Long-Range White Matter Microstructural Alterations in Drug-Naive Children with Attention Deficit Hyperactivity Disorder: A Tract-Based Spatial Statistics Study

Ronghui Zhou

Wenzhou Medical College First Affiliated Hospital: The First Affiliated Hospital of Wenzhou Medical University

Peng Dong

Ningbo Medical Treatment Centre Li Huili Hospital

Shuangli Chen

Wenzhou Medical University First Affiliated Hospital: The First Affiliated Hospital of Wenzhou Medical University

Andan Qian

Wenzhou Medical University First Affiliated Hospital: The First Affiliated Hospital of Wenzhou Medical University

Jiejie Tao

Wenzhou Medical University First Affiliated Hospital: The First Affiliated Hospital of Wenzhou Medical University

Xiangwu Zheng

Wenzhou Medical University First Affiliated Hospital: The First Affiliated Hospital of Wenzhou Medical University

Jingliang Cheng

Zhengzhou University First Affiliated Hospital

Chuang Yang

Wenzhou Medical University First Affiliated Hospital: The First Affiliated Hospital of Wenzhou Medical University

Xiaoqi Huang

West China School of Medicine: Sichuan University West China Hospital

Meihao Wang (✉ wzwmh@wmu.edu.cn)

Wenzhou Medical University First Affiliated Hospital <https://orcid.org/0000-0002-7055-993X>

Research Article

Keywords: Anisotropy, diffusion tensor imaging, eigenvalue, myelination

Posted Date: December 22nd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1100585/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background

Microstructural changes might underlie white matter (WM) pathology in attention deficit hyperactivity disorder (ADHD). To investigate WM alterations, particularly the changes in long-range fibers, in drug-naive children with ADHD, we conducted tract-based spatial statistics (TBSS) analysis on diffusion tensor imaging (DTI) data.

Materials and Methods

In this study, 57 children with ADHD and 41 healthy controls (HCs) were enrolled. None of the enrolled ADHD children received any medication before data collection. The difference in fractional anisotropy (FA), and in mean (MD), axial (AD), and radial diffusivity (RD) between both groups were calculated using TBSS. WM changes were then correlated with clinical symptoms, including the hyperactivity index score and the impulsivity score.

Results

Whole-skeleton analysis identified several long-range fibers of decreased FA and increased RD in the ADHD group as compared to the HC group. ADHD children demonstrated decreased FA in the right corpus callosum (CC) splenium, left inferior fronto-occipital fasciculus, and intersection of the anterior and posterior internal capsule. Moreover, higher RD was observed in the right CC splenium, superior longitudinal fasciculus, and posterior corona radiata. No regions of increased FA or reduced RD were observed, and no differences in MD or AD were noted.

Conclusion

Our results demonstrate that microstructural WM alterations and changes in the long-range WM connections are present in children with ADHD. We speculate that these changes may relate to the symptoms of hyperactivity and impulsivity.

1. Introduction

ADHD is a common childhood psychological disorder characterized by inattention, impulsiveness, and hyperactivity. Accumulating evidence indicates that abnormalities in brain structure may play an important role in the pathophysiology of ADHD. However, the role of altered development of brain white matter (WM) in ADHD has not yet been fully elucidated.

Diffusion tensor imaging (DTI) is an efficacious tool for providing information on WM features in vivo at the microscopic level, and can reveal the brain substrates of pathological changes in structural connectivity. Tract-based spatial statistics (TBSS) analysis is an approach that involves first determining a mean fractional anisotropy (FA) skeleton, and then mapping DTI data from each participant directly onto the skeleton for group comparisons¹. As the centers of the major tracts are easily definable despite anatomical heterogeneity across individuals², TBSS has been widely used in research on various diseases, including multiple sclerosis, schizophrenia, epilepsy, neonatal disease, as well as ADHD.

