Research Paper

Thalamocortical functional connectivity in youth with attention-deficit/hyperactivity disorder

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Background: Few studies have empirically tested the relationships between anatomically defined thalamic nuclei and functionally defined cortical networks, and little is known about their implications in attention-deficit/hyperactivity disorder (ADHD). This study aimed to investigate the functional connectivity of the thalamus in youth with ADHD, using both anatomically and functionally defined thalamic seed regions. **Methods:** Resting-state functional MRIs obtained from the publicly available ADHD-200 database were analyzed. Thalamic seed regions were defined functionally and anatomically based on Yeo's 7 resting-state-network parcellation atlas and the AAL3 atlas, respectively. Functional connectivity maps of the thalamus were extracted, and thalamocortical functional connectivity was compared between youth with and without ADHD. **Results:** Using the functionally defined seeds, significant group differences in thalamocortical functional connectivity and significant negative correlations between thalamocortical connectivity and ADHD symptom severity were observed within the boundaries of corresponding large-scale networks. However, in the analysis using the anatomically defined thalamic seeds, significant group differences in connectivity and significant positive correlations were observed outside the expected boundaries of major anatomic projections. The thalamocortical connectivity originating from the lateral geniculate nuclei of the thalamus was significantly correlated with age in youth with ADHD. **Limitations:** The small sample size and smaller proportion of girls were limiting factors. **Conclusion:** Thalamocortical functional connectivity based on the intrinsic network architecture of the brain appears to be clinically relevant in ADHD. The positive association between thalamocortical functional connectivity and ADHD symptom severity may represent a compensatory process recruiting an alternative neural network.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder in youth[1] that frequently persists into adulthood.[2,3] It is characterized by a number of inattentive, hyperactive or impulsive symptoms, and dysfunction of the corticostriatothalamocortical circuit has been considered an important neural correlate of ADHD.[4]

The thalamus is the largest subcortical structure in the brain, and it is an important component of the corticostriatothalamocortical circuit.[5] It is often described as a relay station for sensory information, and studies on the anatomic connectivity of the brain have revealed that different parts of the thalamus are connected with different cortical regions. In the postmortem brains of nonhuman primates, the mediodorsal thalamic nucleus is connected to the prefrontal cortex,[6,7] the ventral posterior nucleus to the somatosensory cortex,[8] and the ventral lateral and ventral anterior nuclei to the primary motor and premotor cortices.[9] In addition, the ventral anterior and ventral lateral nuclei, as well as the intralaminar and mediodorsal nuclei of the thalamus, are connected to the anterior midcingulate cortex.[10,11] A similar topography of thalamocortical connections has been observed in living human brains using diffusion tractography.[12–14]

More recently, accumulating evidence has demonstrated altered intrinsic functional architecture of the brain in ADHD, and large-scale brain networks observed at rest have been implicated in the neurobiology of ADHD.[15,16] Paralleling advances in systems neuroscience, efforts have been made to delineate the organization of the human thalamus based on its functional connectivity.[17,18] One typical example of such efforts involves mapping the thalamic subregions in reference to intrinsic brain networks by assigning each thalamic voxel to its most strongly correlated cortical network.[19,20] However, the internal boundaries of the thalamus created from this approach may not be consistent with the anatomically or histologically defined topography of the thalamus. An alternative approach would be to predefine thalamic subregions or nuclei on an anatomic or histological basis and then assign them to the most relevant functional cortical architecture. From this perspective, it has been postulated that the

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mediodorsal nucleus of the thalamus is involved in the lateral frontoparietal control network, the basal ventromedial nucleus in the salience network, and the lateral geniculate nucleus in the visual network.[21] Others have associated the intralaminar or mediodorsal thalamus with the salience network.[22,23] In addition, the ventral and intralaminar thalamus may be part of the somatomotor network, considering its anatomic connectivity.[8,9] However, few studies have empirically tested these relationships between anatomically defined thalamic nuclei and functionally defined cortical networks, and little is known about their implications for ADHD.

Although disruption of the corticostriatothalamocortical circuit has been implicated in ADHD,[4] the role of the thalamus in ADHD has not been as thoroughly investigated, and even fewer studies have explored the subdivisions of the thalamus and their functional connectivity in ADHD. Mills and colleagues[24] defined thalamic parcellations based on their functional connectivity with predefined cortical subdivisions[17] and reported a list of observations. Connectivity strength between the prefrontal thalamic region of interest (ROI) and the right superior and middle frontal gyri was greater in children with ADHD and related to better working-memory performance. Connectivity strength between the premotor–motor thalamic ROI and the left inferior frontal and left superior temporal gyri, and between the temporal thalamic ROI and the left and right middle temporal gyri, was greater in children with ADHD and related to worse working-memory performance. Connectivity strength between the prefrontal thalamic ROI and the right precentral gyrus was greater in typically developing children and related to worse working-memory performance. Connectivity strength between the premotor–motor thalamic ROI and the left and right lingual and left and right inferior occipital gyri, and between the somatosensory thalamic ROI and the left fusiform and left lingual gyri, was greater in typically developing children and related to better working-memory performance.[24] These varying findings for different thalamic ROIs — shown in terms of increase or decrease in functional connectivity as well as mixed directions of association with cognitive performance — suggest the need to establish and investigate thalamic functional connectivity separately for its subdivisions, rather than as a whole.

