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Larger thalamus correlated with inattentive severity in the inattentive subtype of ADHD without comorbidity

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ABSTRACT

Previous studies of brain structural abnormalities in attention-deficit/hyperactivity disorder (ADHD) samples scarcely excluded comorbidity or analyzed them in subtypes. This study aimed to identify neuroanatomical alterations related to diagnosis and subtype of ADHD participants without comorbidity. In our cross-sectional analysis, we used T_1-weighted structural MRI images of individuals from the ADHD-200 database. After strict exclusion, 121 age-matched children with uncomorbid ADHD (54 with ADHD-inattentive [iADHD] and 67 with ADHD-combined [cADHD]) and 265 typically developing control subjects (TDC) were included in current investigation. The established method of voxel-based morphometry (VBM8) was used to assess global brain volume and regional grey matter volume (GM). Our results showed that the ADHD patients had more regional GM in the bilateral thalamus relative to the controls. Post hoc analysis revealed that regional GM increase only linked to the iADHD subtype in the right thalamus and precentral gyrus. Besides, the right thalamus volume was positively related to inattentive severity in the iADHD. There were no group differences in global volume. Our results provide preliminary evidence that cerebral structural alterations are tied to uncomorbid ADHD subjects and predominantly attribute to iADHD subtype. Furthermore, the volume of the right thalamus may be relevant to inattentive symptoms in iADHD possibly related to a lack of inhibition of irrelevant sensory input.

1. Introduction

Attention-deficit hyperactivity disorder (ADHD) prevalence has been estimated at 5.0–7.1% in children and adolescents worldwide (Polanczyk et al., 2007; Willcutt, 2012). And efforts are still underway to uncover etiologies for this complex disorder both at the level of neural circuitry and genetics. Alterations in the brain structure as candidate endophenotype in ADHD are vital to further insights into the neural substrates of ADHD (Gallo and Posner, 2016).

Some structural MRI studies examining volumetric differences in ADHD draw consistent conclusions. For example, meta-analyses have documented smaller volumes in ADHD across several specific brain regions, most consistently in basal ganglia and prefrontal areas (Frodl and Skokauskas, 2012; Nakao et al., 2011; Valera et al., 2007). However, there are also some inconsistencies among findings of brain structural alterations in ADHD (e.g., one meta-analysis reported that only 25% to 50% of included studies revealed similar results) (Frodl and Skokauskas, 2012). First, abnormalities in other brain regions have also been reported, including the thalamus, posterior cingulate and motor cortices (Ivanov et al., 2010; Nakao et al., 2011; Sutcubasi Kaya et al., 2018). These abnormalities are in accordance with their crucial role in motivation, attention, planning movements, regulation of emotion (Ivanov et al., 2010; Nakao et al., 2011; Sutcubasi Kaya et al., 2018), all of which are putative dysfunctional cognitive domains in ADHD (Dickstein et al., 2006; Mostofsky et al., 2006; Rubia et al., 2005). Besides, there are other inconsistent findings such as increased grey matter volume in ADHD (Garrett et al., 2008; Greven et al., 2015; Li et al., 2015; Sutcubasi Kaya et al., 2018). Garrett et al. detected that volumes of the right caudate and

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right inferior frontal lobe were larger in the ADHD youth compared to the control youth in familial ADHD (Garrett et al., 2008). Also, Sutcubasi et al. reported the increased GM in the precentral and supplementary motor areas (Sutcubasi Kaya et al., 2018).

Those disparate findings among studies might attribute to differences in subject selection. The majority of the researches above are valuable, partly due to a large number of subjects (Hoogman et al., 2017; Nakao et al., 2011). Nevertheless, large samples of ADHD patients without strict screening might also lead to the heterogeneity in sample composition within and between studies. A study including a more homogeneous sample would probably contribute to our understanding of the neural substrates of the disorder and may yield additional information about this disorder.

Psychiatric comorbidity is one of the clinically essential dimensions of ADHD heterogeneity. Mental disorders comorbid with ADHD in children include oppositional defiant disorder (ODD), conduct disorder (CD), mood disorders (both unipolar and bipolar), anxiety disorders, and learning disorders (Pliszka, 1998). Among all of the disorders above, ODD and CD are common disorders that are present in up to 60% of clinic-referred children with ADHD (Noordermeer et al., 2017; Stevens and Haney-Caron, 2012). Such high comorbidity rates alert us that whether these comorbid disorders might also show neuroanatomical abnormalities specific to themselves or shared same regions with ADHD, all of which hinder our real understanding of brain volume abnormalities with ADHD.