Previous literature using TBSS has demonstrated solid microstructural changes in neuronal development among children with ADHD as compared with typically developing controls. Recent studies have also reported evidence of changes in a number of different networks involving large-scale brain regions, such as the interhemispheric pathways, the occipital and temporal lobes³, the corpus callosum (CC), and the sagittal stratum (SS) in ADHD. A quantitative meta-analysis found that the most robust WM alterations identified in ADHD-TBSS studies were located in the splenium of the CC, right SS, and left tapetum, as well as in the tracts of the right cingulum, right inferior longitudinal fasciculus (ILF), and bilateral inferior fronto-occipital fasciculus (IFOF)⁴.

Interestingly, methylphenidate (MPH), a psychostimulant used to treat ADHD, which effectively reduces symptoms of inattention, hyperactivity, and impulsivity in up to 80% of children with ADHD⁵, has been shown to increase the WM volume in children with ADHD, as compared to unmedicated children with ADHD⁶. Moreover, a study of stimulant treatment history in ADHD found that cumulative stimulant intake correlated negatively with orbitofrontal-striatal mean diffusivity (MD) on DTI, suggesting higher structural connectivity with more and/or longer stimulant treatment⁷. Thus, the history of drug use will have marked effects on studies of the pathogenesis of ADHD. Nevertheless, TBSS studies of drug-naïve children with ADHD are rare. In a meta-analysis, data on seven non-adult patients were included in 2016⁸. Additionally, one other study focused on the maturation of brain WM in treatment-naïve male ADHD children⁹, but found no WM alterations in treatment-naïve children.

Long-range fibers are defined as connections between regions across different lobes and/or hemispheres. The long-range fibers, including but not limited to the area of the CC, SS, and superior longitudinal fasciculus (SLF), play essential roles in ADHD. Recently, the studies of WM microstructure have mentioned that primarily higher MD and radial diffusivity (RD) in WM microstructure, particularly in long-range fibers, could influence attention and executive functioning in some psychiatric disorders, such as schizophrenia and autism^{10–11}. Attention and executive functioning is generally regarded as the main performance issues in ADHD. This provides a solid theoretical basis for ADHD research on long-range fibers.

Therefore, we focused on a sample of drug-naïve Chinese children with ADHD and sex-, age-, and intelligent quotient (IQ)-matched controls. In this study, we used TBSS and whole-brain deterministic tractography to perform a hypothesis-free search for WM differences in children with ADHD, as compared

to typically developing controls. We hypothesized that, compared with the HC group, children with ADHD would show significantly altered parameters of WM in long-range WM connections, specifically in the portions of the tract that pass through the brain regions previously shown to be abnormal in ADHD, including the SS and the tracts of the basal ganglia and CC. We further hypothesized that these abnormalities would be significantly associated with ADHD symptoms.

2. Material And Methods

2.1. Subjects and procedures

Ninety-eight children (57 patients with ADHD, 41 healthy controls [HCs]) were recruited from the First Affiliated Hospital of the Wenzhou Medical University between December 2012 and September 2014. None of the ADHD children had received any ADHD medication before data collection.

An estimated full-scale IQ > 75, right-handedness, and the absence of known neurological, cognitive, or chronic medical diseases were required for all subjects. The Diagnostic and Statistical Manual of Mental Disorders (fourth edition) diagnosis of ADHD was assessed by licensed clinicians or supervised trainees, based on the Schedule of Affective Disorders and Schizophrenia for Children—Present and Lifetime Version, which was administered to each child and their parent.

The exclusion criteria included: (1) left-handedness; (2) a history of stimulants or any other drugs or therapy for ADHD; (3) a full-scale IQ score < 75, according to the Wechsler Intelligence Scale for Chinese Children-Revised ^[14]; (4) a history of head trauma with loss of consciousness; (5) a history of neurological disorders or other severe diseases, such as pediatric stroke and seizure disorder; and (6) a history of psychiatric disorders, including affective disorders, emotional disorders, oppositional defiant disorder, Tourette's syndrome, conduct disorder, or any other Axis I psychiatric disorder.

This study was conducted in accordance with the latest version of the Declaration of Helsinki. The protocol was reviewed and approved by the ethics committee of the First Affiliated Hospital of Wenzhou Medical University. Written informed consent was obtained from the guardians of all subjects.