The present study aimed to investigate the functional connectivity of the thalamus in youth with ADHD, using both anatomically and functionally defined thalamic seed regions. Using the functionally defined seeds, it was expected that the difference in thalamocortical functional connectivity between youth with and without ADHD would be observed within the expected boundaries of each specific large-scale cortical network used to parcellate the thalamus. Using anatomically defined seeds, on the other hand, it appears that each thalamic nucleus projects to more than 1 cortical region,[25,26] and more importantly, because functional connectivity may extend beyond the range of direct anatomic projections,[27,28] it was expected that a difference in thalamocortical functional connectivity would be observed beyond the boundaries of the corresponding large-scale cortical networks postulated based on studies of anatomic connections. More specifically, the hypothesis of this study was that significant differences in connectivity and significant correlations between connectivity and symptom severity would be found within the boundaries of corresponding large-scale thalamocortical networks only when the thalamus was mapped using Yeo's 7 resting-state-network parcellation[29] in contrast to the Automated Anatomical Labelling (AAL) 3 atlas.[30]

Methods

Participants and data acquisition

The study data were obtained from the publicly available ADHD-200 database (fcon_1000.projects.nitrc.org/indi/adhd200/). Data from Peking University were used, given the large sample size and large number of resting-state functional MRI (fMRI) scans per session. The presence of ADHD was based on evaluations using the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version. The severity of ADHD symptoms was assessed using the ADHD Rating Scale-IV (ADHD-RS-IV), in which a higher score indicates more severe ADHD symptoms and behaviours. Psychostimulants were withheld at least 48 hours before scanning. The present study used deidentified data and was granted exemption from review by the institutional review board at the corresponding author's institution.

The ADHD-200 data include in-house quality assessment results for structural MRI and resting-state fMRI, which are binary findings of either "pass" or "questionable." The quality assessment of image data was facilitated using quality metrics derived from the preprocessed data, and 2 evaluators performed a rigorous visual inspection of registration quality. Only participants with a "pass" for both structural MRI and resting-state fMRI scans and no missing IQ scores were included. Only right-handed participants were included in the present study. Among 194 participants, 178 passed the scan quality, and 3 were excluded for IQ or handedness.

Image processing

The preprocessed resting-state fMRI data released by the Neuro Bureau ADHD-200 preprocessed repository were used (preprocessed-connectomes-project.org/adhd200/). The images were preprocessed using the Athena pipeline.[31] In brief, the pipeline involved removing the first 4 volumes; slice timing correction; realigning each volume to correct for motion; masking the data set to exclude nonbrain; creating a mean image and coregistering it to the corresponding structural image; writing the functional data into template space; regressing out white matter, cerebrospinal fluid, motion time courses and a low-order polynomial; band-pass filtering; and smoothing. The repository provided basic head-motion statistics as well, calculated using the geometric mean of the x, y, and z components, as well as the roll, pitch and yaw at each time point (translation and angular motions). Whole-brain functional connectivity maps of the bilateral thalamic seed regions were obtained using Data Processing & Analysis of Brain Imaging.[32]

Yeo's 7 resting-state-network parcellation atlas of the thalamus was used; the atlas mapped the thalamus based on its connectivity to the 7 functionally coupled large-scale networks identified across the cerebral cortex.[29] Functional maps of the striatum and cerebellum have also been defined using a similar clustering approach in a series of companion papers.[19,20] This thalamic atlas can be downloaded from www.dropbox.com/s/b0cz132fxva7yox/ThalamusParcellation.zip?dl = 0.

The AAL3 atlas was also used; it is based on the widely used AAL atlas, but with the addition of a number of newly defined brain areas, including subdivisions of the thalamus.[30] Based on the literature review summarized in the introduction, 3 thalamic seed regions—the mediodorsal, the ventral and intralaminar, and the lateral geniculate nuclei of the thalamus — and their functional connectivity with the frontoparietal and salience networks, the salience and somatomotor networks, and the visual network, respectively, were of interest.[21–23] The mediodorsal seed was generated by combining the mediodorsal medial and mediodorsal lateral nuclei in the AAL3 using the MarsBaR toolbox.[33] Similarly, the ventral and intralaminar seed was created by combining the ventral anterior, ventral lateral, ventral posterolateral and intralaminar nuclei. The lateral geniculate seed was employed as defined in the AAL3. Both the functional and anatomic thalamic atlases were resampled to the space of the functional images.

Data analysis

Youth with and without ADHD were matched for sex and IQ using the coarsened exact matching algorithm (gking.harvard.edu/cem). The algorithm matched 53 participants in each group, whose identifiers in the ADHD-200 database are presented along with their sex and age in Appendix 1, Table S1 (available at www.jpn.ca/lookup/doi/10.1503/jpn.220109/tab-related-content) for data transparency. Between-group differences in descriptive statistics and head-motion parameters were estimated using Student t tests and χ^2 tests for continuous and categorical variables, respectively. Statistical tests were performed using SPSS (version 25.0; IBM), and the results are reported with a significance threshold of uncorrected $p < 0.05$.

First, the thalamocortical functional connectivity between youth with and without ADHD was compared, in which performance IQ was included as a covariate owing to its significant difference between the groups. Second, the association between thalamocortical functional connectivity and ADHD symptom severity was examined separately in youth with or without ADHD. The ADHD-RS-IV total score is the simple sum of the inattention and hyperactivity/impulsivity subscores; therefore, an investigation was conducted into whether thalamic functional connectivity was correlated with each of these subscores to delineate neural correlates of specific symptom domains. Third, for thalamocortical functional connectivity that was significantly associated with symptom severity scores, the interaction effects were further investigated to explore whether the relationship between thalamocortical functional connectivity and ADHD symptom severity varied depending on the presence of ADHD; performance IQ was included again as a covariate. These analyses were performed using statistical parametric mapping and the CONN functional connectivity toolbox (www.nitrc.org/projects/conn; RRID:SCR_009550),[34] which are based on MATLAB (MathWorks).

