Research Paper

Functional dysconnectivity of corticostriatal circuitry and differential response to methylphenidate in youth with attention-deficit/hyperactivity disorder

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Background: Brain frontostriatal circuits have been implicated in the pathophysiology of attention-deficit/hyperactivity disorder (ADHD). However, effects of methylphenidate on circuit-level functional connectivity are as yet unclear. The aim of the present study was to comprehensively investigate the functional connectivity of major striatal subregions in children with ADHD, including subanalyses directed at mapping cognitive and treatment response characteristics. **Methods:** Using a comprehensive seeding strategy, we examined resting-state functional connectivity of dorsal and ventral subdivisions of the caudate nucleus and putamen in children and adolescents with ADHD and in age- and sex-matched healthy controls. **Results:** We enrolled 83 patients with ADHD and 22 controls in our study. Patients showed significantly reduced dorsal caudate functional connectivity with the superior and middle prefrontal cortices as well as reduced dorsal putamen connectivity with the parahippocampal cortex. These connectivity measures were correlated in opposite directions in patients and controls with attentional performance, as assessed using the Continuous Performance Test. Patients showing a good response to methylphenidate had significantly reduced ventral caudate/nucleus accumbens connectivity with the inferior frontal cortices compared with poor responders. **Limitations:** Possible confounding effects of age-related functional connectivity change were not excluded owing to the wide age range of participants. **Conclusion:** We observed a region-specific effect of methylphenidate on resting-state functional connectivity, suggesting the pretreatment level of ventral frontostriatal functional connectivity as a possible methylphenidate response biomarker of ADHD.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a highly prevalent neurobehavioural disorder in children and adolescents, which frequently persists into adulthood and manifests with symptoms of inattention and/or hyperactivity and impulsivity.[1] The neurobiological mechanisms of ADHD reportedly involve abnormalities of frontal and striatal regions,[2] and a frontostriatal model of ADHD has been supported by a large number of structural and functional MRI (fMRI) studies.[3] However, discrepancies exist regarding the primacy of specific frontostriatal circuits in individuals with ADHD.[2] Whether the dorsal and ventral frontostriatal circuits, which have been largely related to cognitive control and reward processing, respectively,[2,4] should be equivalently considered in the pathophysiology of ADHD remains to be clarified.[3,5]

Resting-state fMRI is a powerful technique for mapping neural networks connecting different functional units of the brain.[6,7] This intrinsic functional architecture can be easily detected during rest,[8] is consistent and reliable,[9,10] appears to be under genetic influences,[11,12] and has been proposed as a useful method for identifying psychiatric endophenotypes.[13–16] Resting-state functional connectivity studies of ADHD have suggested that the dorsal frontal network may be more strongly implicated than the ventral counterpart.[17] Recently, however, Posner and colleagues[18] reported that children with ADHD have reduced resting-state functional connectivity in both of the 2 distinct neural systems: the executive attention system including the dorsolateral prefrontal cortex and dorsal caudate nucleus, and the emotional regulation system including the ventromedial prefrontal and orbitofrontal cortices and ventral striatum, as posited by the

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dual pathway model of ADHD.[19,20] In contrast, Costa Dias and colleagues[21] reported that resting-state functional connectivity between the ventral striatum and ventromedial prefrontal cortex was increased in children with ADHD compared with control children. Another line of research has focused on the altered connectivity of the default mode network,[22,23] a set of brain regions showing strongly correlated neural activity during rest, where the ventromedial rather than the dorsolateral area of the prefrontal cortex is implicated.[24,25] On the other hand, few studies have applied resting-state fMRI to investigate the neural network correlates of treatment response for ADHD.[26] There is some evidence that psychostimulants modulate task-related activation in inferior frontal regions,[27–29] suggesting a therapeutic action on ventral frontostriatal systems, although the effects of established treatments, such as methylphenidate, on circuit-level functional connectivity are as yet unclear.

In the present study, we investigated the commonalities and differences of frontostriatal functional connectivity involved in either the diagnosis of ADHD or its response to methylphenidate. We hypothesized that dorsal frontostriatal connectivity would be more strongly implicated in the diagnosis of ADHD. In addition, we examined whether pretreatment differences in dorsal or ventral frontostriatal functional connectivity were related to methylphenidate response. We hypothesized that ventral frontostriatal connectivity might be more strongly implicated in the therapeutic response to methylphenidate.

Methods

Participants

We recruited children and adolescents with ADHD from the Seoul National University Hospital in Korea. We excluded patients with ADHD who had an IQ below 70; past or ongoing tic disorder, obsessive–compulsive disorder, language disorder, learning disorder, convulsive disorder, pervasive developmental disorder, schizophrenia, bipolar disorder or brain damage; history of taking stimulants or atomoxetine longer than 6 months; or a recent history of taking stimulants or atomoxetine over the last 4 weeks.

We recruited healthy controls using the same criteria as above, but we also excluded those with past or ongoing history of ADHD. The healthy controls did not participate in the methylphenidate trial of the present study. The institutional review board for human subjects at the Seoul National University Hospital approved our study protocol. Detailed information about the study was given to parents and children, and written informed consent was obtained before study entry, according to the Declaration of Helsinki.

Diagnostic and clinical evaluations

We assessed the presence of ADHD and other psychiatric diagnoses among the patients and controls using a semistructured diagnostic interview, the Kiddie-Schedule for Affective Disorders and Schizophrenia — Present and Lifetime Version.[30,31] Level of attention and response inhibition was assessed in both groups using a standardized visual version of the computerized Continuous Performance Test (CPT).[32,33] Omission errors and commission errors are measures of inattention and impulsivity, respectively. We determined the IQ of the participants using the abbreviated form of the Korean Educational Development Institute's Wechsler Intelligence Scales for Children.[34]

Methylphenidate administration and definition of treatment response

The patients with ADHD were enrolled in an 8-week, open-label trial of methylphenidate. Initial doses of methylphenidate were subsequently adjusted every 2 weeks until sufficient therapeutic effects were achieved, and then the doses were maintained for the remainder of the 8 weeks. This study was part of a registered clinical trial (ClinicalTrials.gov; NCT01912352).