2.2. Clinical symptom assessment

Each participant was assessed by the parents, using a Conner's Parent Symptom Questionnaire—Chinese revised version, to evaluate hyperactivity and impulsivity symptoms of ADHD. The 48 items covered six aspects of ADHD: (1) conduct problems; (2) learning problems; (3) physical and psychological problems; (4) impulsivity–hyperactivity; (5) anxiety; and (6) hyperactivity index.

2.3. Acquisition of diffusion-weighted images

Images were acquired on a 3.0 T GE Signa HDx scanner (GE Healthcare, Milwaukee, WI) with Echo speed gradients using a custom-built whole-head coil. DT image acquisition was accomplished with single shot spin-echo echo-planar imaging sequence with diffusion sensitizing gradients applied on either side of the

180° refocusing pulse. Imaging parameters for the diffusion-weighted sequence were as follows: field-of-view, 24 cm; matrix size, 128 × 128; TE/TR, 76.2/8000 ms; 30 axial-oblique slices; slice thickness 4 mm with 0 mm interslice spacing; and fractional k-space acquisition. A spectral-spatial excitation RF-pulse was used to select water protons only and served to avoid ghost artifacts from lipid-bound protons. The scan was prescribed from the top of the brain and included only the most superior part of the cerebellum. Diffusion gradient duration was 32 ms, and diffusion weighting was $b = 1000 \text{ s/mm}^2$. In addition, one reference scan (b_0 -scans) was performed and averaged for each slice with the diffusion-encoding gradients turned off. All subjects underwent T2-weighted imaging scans before DTI to exclude basic structural brain lesions.

To reduce any influence of movement that could confound the results, we visually inspected the raw diffusion images of all subjects for head movement and excluded subjects with significant alterations. Additionally, we fixed the patients' position by placing cushions inside the head coil of the MR scanner to reduce any head movement. Finally, a radiologist was present throughout the examination to detect strong movements.

2.4. Preprocessing and skeletonization of diffusion-weighted images

Voxelwise statistical analysis of FA, MD, AD, and RD was performed using TBSS¹², a part of the FSL¹²⁻¹³. First, all FA images were registered into a common space using nonlinear registration. A study-specific child template was used as a registration target image. Next, the transformed images were averaged to create a mean FA image and then a study-specific skeleton was generated. The FA threshold was set to 0.3 in order to include the major WM pathways, while avoiding peripheral tracts, which are more vulnerable to inter-subject variability and/or partial volume effects with gray matter. Each participant's normalized FA images were then projected onto this common skeleton to minimize any residual misalignment of tracts.

Differences in WM DTI metrics were corrected for multiple comparisons, family-wise error and used Threshold-Free Cluster Enhancement, which avoids arbitrary initial cluster forming thresholding. Data from FA maps were compared to detect differences between participants with ADHD and HCs. The same transformations applied to the FA images were then applied to the AD and RD images.

2.5. Statistical analysis

Two independent sample *t*-tests and chi-square tests were performed using SPSS 22.0 (SPSS Inc, Chicago, IL) to investigate differences in age, IQ, and sex between the ADHD group and the HC group. A two-tailed *p* value < 0.05 was considered statistically significant.

For the purpose of defining the region of WM alterations and improving the interpretation of these microstructural alterations, the JHU White-Matter Tractography Atlas of WM labels was registered to the mean FA image that showed significant differences between groups, to estimate the association with neuropsychological measures. We defined each significant cluster of FA between the two groups as a

region-of-interest (ROI), and averaged FA values were extracted to perform correlation analysis with the clinical scale score. The association of FA values (extracted from significant regions between groups from FSL analysis) with disease severity indexes were evaluated using linear regression.

3. Results

3.1 Demographic variables and neuropsychological assessment results

After data preprocessing, controlling for the subject's head movement, and removing image artifacts and other confounding factors, the subjects who finally met the requirements for this study were as follows. The ADHD group consisted of 57 subjects (46 males and 11 females), with an average age of 9.33 ± 1.75 years, and an average IQ of 116.05 ± 16.84 . The HC group consisted of 41 subjects (23 males and 18 females), with an average age of 9.63 ± 1.48 years, and an average IQ of 120.9 ± 14.84 . There were no significant differences between the two groups in terms of age ($p = 0.36$), IQ ($p = 0.65$), or sex ($p = 0.25$). As expected, children with ADHD showed a higher hyperactivity index score and impulsivity score. Table 1 summarizes the participants' characteristics.