The cluster-forming height threshold was set at $p < 0.001$ (uncorrected), and results were reported if they exceeded a family-wise error (FWE)–corrected, cluster-defining threshold of $p < 0.05$. Following the hypothesis for this study, small-volume correction was employed to restrict the analysis to the target ROIs defined based on Yeo's 7 resting-state-network parcellation atlas of the human cerebral cortex.[29] For analysis with the 7 functionally defined thalamic seeds, the corresponding 7 major cerebral networks were the target ROIs that the thalamus parcellation was based on. For analysis with the 3 anatomically defined thalamic seeds (i.e., the mediodorsal, ventral and intralaminar, and lateral geniculate nuclei of the thalamus), the target ROIs were defined a priori as the frontoparietal and salience networks, the salience and somatomotor networks, and the visual network, respectively. However, the analyses were also expanded beyond these target ROIs to explore thalamic functional connectivity with other cortical ROIs among Yeo's 7 resting-state-network parcellation atlas. In addition, whole-brain analyses without small-volume correction were performed to supplement the main results and provide additional information.

The results were also reported using Bonferroni correction for the number of seeds and target ROIs tested. In the analysis using the functionally defined thalamic seeds, 7 thalamic seeds were tested for their connectivity with each of their corresponding target ROIs based on Yeo's 7 resting-state-network parcellation (small-volume correction) or the whole brain. Therefore, correction was required for 7 seeds, regardless of whether the analysis was corrected for a small volume or the whole brain (Bonferroni-corrected $p < 0.007$; 0.05 divided by 7). In the analysis using the anatomically defined thalamic seeds, 3 thalamic seed regions (defined a priori) were used; however, based on the literature review summarized in the introduction, the mediodorsal seed was tested for its connectivity with 2 target ROIs (i.e., the frontoparietal and salience networks), the ventral and intralaminar seed for its connectivity with 2 target ROIs (i.e., the salience and somatomotor networks), and the lateral geniculate seed for its connectivity with 1 target ROI (i.e., the visual network). Therefore, correction was required for 5 tests rather than 3 in the small-volume analysis (Bonferroni-corrected $p < 0.01$; 0.05 divided by 5). In the whole-brain analysis, correction was required for 3 seeds (Bonferroni-corrected $p < 0.016$; 0.05 divided by 3).

Results

Participant characteristics

There were no significant differences in age, sex or 10 head-motion parameters between youth with and without ADHD (Table 1). The groups differed significantly in terms of performance IQ and ADHD symptom severity scores. Three additional head-motion estimates (mean root mean square,

Table 1: Participant characteristics*

Characteristic	ADHD *n* = 53	Control *n* = 53	*p* value
Age, yr	12.56 ± 2.00	12.44 ± 1.53	0.74
Female	4 (7.5)	4 (7.5)	> 0.99
IQ			
Verbal	115.06 ± 15.22	115.51 ± 13.83	0.87
Performance	100.30 ± 13.47	107.77 ± 14.86	0.008
Full-scale	109.21 ± 12.32	113.26 ± 13.88	0.12
ADHD-RS			
Inattention score	28.04 ± 3.77	15.78 ± 3.97	< 0.001
Hyperactivity/impulsivity score	22.20 ± 6.48	12.47 ± 2.89	< 0.001
Total score	50.24 ± 9.03	28.25 ± 5.87	< 0.001
Head motion parameters			
Maximum motion, mm	1.14 ± 0.73	1.15 ± 0.96	0.93
Maximum motion, time point	188.30 ± 46.67	201.00 ± 37.70	0.13
Maximum rotation, degree	1.03 ± 0.73	1.02 ± 1.17	0.97
Maximum rotation, time point	175.04 ± 61.20	187.89 ± 55.77	0.26
Maximum translation, *x* axis, mm	0.10 ± 0.32	0.16 ± 0.34	0.39
Maximum translation, *y* axis, mm	–0.25 ± 0.48	–0.42 ± 0.53	0.09
Maximum translation, *z* axis, mm	0.17 ± 1.10	0.09 ± 1.24	0.73
Maximum roll rotation, degree	0.07 ± 0.33	0.06 ± 0.32	0.82
Maximum pitch rotation, degree	–0.01 ± 1.01	–0.08 ± 1.11	0.74
Maximum yaw rotation, degree	0.14 ± 0.51	0.16 ± 0.43	0.81
Mean root mean square, mm	0.50 ± 0.29	0.50 ± 0.35	0.96
Mean frame-wise displacement, mm	0.14 ± 0.06	0.13 ± 0.09	0.38
Mean DVARS	28.29 ± 3.54	27.07 ± 4.59	0.13

ADHD = attention-deficit/hyperactivity disorder; ADHD-RS = ADHD Rating Scale.
*Values are mean ± standard deviation or *n* (%). No observations were missing except for the ADHD-RS scores, which were available for 49 patients with ADHD and 48 control participants.

mean frame-wise displacement and mean DVARS) were included in the analysis, using publicly available motion data derived from a previous study using the ADHD-200 data set (sites.google.com/site/hpardoe/motion).[35] Root mean square measures the root mean square deviation for each successive pair of image volumes in the resting-state fMRI acquisition; frame-wise displacement and DVARS measure head movement and signal intensity changes between sequential volumes, respectively. No significant differences were observed in mean root mean square, frame-wise displacement or DVARS. Because there were no significant differences in head-motion estimates, they were not included as covariates in the main analyses.

Differences in thalamocortical functional connectivity in youth with and without ADHD

In the analysis using the functionally defined thalamic seeds, youth with ADHD showed significant decreases in thalamocortical functional connectivity in the dorsal attention network compared to youth without ADHD (Table 2). This cluster remained significant in whole-brain analysis without small-volume correction (Table 2 and Figure 1). However, the findings were no longer significant after Bonferroni correction ($p < 0.007$). No other significant differences were found between groups.

In the analysis using the anatomically defined thalamic seeds, no significant difference was found between groups in terms of functional connectivity between the 3 thalamic seeds and the corresponding cortical ROIs defined a priori.

To assess the robustness of the findings, sensitivity analyses were performed that included performance IQ and mean frame-wise displacement as covariates.

