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Anatomical substrates of symptom remission and persistence in young adults with childhood attention deficit/hyperactivity disorder

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Abstract

Attention deficit/hyperactivity disorder (ADHD) is a highly prevalent neurodevelopmental disorder that emerges in childhood and persists into adulthood in a sizeable portion of afflicted individuals. The persistence of ADHD symptoms elevates the risk of adverse outcomes that result in substantial individual and societal burden. The objective of this study was to delineate neuroanatomical substrates associated with the diversity of adult outcomes of childhood ADHD, which may have considerable value for development of novel interventions that target mechanisms associated with recovery. Structural MRI and diffusion tensor imaging data from 32 young adults who were diagnosed with ADHD combined-type during childhood and 35 group-matched controls were analyzed. Adults with childhood ADHD were divided into 16 remitters and 16 persisters based on DSM-IV criteria. Compared to the controls, ADHD probands showed significantly reduced gray matter (GM) volume in right putamen and white matter (WM) volume in left parieto-insular fiber tracts. Within the ADHD probands, the remitters, as compared to persisters, showed significantly greater volume of right hippocampo-frontal and right parieto-insular WM fiber tracts, and those connecting caudate with the frontal, parietal, occipital, temporal, and insular cortices. Among ADHD probands, increased fractional anisotropy value of left caudate-parietal tract was significantly correlated with reduced hyperactive/impulsive symptoms. These findings suggest that optimal structural development in the WM tracts that connect caudate with cortical areas,

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Contributors

Dr. Xiaobo Li designed the study. Yuyang Luo managed literature searches, analyzed the clinical and imaging data, and wrote the first draft of the manuscript. Drs. Li and Halperin edited and revised the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of Interest

All authors declare that they have no conflicts of interest.

especially in the caudate-parietal path, may play an important role in symptom remission in young adults with childhood ADHD.

Keywords

ADHD; Adult Outcome; Remission; Persistence; Magnetic Resonance Imaging (MRI); Diffusion Tensor Imaging (DTI)

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is one of the most commonly diagnosed neurodevelopmental disorders with a prevalence of approximately 9.5% in school-age children in the United States (Pastor, et al., 2015; Visser, et al., 2014). It is characterized by pervasive symptoms of inattentiveness, hyperactivity, and impulsivity, and a wide-range of behavioral and cognitive impairments in working memory, inhibitory control, and motivation (Sonuga-Barke, 2002). Approximately 65% of the children with ADHD have persistent impairing symptoms into adulthood, which elevates the risk of adverse outcomes linked to substantial individual and societal burden (Faraone, et al., 2006). Neural determinants of the diverse adult outcomes of childhood ADHD remain unknown. Elucidation of these mechanisms could set the stage for the development of novel interventions that yield enduring benefits and improve long-term outcomes.

A large number of existing studies suggest that ADHD symptoms in children are associated with widespread neuroanatomical and functional alterations of brain. Structural neuroimaging studies have found ADHD symptoms in childhood to be associated with decreased regional gray matter (GM) volume in frontal cortex, striatum and cerebellum (Bledsoe, et al., 2011; Ellison-Wright, et al., 2008; Mahone, et al., 2011). Reduced regional cortical GM thickness in frontal and parietal cortices have also been linked with ADHD symptoms (Almeida Montes, et al., 2013; Batty, et al., 2010). White matter (WM) structural deficits, especially reduced WM volume and/or fractional anisotropy (FA) in the fronto-parietal, fronto-limbic, corona radiate, cerebellar- and temporo-occipital, and internal capsule fiber tracts have been consistently demonstrated in children with ADHD (Durston, et al., 2004; Nagel, et al., 2011; Peterson, et al., 2011; Qiu, et al., 2011; Xia, et al., 2012). Additionally, a number of task-based functional MRI (fMRI) studies have reported significantly reduced task-responsive activation in frontal and parietal areas, dorsal anterior cingulate cortex (dACC), thalamus, and striatum in children with ADHD relative to the group-matched controls, when performing behavioral tasks that assess attentional and inhibitory control functions (such as the go/no-go task, stop signal task, continuous performance task, stroop task, etc) (Booth, et al., 2005; Durston, et al., 2007; Durston, et al., 2006; Durston, et al., 2003; Li, et al., 2013; Li, et al., 2012; Pliszka, et al., 2006; Smith, et al., 2006; Suskauer, et al., 2008). Significantly reduced activation in these cortical and subcortical regions have also been consistently reported in children with ADHD relative to controls, when performing tasks assessing working memory, decision making, reward processing, and interference control functions (Cao, et al., 2008; Konrad, et al., 2006; Vaidya, et al., 2005; Vance, et al., 2007). A meta-analysis of 55 task-based fMRI studies