Table 1
Clinical demographics differences between the ADHD-group and HC-group.

	ADHD (n = 57)	Control (n = 41)	P-value
Sex (female/male)	11/46	18/23	0.25
Age (years)	8 ± 1.85	8.41 ± 1.66	0.36
IQ	116.05 ± 16.84	120.9 ± 14.84	0.65
Hyperactivity index score	1.55 ± 0.57	0.46 ± 0.39	<0.05
Impulsivity score	1.65 ± 0.66	0.48 ± 0.48	<0.05
Right-hand	57(100%)	41(100%)	

ADHD, attention-deficit/hyperactivity disorder; HC, healthy control; IQ, intelligence quotient

3.2 WM differences between children with ADHD and HCs

We compared different eigenvalues between the ADHD and HC groups. Whole-skeleton voxel-based analysis identified several clusters of decreased FA (Table 2, Figure 1) and increased RD in the ADHD group as compared to the HCs (Table 2, Figure 2). This revealed that the right CC splenium, left inferior fronto-occipital fasciculus (IFOF), and intersection of the anterior and posterior internal capsule ($p < 0.05$, FDR) seemed to have a lower FA value, while higher RD was observed in the right CC splenium, superior longitudinal fasciculus (SLF), and posterior corona radiata (PCR) ($p < 0.05$). No regions of increased FA or

reduced RD were observed, and no differences were observed for MD or AD. All results remained significant after correction for multiple testing.

Table 2

Clusters showing significant differences in FA and RD between the ADHD-group and HC-group.

TBSS	WM tracts	Size (voxels)	Coordinate
FA	CC Splenium R	65	28.1-57.216
	Intersection of anterior and posterior Internal capsule L	203	-10.7-0.887-0.611
	Inferior fronto-occipital fasciculus L	226	-28.331.49.94
RD	CC Splenium R	104	22.3-62.629.3
	Posterior corona rad R	148	30.7-67.8 3.37
	Superior longitudinal fasciculus R	761	36.8-64.5 30.8

Green color indicates white matter skeleton where no significant results were found; red regions indicate where participants in the ADHD-group (n = 57) had significantly lower FA than those in the HC-group (n = 41). Arrows indicate the specific cluster of interest for each column. CC: corpus callosum; IFOF, Inferior fronto-occipital fasciculus.

Green color indicates white matter skeleton where no significant results were found; blue regions indicate where participants in the ADHD-group (n = 57) had significantly higher RD than those in the HC-group (n = 41). Arrows indicate the specific cluster of interest for each column. CC, corpus callosum; PCR, posterior corona radiata; SLF, superior longitudinal fasciculus.

3.3 WM alterations correlated with symptom in children with ADHD

The mean FA values were derived from every cluster and assessed for Pearson correlation with the clinical score. We found that higher hyperactivity/impulsivity symptom scores were negatively correlated with the mean FA value in the right CC splenium, left IFOF, and the intersection of the anterior and posterior internal capsule (Figures 3, 4).

4. Discussion

In this study, we explored changes in brain WM microstructural properties of drug-naïve children with ADHD. We found that, compared to HC children, drug-naïve ADHD children showed significantly reduced FA in the right CC splenium, left IFOF, and the intersection of the anterior and posterior internal capsule, as well as increased RD in the right CC splenium, SLF, and PCR; however, there were no differences in AD and MD. These data supported the hypothesis that the function of long-distance connectivity in WM, particularly the connections among the occipital, temporal, and frontal lobes and the cingulum, are

essential for the development of ADHD. We also confirmed that the higher the hyperactivity/impulsivity symptom score, the lower the FA value of long-range fibers in drug-naïve patients.