In the analysis using the functionally defined thalamic seeds and small-volume correction, the decreases in thalamocortical functional connectivity in the dorsal attention network in youth with ADHD were replicated without changes in peak coordinates (Appendix 1, Table S2). Among the 2 significant clusters, 1 remained significant in the whole-brain analysis without small-volume correction, but the other did not pass the brain-wide FWE-corrected significance threshold.

In the analysis using the anatomically defined thalamic seeds that included performance IQ and mean frame-wise displacement as covariates, no significant between-group differences in functional connectivity were found for the 3 thalamic seeds and the corresponding cortical ROIs defined a priori.

To summarize, both the main and sensitivity analyses showed differences in thalamic functional connectivity between youth with and without ADHD within the boundaries of corresponding large-scale thalamocortical networks when the analyses were based on the functionally defined thalamic seeds. In contrast, no significant differences were found

Table 2: Altered thalamocortical functional connectivity in youth with ADHD based on functionally defined thalamic seeds*

Functional connectivity	Peak coordinates, *x, y, z*	Statistics		*p* value
		K_E, voxels	*Z*	
ADHD < controls				
Dorsal attention thalamocortical network (small-volume correction)	–36, –56, 54	24	3.77	0.011
Dorsal attention thalamocortical network (small-volume correction)	12, –52, 54	20	4.24	0.018
Dorsal attention thalamic seed (whole-brain analysis)	–36, –56, 54	33	3.77	0.040
Dorsal attention thalamic seed (whole-brain analysis)	12, –52, 54	34	4.24	0.036
Negative correlation with IA score in ADHD				
Somatomotor thalamocortical network (small-volume correction)	56, –12, 22	47	4.09	0.001
Somatomotor thalamic seed (whole-brain analysis)	44, –4, 42	117	4.56	< 0.001
Negative correlation with HI score in ADHD				
Default mode thalamocortical network (small-volume correction)	–56, –52, 26	20	4.73	0.030
Default mode thalamic seed (whole-brain analysis)	–56, –52, 26	39	4.73	0.018
Interaction effect (connectivity × diagnosis) on IA score				
Somatomotor thalamocortical network (small-volume correction)	52, –16, 22	56	4.45	< 0.001
Somatomotor thalamocortical network (small-volume correction)	52, –4, 42	14	3.67	0.045
Somatomotor thalamic seed (whole-brain analysis)	48, –40, 18	92	4.63	< 0.001
Somatomotor thalamic seed (whole-brain analysis)	44, –4, 42	54	4.75	0.004

ADHD = attention-deficit/hyperactivity disorder; FWE = family-wise error; HI = hyperactivity/impulsivity; IA = inattention; K_E = cluster extent.
*Positive and negative *x* coordinates indicate right and left hemispheres, respectively. Results are displayed with a cluster-defining threshold of $p_{FWE} < 0.05$.

between groups based on anatomically defined seeds and the expected targets of their anatomic projections.

Additional between-group differences in thalamocortical functional connectivity

The analyses were expanded beyond the a priori defined target ROIs and explored between-group differences in thalamic functional connectivity with other cortical ROIs in Yeo's 7 resting-state-network parcellation atlas. In the analysis using functionally defined thalamic seeds, no significant difference was found between youth with and without ADHD for any other pair of thalamic seed and cortical parcellation.

In the analysis using the anatomically defined thalamic seeds, youth with ADHD showed significant decreases in mediodorsal thalamic functional connectivity with the visual and default mode networks (Table 3). Two of the 3 significant clusters separately observed in each of these networks were actually connected across the boundaries of the networks and remained significant in the whole-brain analysis without small-volume correction (Table 3 and Figure 2). Only the findings from the whole-brain analysis remained significant following Bonferroni correction ($p < 0.016$). No other significant differences were found between groups in the analysis using the anatomically defined thalamic seeds.

In the sensitivity analysis using the functionally defined thalamic seeds that included performance IQ and mean frame-wise displacement as covariates, no significant between-group differences were found in thalamic functional connectivity with any cortical parcellation beyond the target ROIs defined a priori.

In the sensitivity analysis using the anatomically defined thalamic seeds that included performance IQ and mean frame-wise displacement as covariates, the decreases in mediodorsal thalamic functional connectivity with the visual and default mode networks in youth with ADHD were replicated with slight changes in peak coordinates (Appendix 1, Table S2). These clusters remained significant bilaterally in the whole-brain analysis without small-volume correction. In addition, a significant decrease was newly identified in youth with ADHD in the ventral and intralaminar thalamic functional connectivity with the dorsal attention network.

To summarize, both the main and sensitivity analyses showed differences in thalamic functional connectivity based on anatomically defined seeds outside the expected boundaries of major anatomic projections. In contrast, no significant between-group differences were found in connectivity outside the target networks defined a priori using functionally defined thalamic seeds.

Association between ADHD symptom severity and thalamocortical functional connectivity

In the analysis using the functionally defined thalamic seeds, thalamocortical functional connectivity in the somatomotor network was negatively correlated with ADHD-RS inattention scores in youth with ADHD, and thalamocortical functional connectivity in the default mode network was negatively correlated with ADHD-RS hyperactivity/impulsivity scores (Table 2). These clusters remained significant in the whole-brain analysis without small-volume correction (Table 2 and Figure 1). The findings for the somatomotor network and ADHD-RS inattention score remained significant after Bonferroni correction ($p < 0.007$). No significant correlation was found between thalamocortical functional connectivity and ADHD-RS inattention or hyperactivity/impulsivity scores