We used the Clinical Global Impression–Improvement Scale (CGI-I) to rate the overall symptom improvement of a disorder on a 7-point scale ranging from 1 (much improved) to 7 (much worse).[35] In this study, the CGI-I was rated after 8 weeks by psychiatrists (S.-B.H. and J.-W.K.) who were blind to the participants' genotype. This measure has been frequently used in ADHD studies, including those designed to assess treatment response.[36,37] We considered patients with ADHD who had a CGI-I score of 1 or 2 at the end of the eighth week of methylphenidate treatment to be good responders; the remaining patients were considered poor responders. The scale was applied by the clinicians (S.-B.H. and J.-W.K.) who treated the patients. In a previous study, a strong interrater reliability was demonstrated in a different sample.[37]

Image acquisition and processing

Whole-brain echo-planar imaging (EPI) was conducted on a 3 T Siemens scanner (Siemens Magnetom Trio Tim Syngo MR B17) with the following parameters: repetition time 3000 ms, echo time 40 ms, acquisition matrix 126×126, field of view 240×240 mm^2, flip angle 90°, voxel size $1.9 \times 1.9 \times 4.0$ mm^3, 35 slices. The total time of the acquisition was 6 minutes, 24 seconds. Participants were instructed to relax, stay awake and lie still with their eyes closed. Head motion was minimized by filling the empty space around the head with sponge material and fixing the lower jaw with tape.

Imaging data were processed on a Linux platform running MATLAB version 7 (MathWorks). Preprocessing was performed using statistical parametric mapping software (SPM8). Motion correction was performed by aligning (within participant) each time series to the first image volume using a least squares minimization and a 6-parameter (rigid body) spatial transformation. Translation and rotation estimates were required to be less than 2 mm or 2°, respectively, for all participants. We also tested 4 head motion parameters, as recently suggested.[38] Data were normalized to the standard EPI template in Montreal Neurological Institute (MNI) space (resliced to 2 mm isotropic resolution). Functional images were

smoothed using a Gaussian filter (full-width at half-maximum, 8 mm). All image sequences were routinely inspected for potential normalization artifacts.

Characterizing striatal regions of interest

We used a previously validated approach to characterize the functional connectivity of dorsal and ventral areas of the caudate nucleus and putamen.[39–41] Following Harrison and colleagues,[40,41] we defined 4 regions of interest (ROIs) along a dorsal–ventral axis. For the caudate nucleus, a horizontal plane at stereotactic coordinate $z = 7$ mm distinguished the dorsal caudate ($x = \pm 13$, $y = 15$, $z = 9$) from the ventral caudate/nucleus accumbens ($x = \pm 9$, $y = 9$, $z = –8$). For the putamen, a plane at $z = 2$ mm distinguished the dorsal-caudal putamen ($x = \pm 28$, $y = 1$, $z = 3$) from the ventro-rostral putamen ($x = \pm 20$, $y = 12$, $z = –3$). To reproduce the finding of segregated dorsal and ventral striatal functional connectivity maps,[41] intermediate seeds (of no-interest) were defined in the mid caudate ($x = \pm 10$, $y = 15$, $z = 0$) and dorsal-rostral putamen ($x = \pm 25$, $y = 8$, $z = 6$). For each striatal location, seeds were defined in both hemispheres as 3.5 mm radial spheres (sampling approximately 25 voxels in 2 mm isotropic space) with a minimum Euclidean distance requirement of 8 mm between any 2 regions.[39] This was performed using the MarsBaR ROI toolbox in MNI stereotaxic space.[42]

Signals of interest were then extracted for each region by calculating their mean value across the time series within participants. In addition, we derived estimates of white matter, cerebrospinal fluid and global brain signal fluctuations to include in subsequent regression analyses. Participants' segmented white matter and cerebrospinal fluid images were thresholded at 50% tissue probability type and binarized to create nuisance variable masks, together with a binary mask of the global brain volume (summed from the grey matter, white matter and cerebrospinal fluid segments). We then extracted nuisance signals for each mask by calculating the mean value across the time series. These covariates remove noise-related variance and increase the anatomic specificity of functional connectivity patterns.[43,44] As global signal correction can introduce artifactual negative correlations between regions,[43,45] we restricted our analysis to positive striatal functional connectivity.

First-level, within-subjects analyses

We estimated functional connectivity maps for each participant by including the striatal regions and nuisance signals as predictors of interest/no interest in whole brain, linear regression analyses in SPM8. We carried out these analyses for each hemisphere separately. A high-pass filter set at 128 seconds was used to remove low frequency drifts below approximately 0.008 Hz. Prior to model estimation, each of the 3 nuisance covariates were orthogonalized (using an iterative Gram–Schmidt method) and then removed from each region's time series by linear regression, resulting in a general linear model that comprised the "noise-cleaned" regions and 3 orthogonal nuisance variables.[41] We generated contrast images for each participant by estimating the regression coefficient between all brain voxels and each region's time series, respectively.