In the current study, we found reduced FA and increased RD in the right splenium of the CC. The CC is the largest WM bundle in the brain and is responsible for interhemispheric communication⁴. This tract connects the bilateral cerebral hemispheres, transferring excitatory and inhibitory signals¹⁴. The splenium of the CC connects interhemispheric somatosensory, auditory, occipital, and motor areas, which are important for visual object recognition and discrimination¹⁵. Moreover, the splenium of the CC influences the speed of visual information transmission and dynamic distribution of processing resources^{16–17}. Thus, the deficits along the splenium pathway might be related to the inattention, distractibility, and visual dysfunctions observed among patients with ADHD. Decreased FA in the splenium of the CC is likely to result from axonal damage, or can be found in areas with decreased or delayed myelination. Moreover, RD has been suggested to indicate increased freedom of cross-fiber diffusion and reflect variations in myelination¹⁸. The impaired WM microstructure in the CC splenium might impede interhemispheric communication and activity in the posterior brain circuitries, particularly the occipital- and temporal-lobe-related pathways, and it might be a pathological component of attention dysfunction in ADHD.

In addition to the CC splenium, we found reduced FA in the left intersection of the anterior and posterior internal capsule; these observed differences in the posterior regions of the corona radiata are consistent with the findings of previous ADHD studies in childhood¹⁹. The posterior regions of the corona radiata are continuations of the posterior limb of the internal capsule to the sensorimotor cortex, and contain axons primarily involved in low-level motor functions. The internal capsule includes connections to cortical areas and subcortical areas, such as the brain stem, thalamus, and basal ganglia, in addition to connections with the corticospinal tract, which conducts nerve impulses from the motor cortex to the spinal cord²⁰. A recent study has found that decreased FA in the right intersection of anterior and posterior internal capsule might contribute to sensorimotor deficits in adult ADHD²¹.

Our finding of reduced FA in the left intersection of the anterior and posterior internal capsule further underscores the possible role of dysfunctions within the visual system in ADHD. Changes in the corona radiata and internal capsule may explain the attention, visual processing, and motor function in ADHD. Higher RD is thought to reflect decreased myelination, while lower AD reflects axonal damage or degeneration. Our findings of decreased FA in the left intersection of the anterior and posterior internal capsule, as well as increased RD in the left PCR connections point to involvement of the basal ganglia in the pathophysiology of ADHD¹⁴, which is consistent with previous TBSS studies involving ADHD children and adolescents^{18, 21}.

Furthermore, we found that the left part of the IFOF, which is a part of the SS, presented significantly lower FA in children with ADHD than in controls. The SS is a large WM tract that is oriented in a sagittal plane along the temporal occipital lobes and cingulum, and it has been associated with altered FA in patients with ADHD, according to voxel-based analyses and ROI studies^{14, 16}. This tract contains fibers of

the IFOF and ILF. The IFOF is a large WM tract connecting the frontal, temporal, and occipital lobes. The IFOF also constitutes one of the major efferent and afferent neuronal projections to the frontal lobes. Additionally, IFOF is implicated in attention-shifting abilities, which are deficient in individuals with ADHD^{17, 22–23}. We found markedly decreased FA in the left IFOF in ADHD children; these changes in the IFOF may explain the attention, visual processing, and language problems involved in ADHD.

Moreover, as in previous studies²⁴, we identified a large area of markedly higher RD in the right SLF in our study. The SLF is a WM bundle spanning the posterior and anterior regions of the cerebrum and contains connections to the frontal, temporal, parietal, and occipital lobes²⁵. The association between the SLF and verbal and spatial working memory has already been reported in healthy children, adolescents, and young adults^{26–27}. In addition, the left SLF also connects Broca's and Wernicke's areas, which are responsible for language comprehension and production. Increased RD is associated with dysmyelination of the nerve sheath in the left SLF, which might also be related to the visual and auditory deficits of ADHD children.

We found that the hyperactivity/impulsivity symptom severity was negatively correlated with FA values in the right CC splenium, left IFOF, and the intersection of the anterior and posterior internal capsule. This result was consistent with previous studies that have shown that WM differences in ADHD are related to disease severity^{26–27}. Given that previous studies in young children with ADHD suggested reduced or delayed myelination, we surmise that our results may reflect alterations of myelination in ADHD. The regions in which there were significant between-group differences in our study were similar to those reported in the previous diffusion studies in ADHD²⁵.