reported significantly decreased activation in frontoparietal and ventral attentional networks in children with ADHD, compared to the group-matched controls (Cortese, et al., 2012).

The majority of existing clinical and neuroimaging studies in ADHD have focused on understanding the neural correlates of symptoms in cross-sectional samples of children or young adults. Far fewer studies have examined neural substrates associated with the diverse adult outcomes of childhood ADHD. Compared to group-matched controls, Schneider et al. reported that adults with childhood ADHD showed significantly reduced activation in caudate, ACC, parietal regions, and increased activation in insular during cognitive control processing, with these functional anomalies positively associated with increased levels of inattentive and hyperactive/impulsive symptoms (Schneider, et al., 2010). In a sample of children with ADHD followed into adulthood, Schulz et al. found lower orbitofrontal, inferior frontal, anterior cingulate and parietal activation in probands with persistent ADHD relative to both probands with remitted ADHD and comparison subjects, with no differences between remitters and comparison subjects (Schulz, et al., 2017). In the same longitudinal sample of adults with childhood ADHD, Clerkin et al. found lower thalamo-frontal functional connectivity in the ADHD persisters relative to remitters during a cued-reaction time task (Clerkin, et al., 2013); and Luo et al. further depicted decreased nodal efficiency in middle frontal gyri (MFG) in the functional brain network for cue-evoked attention processing in the ADHD persisters relative to the remitters (Luo, et al., 2018). Finally, resting-state fMRI studies found that higher fronto-ACC connectivity in the executive control network may contribute to symptom reduction in adults with childhood ADHD (Francx, et al., 2015; Mattfeld, et al., 2014).

Neuroanatomical studies showed diverse results in adults with childhood ADHD. With structural MRI, Proal et al. found that compared to matched controls, ADHD probands had significantly decreased GM volume in prefrontal lobe, cerebellum, thalamus, and caudate, regardless of ADHD symptom remission or persistence (Proal, et al., 2011); while Shaw et al. showed that significantly reduced cortical thickness was linked with symptom persistence (Shaw, et al., 2013). A diffusion tensor imaging (DTI) study suggested that ADHD probands had WM disruptions in the superior longitudinal fasciculus (SLF) and cortico-limbic areas regardless of symptom remission or persistence (Gehricke, et al., 2017); another study found that greater adult inattentiveness, but not hyperactivity/impulsivity, was associated with lower FA in inferior occipito-frontal fasciculus and uncinated fasciculus (Shaw, et al., 2015); while Cortese et al. indicated no significant WM differences between the ADHD-remitters and -persisters (Cortese, et al., 2013). The inconsistent findings from these neuroimaging studies in adults with childhood ADHD may be partially explained by differences in imaging modalities, analytic methods, and study cohorts. These existing studies have demonstrated neuroanatomical alterations in adults with childhood ADHD. However, most of them applied only single imaging modality (either structural MRI or DTI) to investigate GM morphometrical or WM integrity properties, without reporting both the GM and WM patterns in the same study cohort, and their potential impact on the adult outcome of childhood ADHD. This study aimed to fill this gap by applying both structural MRI and DTI in the same study sample to identify the structural markers in GM and WM, that are associated with symptom persistence and remission in young adults with childhood ADHD. Based on findings of previous studies from our group and others, we hypothesized that more

optimal structural development associated with the frontal and parietal lobes, such as greater regional GM thickness, higher FA of the WM tracts that connect subcortical structures (i.e. thalamus, caudate) and frontal/parietal cortices, may play an important role in symptom remission in young adults with childhood ADHD.