Second-level, between-group analyses

For each striatal region, participants' contrast images were included in group-wise random-effects analyses adopting a 2 × 2 mixed design factorial model (group [controls, patients] × hemisphere [right, left]), adjusting for age, sex and IQ. Within-group statistical maps were thresholded at a false-discovery rate (FDR) of $p_{FDR} < 0.05$ for the whole brain volume and displayed with a minimum cluster extent (K_E) of 8 voxels. To identify between-group differences in striatal functional connectivity, we used a cluster-wise corrected threshold of $p < 0.05$ determined using the AlphaSim[46] permutation procedure implemented in the REST toolbox.[47] The simulations were run with a primary cluster-forming threshold of $p < 0.01$, uncorrected, 2000 permutations, and a search volume defined by the union of significant within-group effects for patients and controls (i.e., large representative image masks capturing the broad patterns of functional connectivity for each striatal region, respectively). We used a similar thresholding approach to that from our prior studies.[40,48]

We next examined whether striatal functional connectivity was correlated with CPT scores in patients with ADHD. Specifically, dorsal and ventral frontostriatal circuits were tested for their association with inattention (i.e., omission errors) and impulsivity (i.e., commission errors), respectively.[2,3] We set up a separate general linear model for each CPT measure, and significant correlations between CPT scores and connectivity measures were estimated by adopting the same threshold approach described above with regard to the assessment of between-group differences.

Descriptive statistics and correlation analyses

Demographic and clinical characteristics of the participants were analyzed using Student t tests for continuous variables and χ^2 (or Fisher exact) tests for categorical variables.

To evaluate the distribution of the functional connectivity estimates using scatter plots, connectivity measures were extracted from a 5 mm sphere centred on each cluster showing significant between-group differences, and we set up a separate model for each extracted connectivity measure. We performed multiple linear regression analyses using the diagnosis, CPT scores and their interactions (i.e., diagnosis × CPT scores) as predictors and striatal functional connectivity measures as outcome variables, adjusting for age, sex and IQ. We performed our analyses using SPSS software version 20.0.

Results

Participant characteristics

We enrolled 83 patients with ADHD and 22 healthy controls in our study. No significant difference was found in age, sex and handedness between the ADHD and control groups

(Table 1). Controls had a higher IQ, and no significant difference was found between the 2 groups in social and obstetric variables. As expected, the CPT omission errors were significantly higher in the ADHD than the control group, and we found a trend-level difference in CPT commission errors. Participants showing either good or poor response to methylphenidate did not differ significantly in the demographic and clinical variables except for lower birth weight and more frequent comorbid oppositional defiant disorder among poor responders than good responders.

We found no significant difference between the patients and controls in mean head displacement (0.09 ± 0.11 mm in the ADHD group v. 0.08 ± 0.06 mm in the control group, $t = 0.34$, $p = 0.73$), maximum head displacement (0.82 ± 1.49 mm in the ADHD group v. 0.65 ± 0.83 mm in the control group, $t = 0.50$, $p = 0.62$), number of micro (> 0.2 mm) movements (9.27 ± 17.33 in the ADHD group v. 9.36 ± 12.65 in the control group, $t = –0.02$, $p = 0.98$) and head rotation (0.10 ± 0.19° in the ADHD group v. 0.06 ± 0.06° in the control group, $t = 0.72$, $p = 0.47$).

Striatal functional connectivity in patients with ADHD and healthy controls

In each group, we obtained robust striatal functional connectivity maps that reproduced the expected connectional anatomy of the dorsal and ventral caudate and putamen regions.[39–41] Figure 1 highlights the significant within-group effects of striatal functional connectivity in patients with ADHD. Overall, a robust pattern of functional connectivity reproduced the spatial topography of the network, as described in former reports.[39,41] However, compared with controls, patients with ADHD were characterized by a significantly more restricted pattern of striatal functional connectivity. Specifically, dorsal caudate connectivity with the left superior frontal and right middle frontal cortices was significantly reduced in patients with ADHD (Table 2 and Fig. 2A). In addition, dorsal putamen connectivity with the left parahippocampal cortex was significantly reduced in patients with ADHD (Table 2 and Fig. 2B). We observed no significant group differences in connectivity for the ventral caudate/nucleus accumbens or the ventral putamen, and there were no regions of significantly heightened striatal functional connectivity in the ADHD group compared with the control group.

Association between CPT scores and striatal functional connectivity

We found that dorsal caudate functional connectivity with the left dorsolateral prefrontal cortex significantly and negatively correlated with CPT omission errors ($x = –27$, $y = 30$, $z = 51$, $K_E = 17$, z score = 3.50; Fig. 2C). Conversely, dorsal caudate functional connectivity with the left inferior parietal cortex positively correlated with CPT omission errors ($x = –60$, $y = -45$, $z = 39$, $K_E = 24$, z score = 3.38). Ventral caudate/nucleus accumbens functional connectivity with the right caudate ($x = 6$, $y = 6$, $z = –6$, $K_E = 42$, z score = 3.23) and left orbitofrontal cortex ($x = –12$, $y = 45$, $z = –21$, $K_E = 16$, z score = 2.83) significantly and negatively correlated with CPT commission errors (Fig. 2D). Interestingly, ventral caudate/nucleus accumbens functional connectivity with a cluster extending across the ventromedial orbitofrontal cortex ($x = 3$, $y = 48$, $z = –3$, $K_E = 66$, z score = 3.51) and the anterior cingulate cortex significantly and positively correlated with CPT commission errors.

Differential association between CPT scores and striatal functional connectivity modulated by ADHD diagnosis

The brain regions characterizing the association between CPT scores and striatal functional connectivity in patients with ADHD did not overlap with the regions depicting significant between-group differences in patients and controls. Instead, the regions with significant between-group differences were characterized by significant interactions for the CPT scores between diagnostic groups (patients v. controls) and functional connectivity strength (Fig. 2A and 2B).

Striatal functional connectivity in good and poor responders to methylphenidate

Good responders to methylphenidate were characterized by significantly reduced functional connectivity compared with poor responders. Most prominently, ventral caudate/nucleus accumbens connectivity with the right rectal and orbitofrontal gyri was significantly reduced in good responders (Table 2 and Fig. 3B). In addition, dorsal caudate connectivity with the bilateral frontal cortices (Table 2 and Fig. 3A) as well as dorsal putamen connectivity with the bilateral insula, left amygdala-hippocampus, left anterior cingulate cortex and left postcentral cortex (Table 2 and Fig. 3C) were significantly reduced in good responders. We observed no significant group differences in connectivity for the ventral putamen, and no regions of significantly increased striatal functional connectivity in the good responders compared with poor responders.