Our study had several limitations. Our sample size was relatively small, resulting in reduced power to examine other potential confounding effects on the DTI metrics. This was because of the strict selection criteria we had adopted. A further study of drug-naïve children, without a history of other psychiatric disorders, could provide more reliable results. Additionally, further longitudinal studies involving the same patient cohort would be required to establish the generalizability of our findings. In addition, TBSS has limitations in analyzing small fiber tracts, regions of crossing fibers, and tract junctions. In later studies, we hope to be able to combine the data of structural and functional data with the help of deep learning to further explore the changes in the brain networks of ADHD children.

5. Conclusions

Our results demonstrated WM microstructural alterations and long-range WM connections in children with ADHD, which may relate to the symptoms of hyperactivity and impulsivity. Our study contributes to the existing controversy regarding the influence of microstructural alterations to ADHD pathophysiology. The results of decreased FA along with increased RD imply that deviant myelination of WM may play a pathogenic role in the emergence and development of ADHD. Although the small sample size may have affected our results, our results encouraged the future investigations of the changes in brain structural connectivity in ADHD. In the near future, we plan to conduct a longitudinal study to investigate ADHD development and evaluate the efficacy of drug treatment objectively.

Declarations

Acknowledgements

The authors thank the First Affiliated Hospital of Wenzhou Medical University for support. We would also like to thank Editage (www.editage.cn) for English language editing.

Funding

This work was supported by the Wenzhou Municipal Science and Technology Bureau, China (No. Y20210231), Key Laboratory of Intelligent Medical Imaging of Wenzhou (No. 2021HZSY0057), and National Natural Science Foundation (Grant No.81671669).

Conflicts of interest

The authors declare that they have no competing or potential conflicts of interest. We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled, “Long-range White Matter Microstructural Alterations in Drug-naïve Children with Attention Deficit Hyperactivity Disorder: A Tract-Based Spatial Statistics Study”.

Ethical approval

This study was conducted in accordance with the latest version of the Declaration of Helsinki. The protocol was reviewed and approved by the ethics committee of the First Affiliated Hospital of Wenzhou Medical University.

Consent to participate

All participants and their parents were fully informed about the purpose and procedures of this study and written informed consent was obtained from the parents

Availability of data and materials

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation

Authors' contributions

Ronghui Zhou, Peng Dong, Shuangli Chen, Andan Qian, Xiaoqi Huang, Meihao Wang contributed to the manuscript's conception, design, and preparation. Ronghui Zhou, Peng Dong, Shuangli Chen, Jiejie Tao contributed to conducting experiments, acquisition, analysis, and interpretation. Xiangwu Zheng, Jingliang Cheng, Chuang Yang, Xiaoqi Huang, Meihao Wang made substantial contributions in drafting

the manuscript and revising it critically for important intellectual content. All authors read and approved the final manuscript.