METHOD

Participants

The initial sample consisted of 106 young adults who had been clinically followed since childhood, including 60 probands who were diagnosed with ADHD combined-type (ADHD-C) when they were 7 – 11 years of age and 46 group-matched comparison subjects with no history of ADHD. Among the 60 ADHD probands, 16 were classified as ADHD persisters (ADHD-P) and 16 as ADHD remitters (ADHD-R), and were able to provide usable T1-weighted and DTI data. Those adults with ADHD-P endorsed at least five inattentive and/or hyperactive/impulsive symptoms and had a minimum of 3 symptoms in each domain. Those classified as ADHD-R endorsed no more than 3 inattentive or 3 hyperactive/impulsive symptoms in adulthood and had no more than 5 symptoms in total, to allow separation from the ADHD-P group.

Among the 46 young adults who were previously classified as non-ADHD, 35 had no more than three inattentive or hyperactive/impulsive symptoms and provided usable clinical and neuroimaging data. Therefore, 67 subjects (32 ADHD proband and 35 controls) were included in group-level clinical and neuroimaging data analyses.

Childhood diagnoses were based upon teacher ratings using the IOWA Conners' Teachers Rating Scale (Loney and Milich, 1982) and parent interview using the Diagnostic Interview Schedule for Children version 2 (Shaffer, et al., 1989). The exclusion criteria in childhood were chronic medical illness; neurological disorder; diagnosis of schizophrenia, autism spectrum disorder, or chronic tic disorder; Full Scale IQ < 70; and not speaking English. The social economic status (SES) of each child was assessed using the Nakao-Treas Socioeconomic Prestige Index (Nakao and Treas, 1994).

Adult psychiatric status was assessed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First, et al., 2002), supplemented by a semi-structured interview for ADHD that was adapted from the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K- SADS) (Kaufman, et al., 1997) and the Conners' Adult ADHD Diagnostic Interview for DSM-IV (Epstein, et al., 2006). Exclusion criteria in adulthood were psychotropic medication that could not be discontinued and conditions that would preclude MRI (e.g., metal in body, pregnancy, too obese to fit in scanner). Clinical and demographic information are listed in Table 1.

All the ADHD probands had a history of treatment with short-acting psychostimulants. Mean duration of treatment was 2.03 years (SD = 3.21) for the subgroup of ADHD-R and 4.18 years (SD = 4.12) for the subgroup of ADHD-P ($t = -1.604$, $p = 0.12$). There were two subjects in the ADHD-P subgroup who were taking psychostimulants at the time of this study, and had a 48-hour medication wash-out period before MRI acquisition.

The study received Institutional Review Board Approval at the participating institutions. Participants provided signed informed consent and were reimbursed for their time and travel expenses.

MRI acquisition protocol

High resolution 3-dimensional T1-weighted structural MRI and DTI data were acquired using the same 3T Siemens Allegra (Siemens, Erlangen, Germany) head-dedicated MRI scanner. T1-weighted data was acquired using magnetization prepared rapid gradient echo (MPRAGE) pulse sequence with the following parameters: repetition time (TR) = 2.5 s, echo time (TE) = 4.38 ms, inversion time (TI) = 1.1 s, flip angle = 8°, voxel size = 0.94 mm × 0.94 mm × 1 mm, field of view (FOV) = 256 mm × 256 mm × 256 mm. DTI data was acquired using an echo planar imaging (EPI) pulse sequence with a b-value = 1250 s/mm^2 along 12 independent, as well as a reference volume without diffusion-weighting b = 0 s/mm^2, non-collinear orientations with the following parameters: TR = 5.2 s, TE = 80 ms, flip angle = 90°, voxel size = 1.875 mm × 1.875 mm × 4 mm, FOV = 128 mm × 128 mm, imaging matrix = 128 × 96, number of slices = 63.