As we feared, the meta-analysis showed smaller volumes of the amygdala, insula and frontal lobe in individuals with ODD/CD (with both ODD and CD), irrespective of the presence of ADHD comorbidity (Noordermeer et al., 2016). Furthermore, a study also detected greater right caudate and left ventrolateral prefrontal cortex volume in the uncombid ADHD than the uncombid conduct disorder group (Stevens and Haney-Caron, 2012). These results indicate that inconsistencies of neuroanatomical abnormalities reported in ADHD are (at least partly) due to comorbidity. The overlap in affected brain areas, which we regarded as alterations due to ADHD, are results of both ADHD and its comorbidity. Nevertheless, most studies on neuroanatomical correlates of ADHD did not investigate or report on the presence of comorbidities, which results in relatively few studies examining ADHD-only samples (Noordermeer et al., 2017). So in this study, we removed all subjects with psychiatric comorbidity for the sake of more precise results of grey matter volumetric alterations in ADHD (see Figure 1).

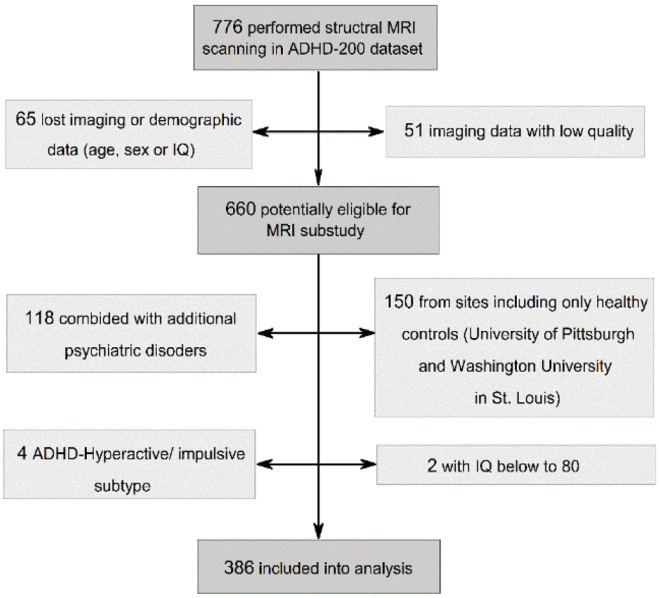

Fig 1. Flowchart of participant population in the study

Patients of ADHD can be assigned to one of three subtypes according to their clinical characteristics: the inattentive subtype (iADHD) with impairments mainly in attentional functioning, the hyperactive subtype (hADHD) with difficulties regarding impulse control and excess motor behaviour, and the combined subtype (cADHD) showing symptoms from both. Not only are three subtypes different in clinical appearance, but Erik et al. also presented a study assessing the family clustering of ADHD subtypes which indicated significant familial clustering of same-subtype combinations and significant genetic influences contributing to these patterns of subtype concordance (Rasmussen et al., 2004).To explore the underlying mechanism of different clinical manifestations of ADHD subtypes, several neuroanatomical investigations were conducted with inconsistent findings. Simon et al. reported that the iADHD subtype was linked to smaller volumes in the left dorsolateral prefrontal cortex (Maier et al., 2016). Sun et al. distinguished iADHD from cADHD depending on the cortical shape in the left temporal lobe, bilateral cuneus, and the left central sulcus using random forest classifiers (Sun et al., 2018). It seems that ADHD subtypes may share with diverse pathophysiological processes and brain volumetric abnormalities may be important indicators to reveal them.

Thus, the purpose of our study is to identify grey matter volume regions that differed between pure ADHD and the control group, as well as among subtypes of pure ADHD. We hypothesize that, after eliminating the effects of psychiatric comorbidity, ADHD may also manifest increased GM volumes in specific areas and aberrant neuroanatomical alterations between iADHD and cADHD possibly uncovering their different pathological substrates.