Additional analyses

Given that good and poor responders to methylphenidate differed significantly in birth weight and comorbid oppositional defiant disorder, we repeated the between-group comparisons of striatal functional connectivity after controlling for these 2 variables. No substantial difference was observed in the pattern of between-group results after adjusting for these variables (see the Appendix, Table S1, available at jpn.ca). We excluded patients with ADHD with past or recent ADHD medication use (see the Methods section); however, 10 (12.0%) of patients with ADHD were not medication-naive. To examine a "cleaner" ADHD phenotype and rule out any potential effects of medication on functional connectivity, we included only stimulant- and atomoxetine-naive participants with ADHD in a subsequent analysis. We obtained similar results in striatal functional connectivity, including decreased dorsal caudate connectivity with the left superior and right middle frontal cortices in patients with ADHD compared with healthy controls and

decreased ventral striatal connectivity with the right inferior frontal cortex in good responders compared with poor responders. However, reduced dorsal putamen connectivity with the left parahippocampal cortex in patients with ADHD was not replicated (Appendix, Table S2).

Discussion

Patients with ADHD were characterized by reduced dorsal caudate functional connectivity with the left superior frontal and right middle frontal cortices as well as reduced dorsal putamen connectivity with the left parahippocampal cortex. These brain regions were further characterized by significant interactions for the CPT scores between diagnostic groups (i.e., patients v. controls) and functional connectivity strength, indicating that functional connectivity measures and attentional performance were correlated in opposite directions in patients and controls. Among the patients with ADHD, good responders to methylphenidate were characterized by reduced frontostriatal functional connectivity compared with poor responders that was particularly prominent between the ventral caudate/nucleus accumbens and right orbitofrontal gyri, as expected a priori based on similar observations reported in task-based fMRI studies.[27–29] We demonstrated that pretreatment difference in the ventral frontostriatal functional connectivity was related to pharmacological treatment response in patients with ADHD.

We observed that dorsolateral prefrontal and orbitofrontal functional connectivity with the striatum was negatively associated with CPT omission and commission errors, respectively, suggesting the involvement of different frontostriatal circuits in sustained attention and response inhibition in individuals with ADHD. Given that dorsal caudate functional connectivity with the inferior parietal cortex also significantly correlated with CPT omission errors, these regions appear to be part of an integrated frontoparietal control circuit.[17] However, relative to controls, patients with ADHD were characterized by reduction of dorsomedial frontostriatal, dorsolateral frontostriatal and

Table 1: Demographic and clinical characteristics of study participants

	Group; no. (%) or mean ± SD					
	All participants, *n* = 105			Methylphenidate response, *n* = 78		
Characteristic*	ADHD, *n* = 83	Control, *n* = 22	*p* value	Good, *n* = 48	Poor, *n* = 30	*p* value
Age, yr	9.58 ± 2.61	9.84 ± 2.57	0.63	9.45 ± 2.37	9.87 ± 2.83	0.47
Female sex	18 (21.7)	8 (36.4)	0.15	11 (22.9)	5 (16.7)	0.50
IQ	106.54 ± 13.56	114.64 ± 10.54	0.011	107.81 ± 12.20	105.23 ± 15.38	0.41
Handedness, right	74 (90.2)	20 (90.9)	0.92	42 (87.5)	28 (93.3)	0.70
CPT						
Omission errors	65.78 ± 20.83	50.86 ± 8.75	< 0.001	64.58 ± 20.34	68.30 ± 21.84	0.44
Commission errors	64.27 ± 16.96	57.09 ± 14.39	0.07	63.19 ± 17.07	66.43 ± 17.96	0.42
Social variables						
Paternal education, yr	15.00 ± 1.81	15.64 ± 1.17	0.06	14.98 ± 1.76	14.89 ± 2.02	0.84
Maternal education, yr	14.88 ± 1.80	15.05 ± 1.74	0.70	14.96 ± 1.77	14.56 ± 1.96	0.38
Socioeconomic status			0.19			0.54
High (very or moderately)	18 (22.8)	1 (4.6)		12 (25.5)	5 (17.9)	
Middle class	47 (59.5)	16 (72.7)		27 (57.5)	17 (60.7)	
Low (very or moderately)	14 (17.7)	5 (22.7)		8 (17.0)	6 (21.4)	
Obstetric variables						
Maternal age at pregnancy, yr	29.60 ± 3.67	29.00 ± 3.46	0.49	29.44 ± 3.65	30.03 ± 3.81	0.51
Birth weight, kg	3.27 ± 0.45	3.45 ± 0.42	0.10	3.35 ± 0.47	3.08 ± 0.36	0.014
ADHD types						0.74
Combined	44 (53.0)			25 (52.1)	14 (46.7)	
Inattentive	32 (38.6)			19 (39.6)	13 (43.3)	
Hyperactive-impulsive	1 (1.2)			0 (0.0)	1 (3.3)	
Not otherwise specified	6 (7.2)			4 (8.3)	2 (6.7)	
Comorbid disorders						
Oppositional defiant disorder	16 (19.3)			4 (8.3)	9 (30.0)	0.012
Anxiety disorder	2 (2.4)			0 (0.0)	1 (3.3)	0.38
Stimulant- and atomoxetine-naive	73 (88.0)			43 (89.6)	26 (86.7)	0.72
Final MPH dose, mg	32.71 ± 13.04			32.52 ± 11.45	33.00 ± 15.47	0.87
Final MPH dose per weight, mg/kg	0.95 ± 0.24			0.98 ± 0.26	0.88 ± 0.20	0.09