Individual-level structural MRI data analyses

T1-weighted data were reconstructed into a 3-dimensional cortical model for thickness and area estimations using FreeSurfer v.5.3.0 (https://surfer.nmr.mgh.harvard.edu). Each data point was first registered with the Talairach atlas to compute the transformation matrix using an affine registration method, which was developed and distributed by the Montreal Neurological Institute (MNI). Then intensity variations caused by magnetic field inhomogeneities were corrected using Voronoi partitioning algorithm. The skull was stripped using a deformable template model. Cutting planes were defined to separate the left and right hemispheres and to remove the cerebellum and brainstem. Two mess surfaces (mess of grids created using surface tessellation technique) were then generated between WM and GM (white matter surface), as well as between GM and cerebrospinal fluid (pial surface). The distance between the two closest vertices of the white matter and pial surfaces presented the cortical thickness at that specific location, validated using training data (Rosas, et al., 2002). Regional cortical thickness and area in 68 bilateral cortical regions were estimated based on the Desikan atlas (Desikan, et al., 2006).

Each of 37 subcortical structures/nuclei was first labelled after the initial registration with the Talairach atlas, and then refined based on a manually labelled model constructed according to prior knowledge of spatial relationships acquired with a training data set (Fischl, et al., 2002). Volume of each subcortical structure was then calculated.

To adjust head-size variation related influence on these cortical and subcortical GM measures, the head-size scaling factor of each subject was calculated by normalizing the T1-weighted data with the template provided in FSL/SIENA (Smith, et al., 2002). The normalized thickness and area of each cortical region and volume of each subcortical structure were finally estimated by multiplying the original value with the scaling factor of that subject.

Individual-level DTI data analyses

DTI data from each subject was first processed using the Diffusion Toolbox (FDT Version 3.0) from FSL (Behrens, et al., 2007). After eddy current and head motion corrections, the diffusion-weight images were registered to the additionally acquired non-diffusion-weighted reference image (b0 image) using an affine, 12 degrees of freedom registration. The FA value and principle diffusion direction at each brain voxel were calculated. WM probabilistic tractography between each pair of 18 regions-of- interest (ROIs) was constructed using the FSL/BEDPOSTX toolbox (Behrens, et al., 2007). These 18 ROIs (including thalamus, putamen and caudate nuclei from striatum, hippocampus, and frontal, parietal, occipital, temporal, and insular cortices in both hemispheres) were created based on the Harvard-Oxford Cortical Atlases and the Julich Histological Atlas from the MNI standard space, and mapped to the DTI data. We used the multi-fiber probabilistic connectivity-based method to determine the number of pathways between each seed and target ROIs. The default setting of parameters for Markov Chain Monte Carlo estimation of the probabilistic tractography was utilized: 5000 individual pathways were drawn on the principle fiber direction of each voxel within the seed ROI; curvature threshold of 80° to exclude implausible pathways; a maximum number of 2000 travel steps of each sample pathway and a 0.2 mm step length. The number of pathways that existed through each voxel from the remainder of the brain was labeled. The non-zero labeling voxels were taken as the initial elements of the tracts between the seed and target ROIs. The brain voxels with low probability of connection were removed from the tract, if one had a number of pathways that was less than the average of the pathway numbers from all the non-zero labeling voxels. A total of 20 cortico-cortical (including bilateral fronto-parietal, fronto-occipital, fronto-temporal, fronto-insular, parieto-occipital, parieto-temporal, parieto-insular, occipito-temporal, occipito-insular, temporo-insular) and 40 subcortico-cortical (including bilateral thalamo-frontal, thalamo-parietal, thalamo-occipital, thalamo-temporal, thalamo-insular, putamen-frontal, putamen-parietal, putamen-occipital, putamen-temporal, putamen-insular, caudate-frontal, caudate-parietal, caudate-occipital, caudate-temporal, caudate-insular, hippocampo-frontal, hippocampo-parietal, hippocampo-occipital, hippocampo-temporal, hippocampo-insular) WM fiber tracts were generated. Average FA and volume (number of voxels times voxel size) of each identified WM tract were estimated.