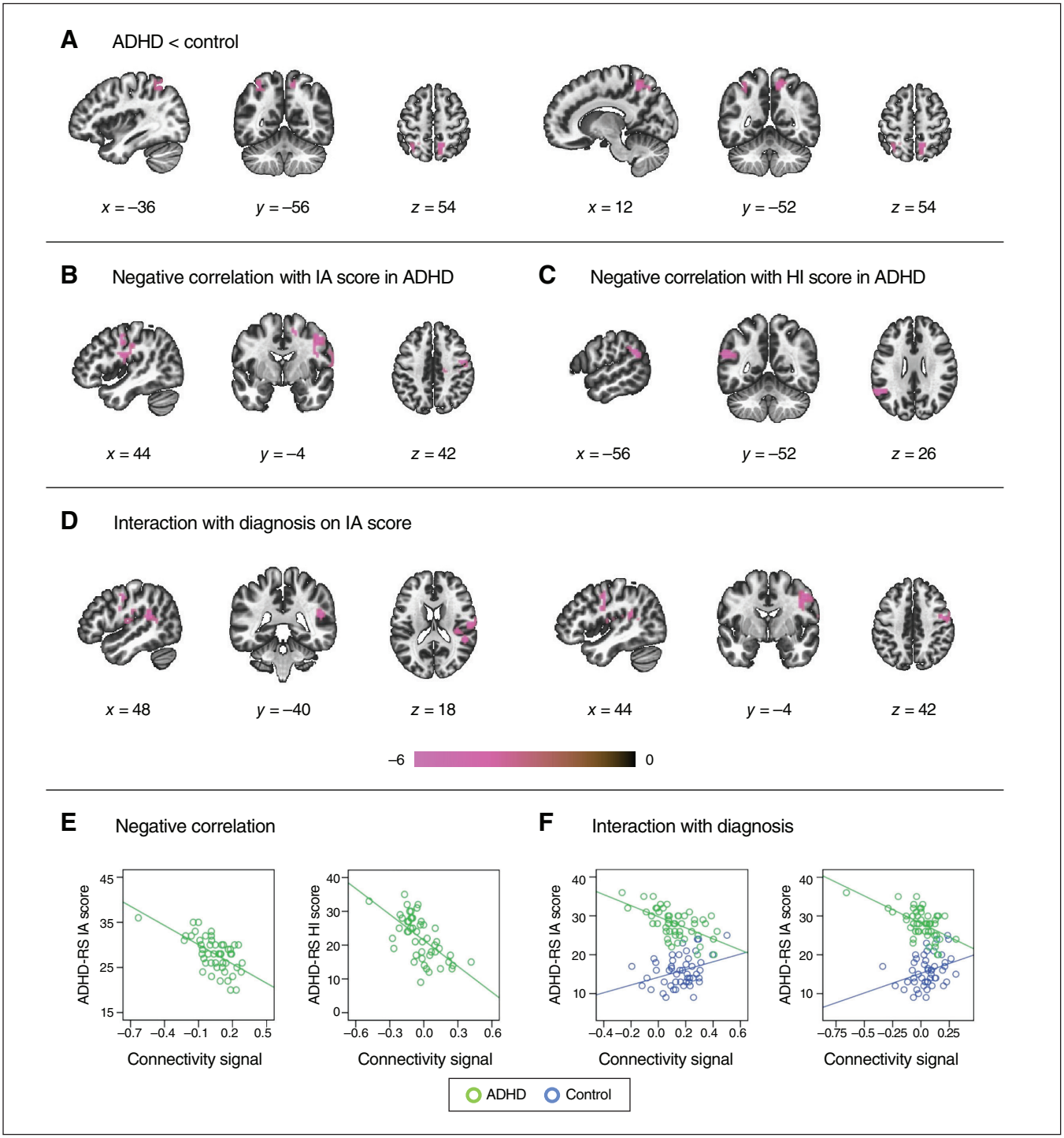

Figure 1: Altered thalamocortical functional connectivity in youth with attention-deficit/hyperactivity disorder (ADHD) observed using functionally defined thalamic seeds. Yeo's 7 resting-state-network parcellation atlas was used to define the thalamic seeds. (A) Reduced thalamic functional connectivity in youth with ADHD compared to healthy controls using the dorsal attention thalamic seed. (B, C) Correlation between thalamic functional connectivity and scores on the ADHD Rating Scale (ADHD-RS) in youth with ADHD using the somatomotor thalamic seed and the default mode thalamic seed. (D) Interaction effect between thalamic functional connectivity and diagnosis of ADHD on ADHD-RS inattention (IA) score using the somatomotor thalamic seed. Results are displayed at $p_{FWE} < 0.05$, corrected at the cluster level across the whole brain, with a cluster-defining threshold of $p < 0.001$, uncorrected. (E, F) Scatter plots showing the relationship between ADHD-RS scores and connectivity signals extracted from the significant clusters ($p_{FWE} < 0.05$, corrected for small volume). FWE = family-wise error; HI = hyperactivity/impulsivity.

Table 3: Altered thalamocortical functional connectivity in youth with ADHD based on anatomically defined thalamic seeds*

Functional connectivity	Peak coordinates, *x, y, z*	Statistics		*p* value
		K_E, voxels	*Z*	
ADHD < controls				
Mediodorsal thalamus to visual network (small-volume correction)	–12, –64, 18	22	3.87	0.018
Mediodorsal thalamus to visual network (small-volume correction)	8, –56, 6	16	3.55	0.040
Mediodorsal thalamus to default mode network (small-volume correction)	–12, –56, 10	21	4.03	0.031
Mediodorsal thalamic seed (whole-brain analysis)	–12, –56, 10	50	4.03	0.008
Positive correlation with IA score in ADHD				
Mediodorsal thalamus to dorsal attention network (small-volume correction)	–28, –72, 30	15	4.11	0.034
Positive correlation with HI score in ADHD				
Lateral geniculate thalamus to frontoparietal network (small-volume correction)	20, 60, –2	19	4.61	0.021
Interaction effect (connectivity × diagnosis) on IA score				
Mediodorsal thalamus to dorsal attention network (small-volume correction)	32, –64, 30	17	4.53	0.027

ADHD = attention-deficit/hyperactivity disorder; FWE = family-wise error; HI = hyperactivity/impulsivity; IA = inattention; K_E = cluster extent.
*Positive and negative *x* coordinates indicate right and left hemispheres, respectively. Results are displayed with a cluster-defining threshold of $p_{FWE} < 0.05$.

in youth without ADHD. Scatter plots were used to visualize the relationship between symptom severity scores and connectivity signals extracted from the significant clusters (Figure 1).