References

1. Smith, S., Johansen-Berg, H., Jenkinson, M., et al. (2007). Acquisition and voxelwise analysis of multi-subject diffusion data with tract-based spatial statistics. *Nature protocols*, 2(3), 499–503. <https://doi.org/10.1038/nprot.2007.45>.
2. Aoki, Y., Cortese, S., Castellanos, F. X., & Review, R. : Diffusion tensor imaging studies of attention-deficit/hyperactivity disorder: meta-analyses and reflections on head motion. *J Child Psychol Psychiatry* **2018**, 59 (3),193-202.<https://doi.org/10.1111/jcpp.12778>
3. Castellanos, F., & Proal, E. (2012). Large-scale brain systems in ADHD: beyond the prefrontal-striatal model. *Trends in cognitive sciences*, 16(1), 17–26. <https://doi.org/10.1016/j.tics.2011.11.007>.
4. Chen, L., Hu, X., Ouyang, L., et al. (2016). A systematic review and meta-analysis of tract-based spatial statistics studies regarding attention-deficit/hyperactivity disorder. *Neuroscience and biobehavioral reviews*, 68, 838–847. .<https://doi.org/10.1016/j.neubiorev.2016.07.022>.
5. Arnold, L. E., Jensen, P. S., Richters, J. E., & Al, E. (1999). A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. The MTA Cooperative Group. Multimodal Treatment Study of Children with ADHD. *Archives of general psychiatry*, 56(12), 1073–1086. <https://doi.org/10.1001/archpsyc.56.12.1073>.
6. Bouziane, C., Filatova, O. G., Schrantee, A., et al., White Matter by Diffusion MRI Following Methylphenidate Treatment: A Randomized Control Trial in Males with Attention-Deficit/Hyperactivity Disorder. *Radiology* **2019**, 293 (1),186–192.<https://doi.org/10.1148/radiol.2019182528>
7. Schweren, L. J., Hartman, C. A., Zwiers, M. P., et al. (2016). Stimulant treatment history predicts frontal-striatal structural connectivity in adolescents with attention-deficit/hyperactivity disorder. *Eur Neuropsychopharmacol*, 26(4), 674–683. <https://doi.org/10.1016/j.euroneuro.2016.02.007>.
8. Chen, L., Hu, X., Ouyang, L., et al. (2016). A systematic review and meta-analysis of tract-based spatial statistics studies regarding attention-deficit/hyperactivity disorder. *Neurosci Biobehav Rev*, 68, 838–847. .<https://doi.org/10.1016/j.neubiorev.2016.07.022>.
9. Bouziane, C., Caan, M., et al. (2018). ADHD and maturation of brain white matter: A DTI study in medication naive children and adults. *NeuroImage. Clinical* 17, 53-59.<https://doi.org/10.1016/j.nicl.2017.09.026>
10. Koolschijn, P. C., Caan, M. W., Teeuw, J., et al., Age-related differences in autism: The case of white matter microstructure. *Hum Brain Mapp* **2017**, 38 (1),82–96.<https://doi.org/10.1002/hbm.23345>
11. Subramaniam, K., Gill, J., Fisher, M., et al. (2018). White matter microstructure predicts cognitive training-induced improvements in attention and executive functioning in schizophrenia. *Schizophrenia research*, 193, 276–283. <https://doi.org/10.1016/j.schres.2017.06.062>.

12. Smith, S., Jenkinson, M., Johansen-Berg, H., et al. (2006). Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *NeuroImage*, 31(4), 1487–1505.
<https://doi.org/10.1016/j.neuroimage.2006.02.024>.
13. Smith, S., Jenkinson, M., Woolrich, Mw, et al. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage* S208-19.
<https://doi.org/10.1016/j.neuroimage.2004.07.051>
14. McNally, M., Crocetti, D., Mahone, Em, et al., Corpus callosum segment circumference is associated with response control in children with attention-deficit hyperactivity disorder (ADHD). *Journal of child neurology* **2010**, 25 (4), 453–62. <https://doi.org/10.1177/0883073809350221>
15. Hung, Y., Uchida, M., Gaillard, S., et al. (2020). Cingulum-Callosal white-matter microstructure associated with emotional dysregulation in children: A diffusion tensor imaging study. *NeuroImage. Clinical*, 27, 102266. <https://doi.org/10.1016/j.nicl.2020.102266>.
16. Hofer, S., & Frahm, J., Topography of the human corpus callosum revisited—comprehensive fiber tractography using diffusion tensor magnetic resonance imaging. *NeuroImage* **2006**, 32 (3), 989–94. <https://doi.org/10.1016/j.neuroimage.2006.05.044>
17. Putnam Mc; Steven Ms; Doron Kw, et al., Cortical projection topography of the human splenium: hemispheric asymmetry and individual differences. *Journal of cognitive neuroscience* (2010). 22 (8), 1662-9. <https://doi.org/10.1162/jocn.2009.21290>
18. Onnink Am, Zwiers, M., Hoogman, M., et al. (2015). Deviant white matter structure in adults with attention-deficit/hyperactivity disorder points to aberrant myelination and affects neuropsychological performance. *Progress in neuro-psychopharmacology & biological psychiatry*, 63, 14–22. <https://doi.org/10.1016/j.pnpbp.2015.04.008>.
19. Nagel, B., Bathula, D., Herting, M., et al. (2011). Altered white matter microstructure in children with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 50(3), 283–292. <https://doi.org/10.1016/j.jaac.2010.12.003>.
20. Chowdhury, F., Haque, M., Sarkar, M., et al. (2010). White fiber dissection of brain; the internal capsule: a cadaveric study. *Turkish neurosurgery*, 20(3), 314–322. <https://doi.org/10.5137/1019-5149.jtn.3052-10.2>.
21. Valera Em; Spencer Rm; Zeffiro Ta, et al., Neural substrates of impaired sensorimotor timing in adult attention-deficit/hyperactivity disorder. *Biological psychiatry* (2010). 68 (4), 359-67. <https://doi.org/10.1016/j.biopsych.2010.05.012>
22. Martínez, K., Merchán-Naranjo, J., Pina-Camacho, L., et al. (2017). Atypical age-dependency of executive function and white matter microstructure in children and adolescents with autism spectrum disorders. *European child & adolescent psychiatry*, 26(11), 1361–1376.
<https://doi.org/10.1007/s00787-017-0990-2>.
23. Fryer Sl; Frank Lr; Spadoni Ad, et al., Microstructural integrity of the corpus callosum linked with neuropsychological performance in adolescents. *Brain and cognition* (2008). 67 (2), 225-33. <https://doi.org/10.1016/j.bandc.2008.01.009>