Group statistical analyses

The clinical, neurocognitive and demographic measures were compared using chi-square tests for discrete variables and unpaired two-sample t-tests for continuous variables, between groups of controls and ADHD probands, and further between the two ADHD subgroups (ADHD-R and ADHD-P) using SPSS18 (SPSS Inc, Somers, NY).

The structural MRI- and DTI-based neuroimaging measures (including regional cortical thickness, surface area, volume of each subcortical structure, FA and volume of each WM fiber tract) were compared between the groups of controls and ADHD probands, as well as between the subgroups of ADHD-R and ADHD-P, using analysis of covariance (ANCOVA) with gender, age, IQ and SES as covariates. Bonferroni correction for multiple comparisons (at a corrected $\alpha = 0.05$) was applied to control potential false positive results of these group comparisons. For group comparisons in the structural MRI-based measures, we controlled

alpha for 105 ROIs (i.e., 68 bilateral cortical regions and 37 subcortical structures). For the DTI-based measures, we controlled alpha for the 60 WM tracts analyzed. The brain-behavior association analyses controlled for the 18 partial correlation procedures conducted.

Partial correlation analysis was utilized to assess associations between the GM and WM brain measures that showed between-group differences (measures listed in Tables 2 and 3) and the clinical symptom measures (the raw scores for inattentive and hyperactive-impulsive symptoms derived from the CAARS collected during the visit of MRI scan) in the group of ADHD probands. Age, gender, IQ and SES were added as covariates. Bonferroni correction was used to correct the number of partial correlation procedures (a total of 16) at a corrected $\alpha = 0.05$.

RESULTS

As shown in Table 1, there were no significant demographic differences between the groups although relative to controls, ADHD probands tended to have lower IQ and SES.

Significantly decreased volume in right putamen was observed in ADHD probands when compared to controls ($p = 0.045$). Compared to the ADHD-P group, those with ADHD-R showed significantly increased cortical surface area in bilateral parahippocampal gyri (Left: $p = 0.05$; Right: $p = 0.008$), left paracentral gyrus ($p = 0.012$), and right transverse temporal gyrus ($p = 0.037$) (see Table 2). Group comparisons of the WM measures showed significantly decreased volume of the left parieto-insular fiber tract ($p = 0.041$) in ADHD probands relative to controls. Compared to ADHD-R, the subgroup of ADHD-P showed significantly decreased volume in two cortico-cortical fiber tracts (right hippocampo-frontal ($p = 0.037$) and right parieto-insular ($p = 0.038$)), and in the WM tracts connecting bilateral caudate nuclei of the striatum with all the five cortical ROIs of the same hemispheres ($p < 0.001$) (see Table 3).

Dimensional analyses between the GM and WM measures (listed in Tables 2 and 3) and the clinical symptom measures indicated that among the ADHD probands, greater FA of the left caudate-parietal WM fiber tract was significantly associated with reduced hyperactive/impulsive symptoms (Figure 1, $r = -0.402$, $p = 0.031$).

DISCUSSION

The present study investigated GM and WM structural differences between young adults with childhood ADHD and group-matched controls, and between the subgroups of remitters and persisters within the ADHD probands. Compared to controls, significantly reduced GM volume of the putamen in right hemisphere was observed in the ADHD probands. The putamen and caudate nucleus together form the dorsal striatum, and play a key role in the cortico-thalamo-striatal-cortical (CTSC) loops for attention and higher order cognitive processes (Alexander, et al., 1986; Ring and Serra-Mestres, 2002). A large number of structural MRI and fMRI studies have reported the linkage of putamen-related anatomical and functional abnormalities and onset of ADHD in children (Ellison-Wright, et al., 2008; Frodl and Skokauskas, 2012; Max, et al., 2002; Nakao, et al., 2011). Putamen-related structural alterations have also been tested in neuroimaging studies focusing on adults with

ADHD which yielded inconsistent results, with some reports of reduced putamen volume in adults with ADHD (Onnink, et al., 2014; Seidman, et al., 2011), and others reporting increased putamen volume (Greven, et al., 2015) or no significant differences (Seidman, et al., 2006) when compared to group-matched controls. The inconsistency of these existing studies may have been caused by technical differences for putamen extractions, and sample-related biases such as the very wide age ranges involved in these studies (Greven, et al., 2015). Adding to the literature, our result of significantly reduced putamen GM volume in young adults with childhood ADHD (regardless of their clinical outcomes) suggests its significant linkage with the emergence of ADHD during their childhood.