ADHD = attention-deficit/hyperactivity disorder; CPT = Continuous Performance Test; MPH = methylphenidate; SD = standard deviation.
*Different number of total respondents for paternal education (*n* = 101), maternal education (*n* = 96), socioeconomic status (*n* = 101), maternal age at pregnancy (*n* = 96), and birth weight (*n* = 95).

parahippocampal-striatal connectivity. Interestingly, the direction of correlation between CPT scores and functional connectivity in these regions was inversed, resulting in significant interactions for the CPT scores between diagnostic groups (i.e., patients v. controls) and functional connectivity strength. The inverse association suggests that patients with ADHD may

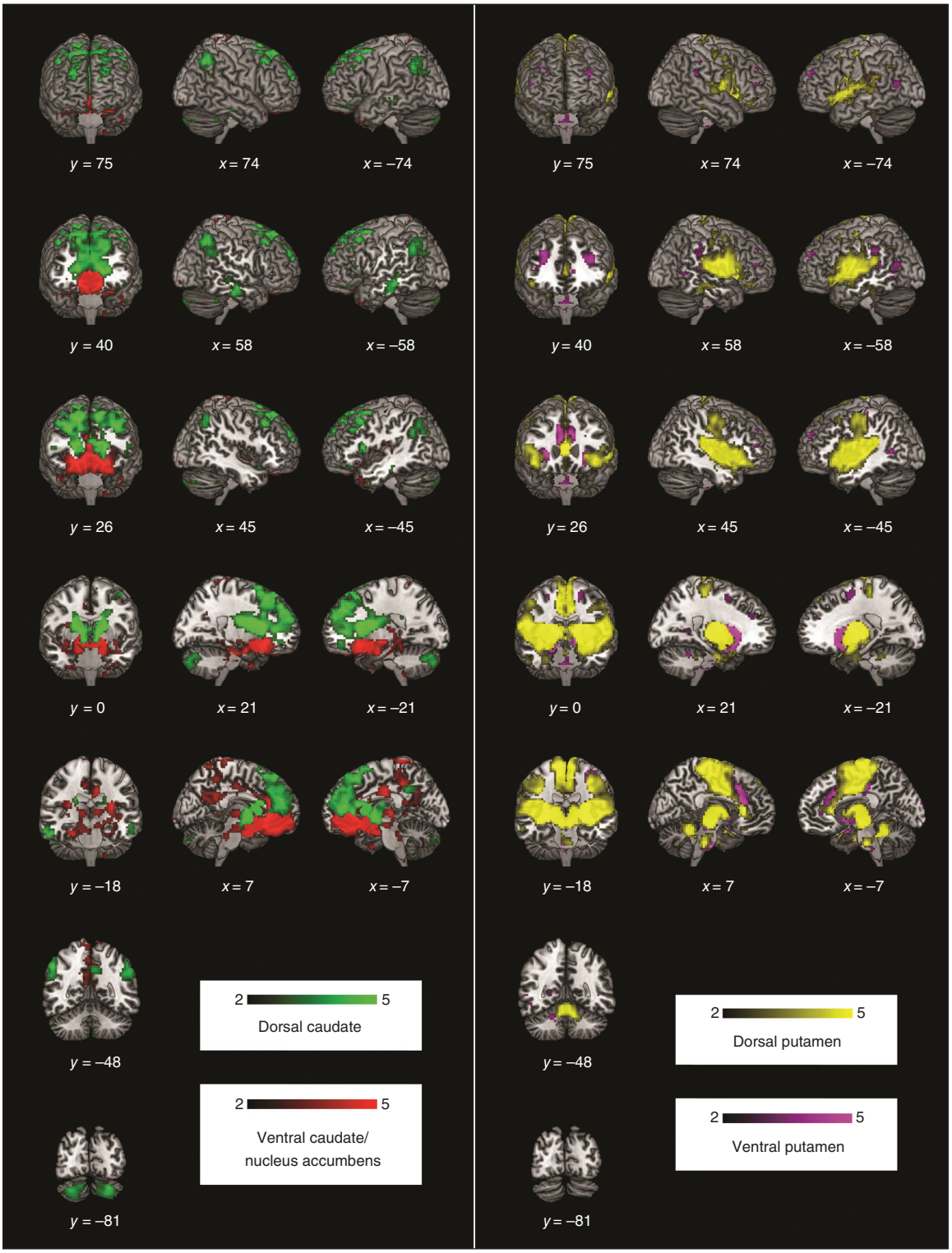

Fig. 1: Significant within-group corticostriatal functional connectivity maps. Results are displayed at $p_{FDR} < 0.05$ for the whole brain volume and with a minimum cluster extent (K_E) of 8 voxels. FDR = false-discovery rate.

engage these networks in a different way than healthy controls. In sum, the present findings suggest that dorsolateral prefrontal and orbitofrontal-striatal circuits in individuals with ADHD are related to sustained attention and response inhibition, respectively, which would be common in both ADHD and non-ADHD brains,[2,4] but disorder-specific disturbance of striatal functional connectivity may be localized in different frontal regions, particularly the dorsomedial frontal cortex and the parahippocampal cortex.