2. Methods

2.1. Participants

The data we used in this investigation are publicly available from the ADHD-200 Consortium (http://fcon_1000.projects.nitrc.org/indi/adhd200/). ADHD-200 database contains both resting-state functional MRI (rs-fMRI) and structural MRI (s-MRI) data, which are shared through the International Neuroimaging Data-sharing Initiative (INDI) (Bellec et al., 2017). The database also includes demographic data: age, sex, IQ, handedness, secondary diagnosis and medication status. Individuals in the ADHD group all met criteria for ADHD on the DICA-IV and had a T-score of 65 or greater on the Conners' Parent Rating Scale (CPRS-R) long form (DSM IV inattentive), or M (DSM IV hyperactive/impulsive), or met criterion on the DuPaul ADHD Rating Scale IV (six out of nine measures marked 2 or 3 for inattentive or hyperactive/impulsivity) (Douglas et al., 2018).

There are 776 structural MRI data aggregated at seven participating sites in the ADHD-200 Consortium. However, we excluded 390 ones, and the reasons for the exclusion were listed in Figure 1. Finally, our current study consists of 386 subjects:265 typically developing control subjects (TDC), 121 ADHD subjects (67 with cADHD, 54 with iADHD). Table 1 summarizes the demographic and psychometric data of patient samples (including ADHD subtypes) and the TDC group.

2.2. Data Acquisition

High-resolution T_1-weighted 3D magnetization-prepared rapid acquisition gradient echo (MPRAGE) images covering the whole brain were collected (at 3.0 Tesla). Moreover, all research protocols from institutes contributing to the ADHD-200 Consortium received local approval by their respective IRB. Each subject was fully anonymized following HIPAA Privacy Rules. Further details about scanning parameters in each scan site can be obtained from the ADHD-200 Consortium.

2.3. Data Processing

Anatomical images were analyzed in SPM8 (University College

Table 1
Demographic Data of All Patients (Including ADHD Subtypes) and Control Subjects

	ADHD	TDC		cADHD	iADHD	
	n=121	n=265	TDC/ADHD	n=67	n=54	TDC/cADHD/iADHD
Segment	Mean SD	Mean SD	c^2 or t p value	Mean SD	Mean SD	c^2 or [a]ANOVA p Value
Female/Male (n)	24/97	126/139	c^2=26.85 < .001[b,c]	12/55	12/42	c^2=27.09 < .001[b,c]
Age	11.3 2.4	11.1 2.3	t_{385}=-.54 .587	11.0 2.4	11.7 2.4	$F_{2,383}$=1.65 .193
IQ	107.3 14.2	114.8 13.5	t_{385}=4.97 < .001[c]	108.3 14.5	106.1 13.9	$F_{2,383}$=12.73 < .001[c]
ADHD index	72.0 9.1	45.3 6.4	$t_{99.56}$=-21.29 < .001[c]	72.8 8.7	71.0 9.8	$F_{2,188}$=332.64 < .001[c]
Inattentive symptoms	70.8 10.0	45.2 5.8	$t_{88.87}$=-19.13 < .001[c]	70.5 9.9	71.2 10.2	$F_{2,188}$=263.65 < .001[c]
Hyperactivity/Impulsive symptoms	69.4 12.3	46.6 5.8	$t_{80.58}$=-14.16 < .001[c]	74.8 10.4	59.8 9.1	$F_{2,188}$=253.36 < .001[c]

TDC, typically developing control subject; cADHD, combined ADHD subtype; iADHD, inattentive ADHD subtype; SD, standard deviation; c^2, chi square test; ANOVA, analysis of variance; ADHD index, Inattentive symptoms and hyperactivity/impulsive symptoms were measured by Conners' Parent Rating Scale-Revised, Long version (CPRS-LV)

[a] ANOVA between cADHD, iADHD and control subjects

[b] c^2 =chi square test

[c] $p < .001$

London, London, United Kingdom, http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) and segmented and spatially normalized using the VBM8 toolbox (Christian Gaser, University of Jena, Jena, Germany; http://dbm.neuro.uni-jena.de/vbm.html) with the default parameters in a MATLAB environment. The toolbox achieves highly accurate intersubject registration of brain images using an algorithm for diffeomorphic 3-D image registration.

After checking for artefacts and misalignments, each participant's native T_1 image was segmented into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF). Then, we generated an average anatomical template using the normalization of the grey and white matter segments of all TDCs via the exponentiated Lie algebra (DARTEL) algorithm. The segmented grey matter was then normalized to the specific DARTEL template with diffeomorphic anatomical registration to obtain individual deformation fields. Next, the GM segments of each subject were nonlinearly registered on the template based on the deformation creating Jacobian-modulated images with a 1.5 mm isotropic voxel resolution. As a result, the value in each voxel represents the local volume of the respective tissue type. Images were smoothed with an 8 mm full width at half maximum Gaussian kernel.