Compared to controls, we also found that the ADHD probands had significantly reduced volume of the left hemisphere parieto-insular WM tract; while relative to the ADHD remitters, the persisters had significantly smaller volume of the right hemisphere parieto-insular WM tract. The parieto-insular WM fiber tract is an important structural component of the vestibular system, and has been suggested to link with static and dynamic balance control (Frank and Greenlee, 2018; Perennou, et al., 2000; Shum and Pang, 2009; Ustinova, et al., 2001). Vestibular system deficiency, which can cause inappropriate postural condition or impaired balance function, has been found to be associated with cognitive deficits and behavioral symptoms in ADHD patients (Clark, et al., 2008; Haghshenas, et al., 2014; Shum and Pang, 2009). Merging with the results of existing studies, our findings of the underdeveloped parieto-insular WM fiber tracts in adults with childhood ADHD, especially in those with persistent ADHD symptoms, suggest that parieto-insular WM structural alterations may interact with the vestibular system functional alterations, and together contribute to the onset and symptom persistence of ADHD.

Within the probands, we further found that the ADHD remitters had significantly larger surface area in bilateral parahippocampal, left paracentral, and right transverse temporal gyri, as well as significantly greater volume of WM fiber tracts connecting caudate with the frontal, parietal, occipital, temporal, and insular cortices when compared to the persisters. Existing studies have reported that ADHD remitters had increased parahippocampal cortical thickness compared to ADHD persisters (Proal, et al., 2011). Further studies have implicated that parahippocampal gyrus interacts with the ventralateral prefrontal cortex (VLPFC), both significantly contribute to appropriate inhibitory control (Deacon, et al., 1983; Schulz, et al., 2005). Parahippocampal cortical volume reduction has been observed in both children and adolescents with ADHD, compared to group-matched controls (Carmona, et al., 2005; Noordermeer, et al., 2017).

Caudate plays a critically important role in cognitive control (Chiu, et al., 2017; Grahn, et al., 2008). Structural and functional deficits associated with caudate have been widely observed in children and adults with ADHD (Frodl and Skokauskas, 2012; Onnink, et al., 2014; Szekely, et al., 2017). Substantial structural MRI studies have revealed that children with ADHD had smaller caudate volume relative to controls (Castellanos, et al., 2002). Task-based fMRI studies showed significantly decreased caudate activation in children with ADHD (Vaidya, et al., 2005) and adults with childhood ADHD (Szekely, et al., 2017), during attention and inhibitory control processes. Our findings of significantly smaller volume of the WM fiber tracts connecting caudate with all five cortices bilaterally in the

ADHD persisters suggest that caudate-associated widespread WM underdevelopment may play important roles in symptom persistence of ADHD. This hypothesis can also be supported by multiple existing DTI studies that showed immature WM organizations involving caudate and cortical structures in children and adults with ADHD (Ashtari, et al., 2005; Casey, et al., 1997; Castellanos, et al., 2002; Shang, et al., 2013).

In addition, we found that the FA of left caudate-parietal tracts was significantly negatively correlated with the CAARS raw score for hyperactive/impulsive symptoms in ADHD probands. The caudate-parietal WM tract is one of the most important structural component of the CTSC loops, which subserves maintaining the modifications of spatial attention via reinforcement learning, and supports the integration of reward, attention, and executive control (Jarbo and Verstynen, 2015). Reduced parietal activation during cognitive control has been linked to the persistence of ADHD symptoms in adults with childhood ADHD (Schulz, et al., 2017; Szekely, et al., 2017). Reduced caudate and parietal lobe activation during inhibitory control processing were found to be associated with increased inattentive and impulsive symptoms in adults with ADHD diagnosed in childhood (Schneider, et al., 2010). Together with these existing findings, we suggest that optimal structural development in the caudate-parietal WM tract may partially modulate the functional integrity of caudate and parietal cortex, and together contribute to symptom remission in adults with childhood ADHD.