24. Bode, M., Lindholm, P., Kiviniemi, V., et al., DTI abnormalities in adults with past history of attention deficit hyperactivity disorder: a tract-based spatial statistics study. *Acta radiologica (Stockholm, Sweden: 1987)* **2015**, 56 (8), 990–6. <https://doi.org/10.1177/0284185114545147>
25. Evans Dw; Lazar Sm; Boomer Kb, et al., Social cognition and brain morphology: implications for developmental brain dysfunction. *Brain imaging and behavior* (2015). 9 (2), 264-74. <https://doi.org/10.1007/s11682-014-9304-1>
26. Peters, B., Szeszko, P., Radua, J., et al. (2012). White matter development in adolescence: diffusion tensor imaging and meta-analytic results. *Schizophrenia bulletin*, 38(6), 1308–1317. <https://doi.org/10.1093/schbul/sbs054>.
27. Vestergaard, M., Madsen, K., Baaré, Wf, et al. (2011). White matter microstructure in superior longitudinal fasciculus associated with spatial working memory performance in children. *Journal of cognitive neuroscience*, 23(9), 2135–2146. <https://doi.org/10.1162/jocn.2010.21592>.

Figures

Figure 1

Regions of significantly lower fractional anisotropy (FA) in the ADHD-group as compared to the HC-group ($q < 0.05$, FDR-corrected for multiple comparisons).

Green color indicates white matter skeleton where no significant results were found; red regions indicate where participants in the ADHD-group ($n = 57$) had significantly lower FA than those in the HC-group ($n = 41$). Arrows indicate the specific cluster of interest for each column. CC: corpus callosum; IFOF, Inferior fronto-occipital fasciculus.

Figure 2

Regions of significantly higher radial diffusivity (RD) in the ADHD-group than in the HC-group ($q < 0.05$, FDR-corrected for multiple comparisons).

Figure 3

Significant correlations between the hyperactivity index score and the mean FA value of the right CC splenium, left intersection of the anterior and posterior internal capsule, and inferior fronto-occipital fasciculus. The abscissa of the mean FA value was derived from every cluster and assessed for correlation with the clinical score. The hyperactivity symptom score was negatively correlated with the mean FA value of clusters 1–3. CC, corpus callosum; IFOF, inferior fronto-occipital fasciculus.

Figure 4

Significant correlations between the impulsivity score and mean FA value of the right CC splenium, left intersection of the anterior and posterior internal capsule, and inferior fronto-occipital fasciculus. The impulsivity score showed a negative correlation with the mean FA value of clusters 1–3. CC, corpus callosum; IFOF, inferior fronto-occipital fasciculus.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Checklist.docx](#)