2.4. Statistical Analysis

2.4.1. Comparison of Demographic Data

Groups were compared on demographic characteristics using chi-square tests for all categorical variables and t tests or Analysis of Covariance (ANCOVA) which appropriate for dimensional data in SPSS software (version 22.0; IBM Corp., Armonk, NY).

2.4.2. Global Structural Volumes

Since the SPM8 unified segmentation method produces total volume measurements (mL) for grey and white matter and CSF tissue classes, we first compared the study groups' global structural signals using analysis of variance (ANOVA) for two groups comparison and then post hoc t tests for comparison among subtypes in SPSS software version 22.0. As the literature recommended, we controlled for age, sex, IQ and scan site (Gong et al., 2005; Ridgway et al., 2008). We calculated the following depending variables: segmented global WM, GM, CSF, total brain volume (TBV), and intracranial volume (ICV).

2.4.3. Regional GM Volumes

Differences in regional GM Volumes between the ADHD and control groups were analyzed using a two-sample t test. And in the further procedure of identifying possible differences among ADHD subtypes, we calculated an identical SPM full factorial analysis and then post hoc t tests with independent variables of ADHD subtypes (TDC, iADHD and cADHD). The above analysis is based on the whole brain structure. We controlled for age, sex, IQ, scan sites and ICV of each participant as covariance; absolute threshold masking with a threshold of 0.1 was applied. Statistical significance thresholds were applied at the voxel level ($p < .0001$, uncorrected), and the cluster threshold was set at 20 voxels.

2.4.4. Dimensional Effect of Psychopathology

To investigate the possible relationship between brain volume and ADHD symptoms, we extracted volumes of regional areas distinguishing ADHD or its subtypes from TDCs via the toolbox Rest 1.8 (Song et al., 2011). The region of interest (ROI) masks were selected from the automated anatomical labelling (AAL) atlas for obtaining an unbiased estimate of GM volume.

As the database aggregated from different scan sites, three measures were included to describe ADHD symptom severity. Within the database, 127 individuals were measured by ADHD Rating Scale IV (ADHD-RS), 191 by Conners' Parent Rating Scale-Revised, Long version (CPRS-LV) and 46 by Connors' Rating Scale-3rd Edition (the other 22 subjects missed their ADHD symptom scores). Due to the small number of subjects measured by Connors' Rating Scale-3rd Edition, we only investigated the correlation between the volume of ROI and ADHD symptom scores measured by ADHD-RS and CPRS-LV. We performed Pearson's bivariate correlation analysis to investigate such relationship in SPSS 22.0.

3. Results

3.1. Comparison of Demographic Data

The mean age of our final participants was 11.2 years (SD 2.34 years [range 7.2–18.0 years]). The diagnostic groups did not differ from the TDC group in age (p= .587) but did differ in IQ (p< .001, both diagnostic groups; higher IQ in the control group) and gender (p< .001, both diagnostic groups; more females in the control group). Furthermore, the diagnostic groups showed higher levels of total ADHD, hyperactive and inattentive symptoms compared with the control group ($p < .001$ for both diagnostic groups; fewer symptoms in the control group). The cADHD and iADHD groups did not differ from each other in IQ (p = .093) or gender (p = .554). However, compared with the iADHD group, the cADHD group showed a higher level of hyperactive/impulsive symptoms (p< .001). The level of total ADHD symptoms (p= .306) as well as inattentive (p= .702) ADHD symptoms didn't differ from each other. Table 1 summarizes the demographic and psychometric data of our study groups.

3.2. Segmented Global Structural Volumes

No significant group differences were found for segmented global structural volumes in ADHD and TDC group or ADHD subtype analysis

after controlling for age, sex, IQ and scan site.

3.3. Regional GM Volumes

Compared to the TDC group, GM volumes were larger in the ADHD group in the left and right thalamus at the p-level threshold of 0.0001. However, the control group > ADHD group comparison did not show any significant cluster. Interestingly, post hoc analysis among subtypes showed only iADHD group increasing volumes in the right thalamus and precentral gyrus compared to the control group ($p < .0001$, uncorrected), but not compared with the cADHD group. The control and cADHD groups did not differ (see Figure 2, Figure 3, Table 2).