In summary, together with existing findings, results of this study suggest that WM structural development in tracts that connect caudate with cortical areas, especially in the caudate-parietal path, is a critical determining factor of outcomes in adults with childhood ADHD. The current study has some limitations. First, our cohort consisted of both male and female subjects, but many more males. It is still unclear whether the neuropathological underpinnings of ADHD differ between males and females. To partially remove gender-related effects, sex was added as a fixed effect covariate in the group-level analyses. Second, the sample size of this study is relatively small. Therefore, the findings must be considered preliminary. Future work will need a much larger cohort from a longitudinal study consisting of multi-scan neuroimaging data, to determine the neural underpinnings of longitudinal trajectories of childhood ADHD.

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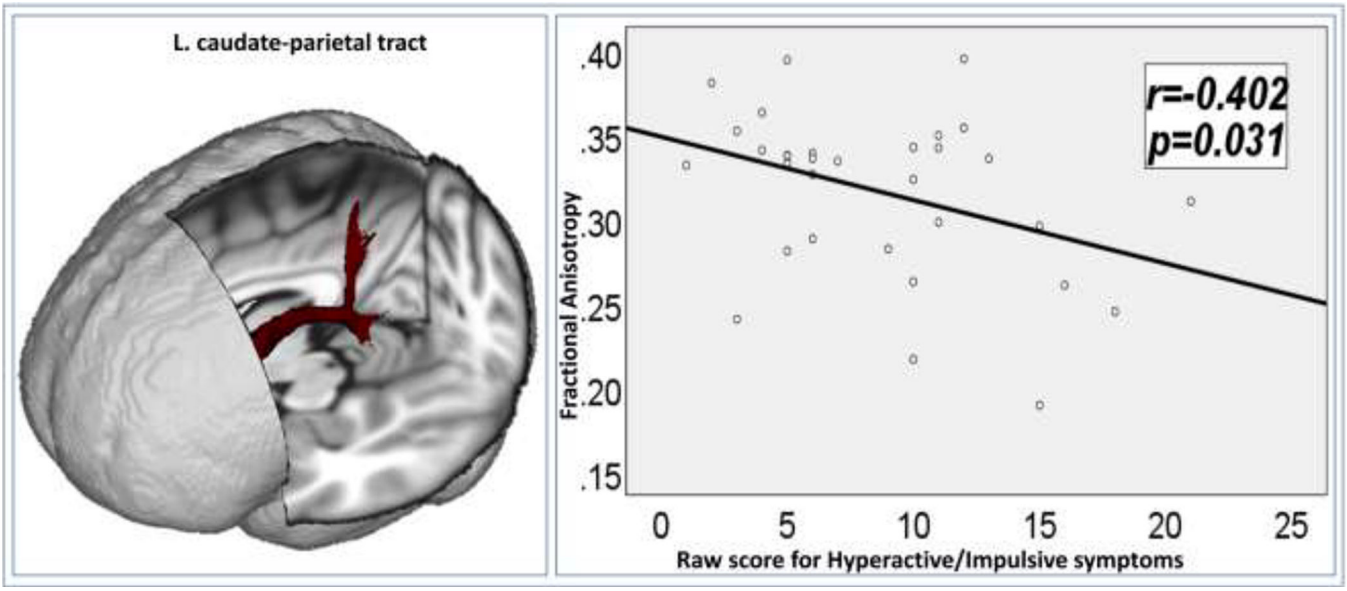

Figure 1:

In the group of ADHD probands, greater fractional anisotropy of the left caudate-parietal white matter fiber tract was significantly associated with reduced hyperactive-impulsive symptoms.

Table 1:

Demographical, neurocognitive and clinical characteristics in groups of controls and ADHD probands (including ADHD remitters and persisters).