In the analysis using the anatomically defined thalamic seeds, no significant correlation was found between thalamic functional connectivity with the cortical ROIs defined a priori and ADHD-RS inattention or hyperactivity/impulsivity scores. Instead, significant correlations were found for other cortical ROIs. In youth with ADHD, mediodorsal thalamic functional connectivity with the dorsal attention cortical network was positively correlated with ADHD-RS inattention scores, and lateral geniculate thalamic functional connectivity with the frontoparietal control network was positively correlated with ADHD-RS hyperactivity/impulsivity scores (Table 3 and Figure 2). Neither of these clusters remained significant in the whole-brain analysis without small-volume correction, and neither was significant after Bonferroni correction ($p < 0.01$). No significant correlation was found between thalamic functional connectivity with any of the 7 cortical ROIs and ADHD-RS inattention or hyperactivity/impulsivity scores in youth without ADHD. The relationship between symptom severity scores and connectivity signals extracted from the significant clusters are visualized in scatter plots (Figure 2).

Differential association between ADHD symptom severity and thalamocortical functional connectivity modulated by ADHD diagnosis

In the analysis using the functionally defined thalamic seeds, a significant group interaction was observed for ADHD-RS inattention scores and thalamocortical functional connectivity in the somatomotor network (Table 2). These clusters remained significant in the whole-brain analysis without small-volume correction (Table 2 and Figure 1), and they passed Bonferroni correction ($p < 0.007$). Clusters were found at coordinates similar to where thalamocortical connectivity in the somatomotor network was significantly correlated with ADHD-RS inattention scores in youth with ADHD.

In the analysis using the anatomically defined thalamic seeds, a significant group interaction was observed for ADHD-RS inattention scores and mediodorsal thalamic functional connectivity with the dorsal attention cortical network (Table 3 and Figure 2), but it did not pass Bonferroni correction ($p < 0.01$). This cluster was not significantly replicated in whole-brain analysis without small-volume correction; however, it was found at similar coordinates in the contralateral hemisphere where mediodorsal thalamic connectivity with the dorsal attention network was significantly correlated with ADHD-RS inattention scores in youth with ADHD.

Additional association between age and thalamocortical functional connectivity

Based on findings showing that thalamocortical connectivity from the anatomically defined seeds was positively correlated with ADHD symptom severity, in an opposite direction of association to those found with the functionally defined seeds, the possibility of a compensatory brain response — adjusting to disability — was considered. To explore this hypothesis further, multiple linear regression analyses were performed using age and IQ as predictors, based on the expectation that compensatory strengthening of connectivity would develop gradually with increasing age, more efficiently with greater cognitive resources or both. The extracted connectivity measures originating from the anatomically defined seeds were used as outcome variables, and the analyses were adjusted for ADHD-RS inattention or hyperactivity/impulsivity scores. Lateral geniculate thalamic connectivity with the frontoparietal control network was significantly associated with age in youth with ADHD ($\beta = 0.234$; $p = 0.044$; 95% confidence interval, 0.000–0.034; adjusted $R^2 = 0.406$).

Discussion

The present study investigated functional connectivity of the thalamus in youth with ADHD, using anatomically and

