15.7 years, 20 male and 6 female participants), and only one 7-year-old boy was diagnosed with the hyperactive/impulsive subtype. As we aimed to investigate the difference between the combined and inattentive subtypes of ADHD, which is the hyperactive/impulsive symptom domain, the child diagnosed with the hyperactive/impulsive subtype was included among the combined subtype group in the subsequent analysis.

A single network showing significantly ($p < .05$, FWE-corrected) decreased connectivity in the combined (and hyperactive/impulsive) subtype patients compared with inattentive subtype patients was identified. The network comprised 18 links connecting 17 different brain regions, most of which were in the right hemisphere and included superior frontal gyrus, anterior cingulate gyrus, and supplementary motor area (Figure 2A; Table S3 in Supplement 1).

The subsequent correlation analysis was performed in participants with ADHD combined type. Multiple significant negative associations were found between FA and the CPT scores (Table 3; Figure 2B,C). No significant positive correlation was found between FA and the CPT scores.

Discussion

Evidence of altered white matter connectivity was found in children and adolescents with ADHD. The aberrant network differentiating ADHD individuals from healthy control subjects involved prefrontal and striatal pathology. Interestingly, ventral frontal regions were implicated, such as orbitofrontal cortex, pars triangularis, and gyrus rectus. Basal ganglia regions included the putamen and globus pallidus but not caudate nucleus. The network identified involved prefrontal and striatal connections, characteristically as part of a larger circuit rather than via direct pair-wise links between the two, as previously implied (12). The functional significance of the white matter disturbances was underscored by the significant correlations observed with attentional performance.

Connectomic Disturbances in ADHD

Voxel-based DTI studies have yielded relatively diffuse and somewhat inconsistent findings. In a recent meta-analysis of nine voxel-based DTI studies, including a total of 173 ADHD patients and 169 healthy control subjects, van Ewijk *et al.* (10) identified five significant clusters robustly found to represent abnormal white matter integrity in ADHD. These clusters were, from largest to smallest, right anterior corona radiata (with fibers from the superior longitudinal fasciculus), left cerebellar white matter, right and left internal capsule, and right forceps minor. These results are consistent with many other studies demonstrating abnormal white matter integrity of large fiber tracts (e.g., superior longitudinal fasciculus, which is known to connect all four major lobes) (28–34). When such large fiber tracts are implicated, it is difficult to infer which end-terminal is specifically affected in association with the white matter pathology.

We tried to identify which specific networks of connections are affected in ADHD using a regionally unbiased, whole-brain, and data-driven approach. The findings suggest frontal, striatal, and cerebellar abnormalities (3,4), as well as potentially important roles for other white matter connections in ADHD pathophysiology (12). Recently, neural systems other than frontostriatal circuits have been proposed to play a role in ADHD pathophysiology based largely on studies of resting-state functional networks such as the frontoparietal network, dorsal and ventral attention networks, visual network, motor network, limbic network, and default mode network (11,35,36). The white matter fibers implicated by the current study interconnect many of the brain regions involved in these intrinsic networks. In sum, the network differentiating ADHD patients from healthy control subjects appears to resonate with current models emphasizing abnormalities of both top-down regulation by the inferior prefrontal cortex with its extensive connections to other cortical and subcortical structures (37), as well as bottom-up multimodal sensory convergence and attention allocation mediated by parietal cortex (4,38). However, the relationship between disturbed white matter architecture and cortical dysfunction, both during tasks and during rest, remains to

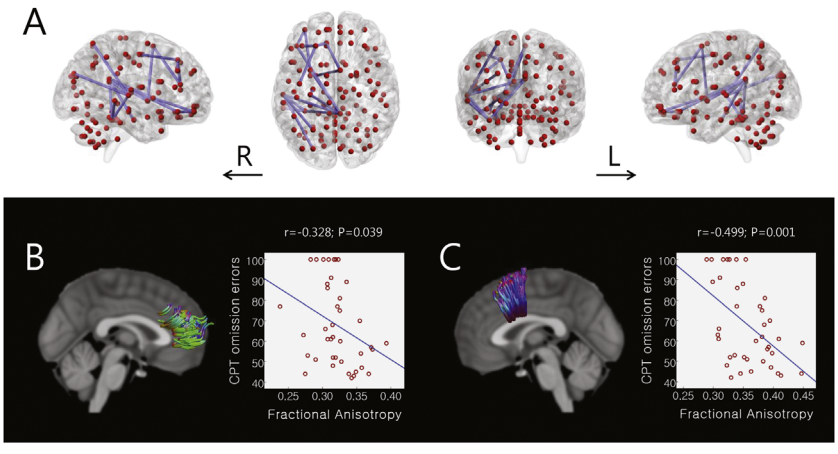

Figure 2. Significantly decreased white matter connectivity in children and adolescents with attention-deficit/hyperactivity disorder combined type compared with those with attention-deficit/hyperactivity disorder predominantly inattentive type. A single abnormal network was identified ($t = 2.1$) **(A)**. Significant correlations between the tract-averaged fractional anisotropy value and the continuous performance test (CPT) omission errors linking superior frontal gyrus, anterior cingulate gyrus, and supplementary motor area are illustrated **(B, C)**. L, left; R, right.