Using task-based fMRI, the pharmacological action of stimulant medications has been associated with the modulation of inferior frontal regions.[27–29] Our findings confirm and extend those of previous task-based reports and indicate that the inferior frontal cortex modulating methylphenidate response in individuals with ADHD may be a robust finding across different neuroimaging measurements. As resting-state fMRI has the advantage of being less constrained by differences among tasks, the pretreatment differences in functional connectivity observed in the present study may be a useful candidate biomarker of treatment response in patients with ADHD. However, we acknowledge that differences in group means may not necessarily translate to a classification accuracy at the individual level that would have clinical utility in psychiatric practice. Interestingly, the good responders were characterized only by reduced striatal functional connectivity compared with poor responders, as were patients with ADHD compared

Table 2: Regions demonstrating significantly decreased striatal functional connectivity in children and adolescents with ADHD compared with healthy controls and in good responders to methylphenidate compared with poor responders

Group; region	Peak anatomical coordinate, *x*, *y*, *z*			Statistics		
				K_E	*z* score	*p* value
ADHD < control						
Seed: dorsal caudate*						
Superior frontal gyrus, left	0	42	45	29	3.12	0.001
Superior frontal gyrus, left	0	33	51			
Middle frontal gyrus, right	33	12	54	18	2.82	0.002
Seed: dorsal putamen†						
Parahippocampal gyrus, left	–18	–9	–33	25	3.06	0.001
Parahippocampal gyrus, left	–27	–6	–30			
Good < poor responders						
Seed: dorsal caudate‡						
Superior frontal gyrus, right	21	57	6	44	3.10	0.001
Superior frontal gyrus, right	15	60	12			
Orbitofrontal gyrus, right	27	45	–9			
Middle frontal gyrus, left	–27	54	6	26	3.07	0.001
Orbitofrontal gyrus, left	–24	57	–3			
Seed: ventral caudate/ nucleus accumbens§						
Rectal gyrus, right	15	15	–12	334	4.11	< 0.001
Orbitofrontal gyrus, right	3	42	–3			
Orbitofrontal gyrus, right	3	57	0			
Seed: dorsal putamen¶						
Insula, right	39	–9	–3	149	3.89	< 0.001
Superior temporal gyrus, right	48	–3	–6			
Putamen, right	36	0	0			
Insula, left	–36	3	–9	81	3.60	< 0.001
Superior temporal gyrus, left	–45	0	–12			
Putamen, left	–30	3	0			
Hippocampus, left	–21	–9	–15	40	3.20	0.001
Hippocampus, left	–33	–12	–15			
Amygdala, left	–21	0	–9			
Anterior cingulate gyrus, left	–3	–3	30	24	3.59	< 0.001
Postcentral gyrus, left	–60	–15	18	19	3.40	< 0.001

ADHD = attention-deficit/hyperactivity disorder; K_E = cluster extent in voxels.
*Cluster size ≥ 17 voxels was considered statistically significant.
†Cluster size ≥ 22 voxels was considered statistically significant.
‡Cluster size ≥ 26 voxels was considered statistically significant.
§Cluster size ≥ 24 voxels was considered statistically significant.
¶Cluster size ≥ 18 voxels was considered statistically significant.

with healthy controls, further suggesting that good response to methylphenidate does not simply reflect a less deviant state from the healthy brain. In summary, patients with ADHD appear to be a heterogeneous population, and frontostriatal connectivity differentially involved among individual patients may account for why methylphenidate is effective only in a subpopulation of patients with ADHD. Whether good responders to methylphenidate are a distinct neurobiological subtype of patients with ADHD (i.e., orbitofronto-striatal subtype)[2] remains to be addressed with additional research.

It is important to remember that we constrained our analysis to corticostriatal circuitry, and thus it was prerequisite that the brain regions reported here demonstrated strong functional connectivity with dorsal or ventral subdivisions of either the caudate nucleus or putamen. The prefrontal–striatal model of ADHD has long been supported and remains an important explanation for the neurobiological mechanisms of ADHD. However, accumulating evidence from the perspective of systems neuroscience suggests that the pathophysiology of ADHD encompasses a number of different large-scale resting-state networks,[17] which then implies that our approach with a specific focus on the corticostriatal circuitry may not comprehensively map all functional connectivity alterations of potential importance to this disorder. On the other hand, methylphenidate is one of the most frequently prescribed first-line therapeutic agents for ADHD,