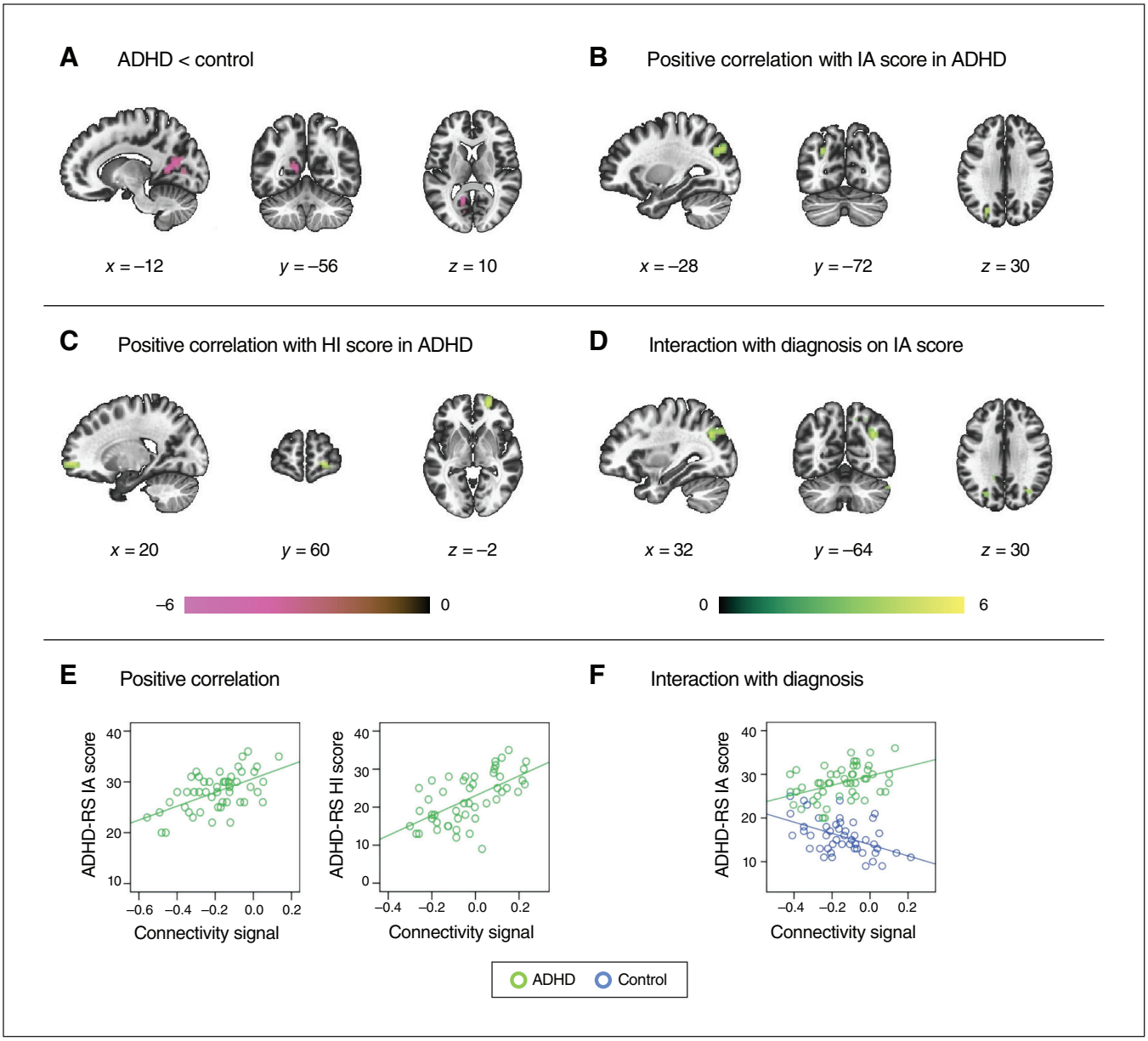

Figure 2: Altered thalamocortical functional connectivity in youth with attention-deficit/hyperactivity disorder (ADHD) observed using anatomically defined thalamic seeds. We used the AAL3 atlas to define the thalamic seeds. (A) Reduced thalamic functional connectivity in youth with ADHD compared to healthy controls using the mediodorsal thalamic seed. Results are displayed at $p_{FWE} < 0.05$, corrected at the cluster level across the whole brain, with a cluster-defining threshold of $p < 0.001$, uncorrected. (B) Correlation between thalamic functional connectivity and ADHD Rating Scale (ADHD-RS) inattention (IA) score in youth with ADHD using the mediodorsal thalamic seed. (C) Correlation between thalamic functional connectivity and ADHD-RS hyperactivity/impulsivity (HI) score in youth with ADHD using the lateral geniculate thalamic seed. (D) Interaction effect between thalamic functional connectivity and diagnosis of ADHD on ADHD-RS IA score using the mediodorsal thalamic seed. (B–D) Results are displayed at the voxel level $p < 0.001$, uncorrected for visualization. (E, F) Scatter plots showing the relationship between ADHD-RS scores and connectivity signals extracted from the significant clusters ($p_{FWE} < 0.05$, corrected for small volume). FWE = family-wise error.

functionally defined thalamic seed regions. As predicted, differences in thalamic functional connectivity between youth with and without ADHD were observed within the boundaries of corresponding large-scale thalamocortical networks when the analysis was based on functionally defined thalamic seeds, but no significant differences between groups were found outside the target networks defined a priori. In contrast, differences in thalamic functional connectivity based on anatomically defined seeds were observed outside the expected boundaries of major anatomic

projections, but no significant between-group differences with the target cortical ROIs selected based on anatomic projections from the thalamus.

Regardless of how the thalamic seed was defined, youth with ADHD showed significantly lower thalamocortical functional connectivity, without significantly higher thalamocortical functional connectivity, compared to youth without ADHD. In addition, significant correlations between thalamocortical functional connectivity and ADHD symptom severity were identified exclusively in youth with ADHD. Using functionally defined thalamic seeds, significant correlations were again observed within the boundaries of corresponding large-scale thalamocortical networks. However, in the analyses using anatomically defined thalamic seeds, significant correlations were observed outside the expected boundaries of major anatomic projections from the thalamus.

Because the hypothesis for this study involved the selection of predefined target ROIs and the comparison of thalamic connectivity with those ROIs, small-volume correction was employed, restricting the analysis over the set of each target ROI. Nevertheless, significant findings from functionally defined thalamic seeds were replicated at a more stringent significance threshold, because the identified clusters remained significant in whole-brain analysis without small-volume correction (in contrast to significant findings from the anatomically defined seeds, which were not well replicated). These findings appeared to be more robust using the functionally defined thalamic seeds than using their anatomic counterparts. Perhaps more importantly, thalamocortical functional connectivity based on Yeo's 7 resting-state-network parcellation appears to be clinically relevant in ADHD.

Interestingly, the directions of association between thalamocortical functional connectivity and ADHD symptom severity were opposite, depending on the nature of the thalamic seed definition. This may have been related to neural compensation.[36–38] Stern[36,37] has proposed 2 components of cognitive reserve: neural reserve and neural compensation. The former is related to interindividual differences in cognitive processing in the normal healthy brain; both young and old individuals may use the same brain networks to mediate task performance, but with differing levels of efficiency and capacity. On the other hand, neural compensation is based on alterations in cognitive processing that help cope with brain pathology or age-related neural changes; older individuals may adopt networks unused by younger individuals.[36]

ADHD has been characterized not only by neural hypoactivity but also by neural hyperactivity in regions of the brain related to compensatory functioning.[39] The mechanism of this compensation may be a greater reliance on neuroanatomically different strategies from those of typically developing individuals, which normally involves more flexible recruitment of optimal brain regions to match given task demands in the typically developing counterpart.[39] This is in line with findings in the present study showing significant group interactions for ADHD symptom severity and thalamocortical connectivity, which suggest recruitment of distinct neurocognitive strategies and associated neural networks, modulated by ADHD diagnosis.