Table 3. Significant Correlations between the Tract-Averaged FA Value and the CPT Scores Within the Altered White Matter Network Differentiating Children and Adolescents with ADHD Combined Type from Those with ADHD Predominantly Inattentive Type

ADHD Combined and Hyperactive/Impulsive Type Participants (n = 40)	r	p	95% CI
CPT Omission Errors			
Superior frontal gyrus, right ↔ anterior cingulate gyrus, right	−.328	.039	−.552 to −.097
Supplementary motor area, left ↔ anterior cingulate gyrus, right	−.499	.001[a]	−.695 to −.279
Superior parietal gyrus, right ↔ superior temporal gyrus, right	−.356	.024	−.570 to −.007
CPT Response Time Variability			
Superior frontal gyrus, right ↔ anterior cingulate gyrus, right	−.380	.016	−.612 to −.125
Supplementary motor area, left ↔ anterior cingulate gyrus, right	−.397	.011	−.646 to −.110
Superior parietal gyrus, right ↔ superior temporal gyrus, right	−.353	.025	−.595 to −.045

ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; CPT, continuous performance test; FA, fractional anisotropy.
[a]Significant after false discovery rate correction for 54 multiple comparisons (i.e., 18 links × 3 CPT variables).

be elucidated (39). Future research using a combination of DTI and functional magnetic resonance imaging measures might be helpful to establish the relationship.

The specific areas of the cerebellum associated with abnormal white matter connectivity in ADHD were the vermis (lobule I, II) and the posterior inferior lobe (lobule VIII). Interestingly, decreased volume of these cerebellar components in ADHD has been consistently reported in the literature, and anatomical abnormalities of the cerebellum in ADHD have been fairly specific to these areas (40). In the current study, the superior parietal gyrus and putamen were also connected to the cerebellum as part of the affected network. Cortico-cerebellar white matter connections are known to include parietal cortex (41). Recently, the existence of a direct anatomical connection between the putamen and cerebellum has been demonstrated (42), raising the possibility that the cerebellum may adjust striatal activity in a similar manner as it adjusts voluntary movement (42,43).

Similarities and differences are evident between the current findings and the previous work by Cao *et al.* (17). Decreased white matter connectivity involving prefrontal regions in the absence of decreased connectivity directly linking prefrontal and striatal regions was a notable similarity between the two studies. However, cerebellum was not examined in the previous study, which may explain the more restrictive pattern of abnormalities in prefrontal-dominant circuitry. In the current study, significant correlations between the tract-averaged FA value and the CPT scores were observed in multiple fibers involving the cerebellum. Another notable difference in the previous study was the increased connectivity in the orbitofrontal-striatal circuitry, which correlated with hyperactivity/impulsivity symptoms, while we did not find any network featuring increased connectivity. In this regard, we may need to consider the clinical characteristics of the study participants. ADHD participants of both studies were clearly inattentive, but our sample appears to have been less impulsive (or our control subjects may have been more impulsive), given a trend-level difference in CPT commission errors from the control group. On the other hand, a higher proportion (37%) of ADHD participants in Cao *et al.* (17) had comorbid oppositional defiant disorder.

Secondary analyses were performed with different subsamples of participants (i.e., ADHD-only, drug-naïve-only, and male-only) and therefore the results may not be directly comparable. However, similar to the main finding, abnormalities of a larger brain-wide network rather than direct frontostriatal connectivity were implicated. Specifically, the aberrant networks from the main and secondary analyses commonly involved 1) all four major cerebral lobes; 2) both the dorsal and ventral prefrontal regions; and 3) predominantly the right cerebellar hemisphere.

Functional Consequences of Disturbed Brain Connectivity in ADHD

The relationship between altered white matter connectivity and ADHD pathology was further evidenced by the significant negative correlations between FA and the CPT scores. The CPT is one of the most widely used neuropsychological tests in ADHD and showed the largest effect size for the diagnosis of ADHD (26). Performance on this task is modulated by variation in dopaminergic genes (44) and has been proposed as an endophenotype of ADHD (45). In the present study, all the significant correlations between FA and the CPT scores were in the hypothesized direction, indicating that the revealed white matter networks may be directly contributing to the core neuropsychological difficulties of ADHD patients. Although ceiling effects were observed, a closer inspection of Figures 1B–G and 2B and C suggests that ceiling effects were usually associated with lower FA values. Therefore, without the constraint of the ceiling effects, even higher CPT scores would have been obtained, thereby resulting in stronger negative correlations.

ADHD Subtypes Differentially Affect Distinct Brain Networks

Neuroimaging approaches identifying distinct neural networks that differentiate between the subtypes of ADHD have been warranted, as the DSM-IV classification of ADHD provides clinical heterogeneity within its diagnostic category. Our relatively large sample size enabled us to examine connectomic disturbances associated with distinct ADHD subtypes. We found that a network of connections largely confined to the right frontal regions was able to differentiate the two groups.