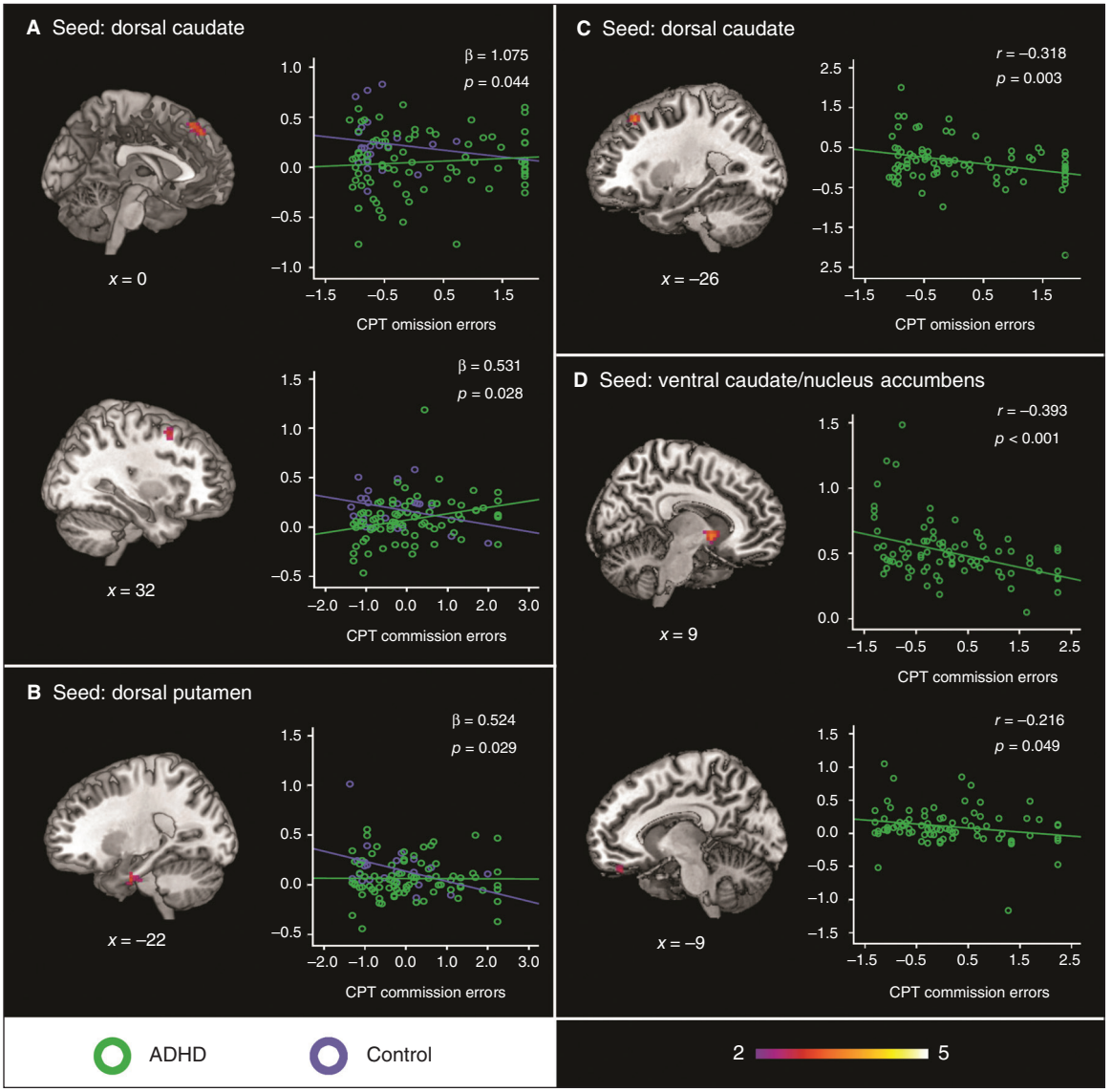

Fig. 2: Striatal functional connectivity in children and adolescents with attention-deficit/hyperactivity disorder (ADHD). We found significantly decreased functional connectivity of the **(A)** dorsal caudate and **(B)** dorsal putamen in children and adolescents with ADHD compared with healthy controls. We also found significant associations between continuous performance test (CPT) scores and strength of functional connectivity of the **(C)** dorsal caudate and **(D)** ventral caudate/nucleus accumbens in children and adolescents with ADHD. Results are displayed at $p < 0.01$, uncorrected.

and its therapeutic action mainly involves occupying and blocking the dopamine transporters.[49] Considering that the dopamine transporters are primarily expressed in the striatum,[50] methylphenidate response may be more closely related to the corticostriatal functional connectivity than the overall neurobiological mechanisms of ADHD, which is in line with the present findings that more extensive differences were observed between good and poor responders to methylphenidate than between ADHD and control participants.

Most prominently, patients showing a good response to methylphenidate were characterized by significantly reduced ventral caudate/nucleus accumbens connectivity with the inferior frontal cortices compared with poor responders. The inferior frontal cortex is known for its role in response inhibition[51] as well as sustained[52] or selective[53] attention, and impairment of these neurobehavioural functions may be related to the clinical features of ADHD. Interestingly, the large cluster differentiating the good and poor responders extended across the inferior frontal cortex and ventromedial prefrontal cortex, with the latter being implicated in emotion regulation,[18] reward and motivation,[21] or as part of the broader default mode network.[24] Therefore, although the present findings indicate that patients