Based on the possibility that compensatory strengthening of connectivity may develop with age,[36] additional analyses were performed to test the association between age and thalamocortical functional connectivity from anatomically defined seeds. IQ was included in the model as a proxy for neural reserve.[36] Lateral geniculate thalamic connectivity with the frontoparietal control network was found to be significantly and positively associated with age in youth with ADHD. Higher resting-state connectivity and stronger functional integration of frontal regions in the executive control network were related to a decrease in the hyperactive or impulsive symptoms of ADHD,[40] suggesting a compensatory role of this network.

The finding that this presumably compensatory association was driven by changes in hyperactive or impulsive symptoms rather than by a change in inattention appears to be clinically relevant, because the long-term course of ADHD is characterized by more improvements in hyperactivity or impulsivity compared to inattention.[41] Moreover, greater functional integration between the thalamus and prefrontal regions during response preparation paralleled symptom recovery in adulthood.[42] Stimulus-driven response preparation, which is associated with ADHD,[43] is a bottom-up process mediated by a thalamocortical network,[42,44] with the thalamus serving as an entry point for information to the cortex.[42]

A positive association was observed between the severity of hyperactive or impulsive symptoms and thalamic connectivity with the frontoparietal control network, consistent with prior reports in terms of implicated neural networks as well as the symptom domain, but inconsistent in its direction of association. Considering that compensatory processes are established gradually over the lifespan, and that increases in functional connectivity are thus generally observed in adults with ADHD,[45] the present findings from a sample of youth may depict an earlier phase of neural compensation, when those with more severe symptoms are beginning to recruit additional neural networks. This hypothesis remains to be confirmed by follow-up observations to determine whether the strength of positive associations is attenuated or reversed as age increases, ultimately reaching a stage when the functional connectivity of the lateral geniculate thalamus with the frontoparietal control network becomes negatively correlated with the severity of hyperactive or impulsive symptoms at a more advanced phase of neural compensation.

The Hebbian theory of synaptic plasticity posits that an increase in synaptic efficacy arises from repeated and persistent firing of pre- and postsynaptic neurons.[46] This phenomenon is thus facilitated based on an existing anatomic connection, coinciding with the finding of the present study that possible evidence for a compensatory change of functional connectivity was observed in analyses using the seed defined based on anatomic structure and histology.[30,47] A compensatory change in neural networks may favour a strengthening of connectivity where part of it is directly linked by white matter fibre tracts, over the functional connectivity possibly mediated through indirect connections.

Limitations

The present study had some limitations. First, the sample size was small. Because the present study used an existing data set, the size could not be altered. The complete data set consisted of MRI scans and phenotypic information collected from 8 international sites. To ameliorate concerns about different scanners and parameters among collection sites, the number of data collection sites used was reduced, but the maximum number of participants was retained. Accordingly, data from a single site (Peking University) were used, considering its large sample size and large number of resting-state fMRI scans per session. The characteristics of the participants with and without ADHD were matched using the coarsened exact matching algorithm, resulting in a further reduction of the study sample size. However, the fact that the 2 groups were well-matched for age, sex, full-scale IQ and all head-motion parameters can be regarded as a strength of the present study. Nevertheless, even though the demographic, clinical and head-motion characteristics were well-matched between the comparison groups, it was not clear whether they could be excluded from the covariates, or whether some of them should still have been included. A comprehensive analysis comparing the 2 different approaches (i.e., matching the variables and including the variables as covariates) may be a topic for another study. Another study might also require more detailed information about the quality control of image data; the binary information of either "pass" or "questionable" may not be sufficient. In particular, head motion is an important confounding factor for functional connectivity studies,[48,49] and more details about the quality of functional series based on head-motion characteristics are warranted.

Second, only a small number of girls was included in the analysis. Again, the number of female participants could not be increased. Although a high male predominance is among the typical characteristics of the population of interest,[1] the disproportionate sex ratio in the sample limits the generalizability of the findings of the present study. The current findings are expected to provide a basis for further studies with more participants, especially girls with ADHD.

Third, Yeo's 7 resting-state-network parcellation atlas was used, and the lack of a gold standard for brain parcellation is another limitation of the present study. Additional studies are needed to verify the robustness of the findings with respect to other parcellation methods.

Fourth, the cross-sectional study design and single measurement of resting-state fMRI limited the ability to interpret the functional implications of altered thalamocortical connectivity, especially whether the positive association observed between thalamocortical functional connectivity and the severity of hyperactive or impulsive symptoms represented a compensatory process. More specifically, although a significant association was observed between thalamocortical functional connectivity and age in youth with ADHD, the present study was cross-sectional and did not directly examine the effect of aging or time; cohort effects cannot be excluded.

Fifth, a relatively large number of seeds and target networks were examined separately, and some of the findings discussed here were uncorrected for these multiple comparisons, warranting caution because of the potential for false-positive results. The inherent arbitrariness in setting the cut-off for significance warrants further confirmatory studies with different and perhaps more stringent thresholds. Moreover, in the present study, a series of different analyses were conducted in a single data set, possibly overestimating the significance of the findings; therefore, the findings of this study need to be replicated in independent data sets in future studies.

Conclusion

The present study investigated thalamocortical functional connectivity in the brains of youth with ADHD using functionally and anatomically defined thalamic seed regions. Significant differences in connectivity and significant correlations between connectivity and ADHD symptom severity were found within the boundaries of corresponding large-scale networks and outside the expected boundaries of major anatomic projections from the thalamus, respectively, when performing analyses using the functionally and anatomically defined thalamic seeds. Given the clinical relevance of functional connectivity based on Yeo's 7 resting-state-network parcellation observed here, further research is warranted related to intrinsic network architecture in the brains of youth with ADHD.

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Data availability: The data used in this study are public and can be accessed from the ADHD-200 database (fcon_1000.projects.nitrc.org/indi/adhd200/) and the ADHD-200 Preprocessed Repository (preprocessed-connectomes-project.org/adhd200/).

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