	Controls (N = 35)	**ADHD (N = 32)**		**Remitters (N=16)**	**Persisters (N=16)**	
	Mean (SD	**Mean (SD)**	***P***	**Mean (SD)**	**Mean (SD)**	***p***
Age	24.24 (2.3)	24.60 (2.1)	*0.51*	24.81 (2.3)	24.39 (1.9)	*0.57*
Full-scale IQ	104.21 (15)	96.81 (14.3)	*0.07*	99.58 (14.2)	94.11 (11.5)	*0.24*
Socioeconomic status	51.59 (14.8)	43.73 (17.2)	*0.06*	43.28 (14.9)	40.56 (19.8)	*0.57*
CAARS (raw score)						
Inattentive	4.03 (3.5)	8.09 (5.1)	*<0.001*	5.75 (4.9)	10.44 (4.3)	*0.007*
Hyperacitive/impuls	4.58 (2.6)	8.66 (4.9)	*<0.001*	5.88 (3.8)	11.44 (4.3)	*0.001*
ADHD Total	8.82 (5.2)	16.59 (9.2)	*<0.001*	11.94 (8.2)	21.25 (7.9)	*0.003*
	N (%)	N (%)	*P*	N (%)	N (%)	*P*
Male	30 (85.7)	27 (84.4)	*0.88*	14 (87.5)	13 (81.3)	*0.63*
Right-handed	31 (88.6)	28 (87.5)	*0.89*	14 (87.5)	14 (87./5)	*1*
Race			*0.41*			*0.70*
Caucasian	14 (40.0)	17 (53.1)		8 (50.0)	9 (56.3)	
African American	13 (37.1)	7 (21.9)		4 (25.0)	3 (18.8)	
More than one race	6 (17.1)	8 (25)		4 (25.0)	4 (25.0)	
Asian	2 (5.7)	0 (0)		0 (0)	0 (0)	
Ethnicity			*0.21*			*0.72*
Hispanic/Latino	12 (34.3)	15 (46.9)		7 (43.8)	8 (50.0)	

CAARS: Conners' Adult ADHD Rating Scale

Table 2:

Gray matter neuroimaging measures that show significant between-group differences with age, gender, IQ and social economic status as covariates.

Group	Anatomical location	Measure	F-value	*p*-value after Bonferroni correction
CON > PRO	R. Putamen	Volume	8.892	*0.045*
ADHD-R > ADHD-P	L./R. Parahippocampal gyrus	Regional Cortical Surface Area	7.921/12.947	*0.05/0.008*
	L. Paracentral gyrus		12.283	*0.012*
	R. Transverse temporal gyrus		8.494	*0.037*

CON: group of controls; PRO: group of ADHD probands; ADHD-R: subgroup of ADHD remitters; ADHD-P: subgroup of ADHD persisters. L.: left hemisphere; R.: right hemisphere; *p* values were corrected using Bonferroni correction.

Table 3:

White matter neuroimaging measures that show significant between-group differences with age, gender, IQ and social economic status as covariates.

Group	White matter fiber tract	Measure	F-value	*p*-value after Bonferroni correction
CON > PRO	L. parieto-insular tract	Volume	9.928	*0.041*
ADHD-R > ADHD-P	L./R. caudate-frontal tracts	Volume	42.755/32.576	*<0.001/<0.001*
	L./R. caudate-parietal tracts		51.553/31.62	*<0.001/<0.001*
	L./R. caudate-occipital tracts		55.169/31.593	*<0.001/<0.001*
	L./R. caudate-temporal tracts		55.088/31.564	*<0.001/<0.001*
	L./R. caudate-insular tracts		55.155/31.527	*<0.001/<0.001*
	R. hippocampo-frontal tract		13.228	*0.037*
	R. parieto-insular		12.785	*0.038*

CON: group of controls; PRO: group of ADHD probands; ADHD-R: subgroup of ADHD remitters; ADHD-P: subgroup of ADHD persisters. L.: left hemisphere; R.: right hemisphere; *p* values were corrected using Bonferroni correction.