Right hemispheric regions are known to play a particularly important role in response inhibition (46) and ADHD (47). Previously, Shaw *et al.* (48) demonstrated that right-handed, typically developing children exhibit relative gain in right-hemispheric thickness in the lateral orbitofrontal and inferior frontal cortex, which was absent in right-handed ADHD children, suggesting that disruption of anatomical asymmetry in the brain may be implicated in the pathogenesis of this disorder. The present finding further suggests that aberrant right-hemispheric development might be specifically associated with hyperactivity/impulsivity than inattention, given that the latter is a shared characteristic of both combined and inattentive subtypes of ADHD.

The altered connectivity linking superior frontal gyrus, anterior cingulate gyrus, and supplementary motor area, together with the significant negative correlations between FA and the CPT scores, is particularly interesting, as it indicates aberrant control of motion. Supplementary motor area has been associated with the intent or the planning of movement (49), and electrical

stimulation to this region was shown to evoke an urge to move (50). The current finding may be indicative of aberrant cognitive control from the superior frontal cortex over the supplementary motor area, which is mediated by the anterior cingulate cortex. Anterior cingulate cortex has been postulated to detect conflicts and then signal the prefrontal cortex to recruit top-down feedback to resolve conflicts and enhance control (11). Similar motor control loop for willed action has been reported in previous studies (51,52). This potentially interesting explanation requires further validation in hyperactive ADHD patients.

Limitations

Patients and control subjects were not strictly matched for gender and IQ. Rather than performing case-by-case matching, we opted to maximize our sample size and thus statistical power. In the current study, we had difficulty recruiting more control subjects to match gender and IQ. Other variables were, however, well-matched, including possible risk factors (e.g., social and obstetric variables) of ADHD and head motion parameters. Although age was comparable between the groups, as the age of the participants spanned a range, possible confounding effects of age-related DTI change were not excluded. However, these limitations may not be pronounced in the findings, given the uniformly negative associations observed between measures of white matter integrity and age-standardized scores for multiple domains of attentional performance. We excluded ADHD patients with a past history of taking stimulants or atomoxetine longer than 6 months or a recent history of taking stimulants or atomoxetine over the last 4 weeks. However, as 14.1% of ADHD participants were not drug-naïve, any potential effects of medication on the brain's microstructural integrity cannot be completely ruled out (53). Diffusion tensor imaging-based tractography may generate spurious fiber pathways in regions where there are crossing fibers, and in this regard, diffusion spectrum imaging was shown to be more successful in resolving the crossing of tracts (54). On the other hand, however, DTI networks were evidenced with better reproducibility (55). Acquisition of diffusion spectrum imaging requires individuals to lie motionless in the scanner for a longer period of time. Compliance with the instruction to remain motionless is particularly challenging for young adolescents with ADHD. To minimize acquisition time, we opted to acquire relatively low angular resolution data, which precluded the use of crossing fiber models. As such, white matter pathways with complex geometries are unlikely to have been reconstructed due to inadequacies of the diffusion tensor model. Anisotropic voxel dimensions were used to minimize acquisition times and thereby minimize the risk of motion-induced artifacts, given the nature of the clinical cohort. However, using anisotropic voxels comes at the cost of introducing potential tracking biases in the out-of-plane orientation. These potential tracking biases are common to both the control and ADHD groups and are therefore unlikely to introduce spurious between-group differences. We have previously investigated the parcellation issue in detail and have reported that network organization is likely unaffected by different parcellations at the same resolution (i.e., the same number of nodes), whereas varying degrees of spatial resolution across different parcellations may, in fact, alter the network organization of the brain (56). In addition, regions of interest defined by anatomically segmented atlases may not represent biologically meaningful entities (57). In sum, the lack of a gold standard for regional parcellation is a limitation of the study. Moreover, the Automated Anatomical Labeling is a single-subject segmentation of a male adult brain. Future studies may profit by applying age- and gender-relevant brain parcellations, although coarse regional definitions at the scale of the Automated Anatomical Labeling are unlikely to change substantially from adolescence to adulthood. Lastly, the cross-sectional study design limits our ability to determine whether the white matter abnormalities observed in the present study reflect the primary pathophysiology of ADHD or are secondary to a compensatory neurodevelopmental process.

Conclusions

In conclusion, our findings indicate that abnormal white matter connectivity in ADHD not only includes circuits implicated by the frontostriatal model but also extends to a larger brain network encompassing other corticocortical, subcortical, and cerebellar circuits. In regard to frontostriatal model, a distributed pattern of white matter abnormalities separately involving frontal, striatal, and cerebellar brain regions was identified. In addition, we detected a network that marginally differentiates between the combined and inattentive subtypes of ADHD, suggesting potential distinct connectivity patterns underlying the clinical heterogeneity of ADHD.

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