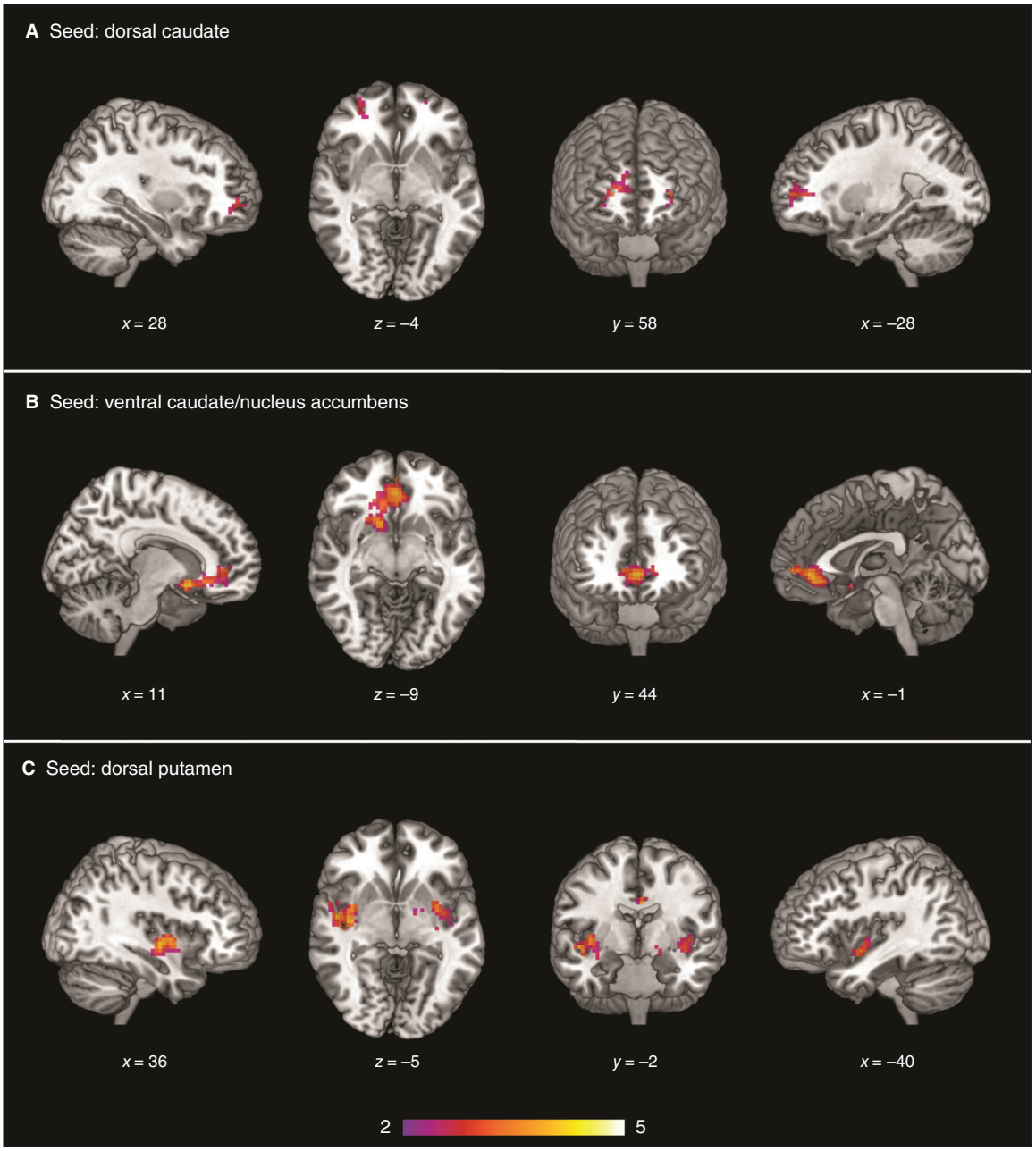

Fig. 3: Significantly decreased striatal functional connectivity in good responders to methylphenidate compared with poor responders. Results are displayed at $p < 0.01$, uncorrected.

with ADHD with reduced ventral frontostriatal functional connectivity have a better chance of a favourable response to methylphenidate, further research is warranted to clarify whether it should be interpreted in the context of possible interactions between a task-positive network and the default mode network. Another prominent finding was that dorsal putamen connectivity with the insula was significantly reduced in good responders. One of the implicated functions of the putamen, in conjunction with the activity of the insula and ventromedial prefrontal cortex, is the modulation of the balance between goal-directed and habitual modes of action control,[54] thus influencing the choice behaviour, and the resting-state functional connectivity between the insula and cingulate cortex has been implicated in environmental monitoring and response selection.[55] Taken together, the present findings that good responders to methylphenidate were characterized by significantly reduced dorsal putamen connectivity with the insula as well as with a region lying between the anterior and middle cingulate cortices warrant further research to examine whether methylphenidate modulates these neural circuits in individuals with ADHD.

The neurobiological mechanisms of how neurotransmitters and functional connectivity interrelate in neural information processing are not yet clearly understood. It has recently been postulated that norepinephrine and dopamine regulate signal and noise in the prefrontal cortex.[56,57] Specifically, norepinephrine was hypothesized to act via α-2A adrenergic receptors, which are negatively coupled to certain ion channels.[58] By inhibiting the leak of the glutamate signal out of these channels, norepinephrine may increase the signal strength and facilitate information processing at pyramidal neurons in the prefrontal cortex.[56,57] On the other hand, as dopamine D1 receptors are positively coupled to these channels, dopamine may stimulate the leak of the glutamate signal and thus increase noise.[56,57] However, the actual association between neurotransmitter levels and neural signal-to-noise can be more complex, possibly showing an inverted U-shaped function.[57,59] Either decreased signal or increased noise would result in reduced interregional functional connectivity; therefore, the findings of the present study can be a plausible consequence of both altered noradrenergic and dopaminergic systems. Accordingly, both dopaminergic and noradrenergic neurotransmitter systems have been implicated to modify the therapeutic response to methylphenidate.[60] However, we had previously reported that the *ADRA2A MspI* polymorphism was associated with decreased regional cerebral blood flow in bilateral orbitofrontal cortices of Korean children with ADHD.[61] The present finding suggests the need for future research on whether resting-state functional connectivity could provide useful information in pharmacogenetic studies of ADHD.

Limitations

Several potential limitations must be noted. Although age was matched between the groups, studying samples with a narrower age range would have been optimal. Instead, we included age as a nuisance covariate to statistically control for its influence. In addition, we suspect that potential confounding effects of age-related functional connectivity change may be minimal in this study, given the uniformly negative associations observed between measures of functional connectivity and age-standardized CPT scores. Even a relatively small amount of head motion in the scanner may have confounding influences in resting-state functional connectivity studies. In the present study, we first realigned the brain images to correct for motion-related changes in position. We restricted the translation and rotation estimates to be less than 2 mm or 2°, respectively. We checked for any difference between the ADHD and control groups in mean head displacement, maximum head displacement, number of micro (> 0.2 mm) movements and head rotation.[38] No significant difference was observed in these head motion parameters between the groups. In addition, global signal regression was found to be effective in reducing the associations between motion and resting-state fMRI metrics across participants.[62] On the other hand, some have argued that a modelling-based approach that regresses time series data on the head motion parameters is inadequate in attenuating the impact of micromovements.[62] However, the lack of a gold standard for dealing with head motion is in itself an important limitation of the study. Finally, although there is likely to be some genuine neurophysiological basis to observed anticorrelations, their characterization has been highly controversial in the resting-state fMRI field with regard to the use of global signal regression techniques.[45,63,64] For this reason, we chose to focus solely on mapping positive functional connectivity effects, as has been favoured in prior studies investigating corticostriatal functional connectivity.[40,41]

Conclusion

Although the association between dorsolateral prefrontal-striatal functional connectivity and attentional control and between orbitofrontal-striatal functional connectivity and response inhibition can be observed in patients with ADHD, the disorder-specific abnormality may be localized in dorsomedial frontal and parahippocampal cortices, characterized by reduced resting-state functional connectivity with the dorsal caudate nucleus and dorsal putamen, respectively. Methylphenidate response among patients with ADHD was characterized by reduced resting-state functional connectivity between the inferior frontal cortex and the ventral striatum.

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