3.4. Dimensional Effect of Psychopathology

We found the right thalamus was positively related to inattentive symptom scores measured by CPRS-LV in the iADHD group (see Figure 3). All other ADHD-RS scores and CPRS-LV scores failed to show any significant correlation in the iADHD group. Correlation analyses for the cADHD group, the combination of ADHD or the whole participants failed to detect any significant correlation of GM values with the ADHD symptoms measured by ADHD-RS or CPRS-LV.

4. Discussion

We found that GM in ADHD patients was increased in the bilateral thalamus. Interestingly, further analysis among subtypes revealed that only the iADHD group showed larger GM in the right thalamus and precentral gyrus relative to TDC. And the volume of right thalamus was positively related to inattentive scores in iADHD. However, no such regional neuroanatomical alterations or clinical correlation were found in the cADHD group. And global brain volume did not show any detectable difference in our diagnostic groups.

As we suspected, additional information of larger GM, which contradicted with most of the previous literature, emerged in the current study. Such inconsistent results are likely to originate from sample differentia. First, previous findings may not reflect neuroanatomical characteristics of ADHD alone but may be confounded by its comorbidity. For instance, ADHD+ODD and ADHD-only simultaneously reduced volumetric brain in frontal areas resulting in a "double burden", whereas ADHD+ODD also uniquely altered structure in areas such as the precuneus (Noordermeer et al., 2017). Analogously, comorbidity like conduct disorder and mood dysregulation also reduce in GM shared with ADHD or unique to themselves (Carballo et al., 2013; Stevens and Haney-Caron, 2012). Second, another interpretation for inconsistencies may be the combination of ADHD subtypes in most of the previous investigation. In our study, only iADHD subtype showed increased regional grey matter compared to TDC. Other studies employing pattern recognition, magnetoencephalography and magnetic resonance spectroscopy also found evidence for distinguishing the cADHD subtype from the iADHD subtype (Fair et al., 2012; Ferreira et al., 2009; Szekely et al., 2017). Additionally, a large twin study supported the notion that cADHD and iADHD subtypes might be genetically different (Rasmussen et al., 2004). It seems that the cADHD and the iADHD subtypes may represent different pathological mechanism, indicating such combinations of different subtypes might introduce noise into studies.

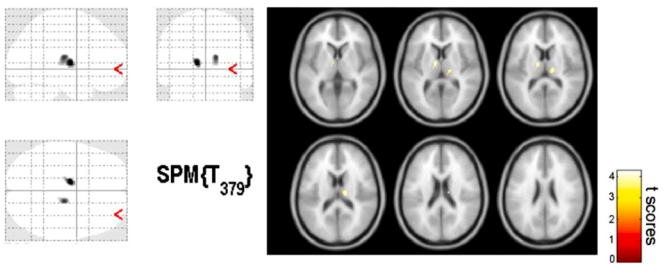

Fig 2. Greater grey matter in the whole ADHD group compared to typically developmental controls (TDC) at a threshold of P< .0001 (uncorrected). The volumetric values for the grey matter of ADHD patients were increased significantly in the bilateral thalamus.

Our results of larger grey matter are consistent with previous reports of thicker central sulcus cortical in children with ADHD (Li et al., 2015). Besides, greater motor cortex, including the precentral gyrus, also reported in recent literature conducting in pediatric ADHD (Sutcubasi Kaya et al., 2018). The increased volume of grey matter could be explained as reduced synaptic pruning or disturbances in normal myelination within these regions (Garrett et al., 2008; Greven et al., 2015; Sowell et al., 2003). It means that a reduction of white matter in the same region could result in an apparent abundance of grey matter. Therefore, larger volumes of the right thalamus and precentral gyrus in iADHD in our study could represent reduced white matter volume in the same areas. Consistent with our findings, Weining et al. detected lower axonal/cellular packing density and volume of white matter from the right thalamus to precentral gyrus in ADHD children (Wu et al., 2019).

In our study, we also found a positive relationship between the volume of the right thalamus and inattentive symptoms in the iADHD subtype. It was reported that the thalamus was a key component of the cortico-striato-thalamo-cortical (CSTC) loop that subserving executive function and effortful control (Ivanov et al., 2010; Rowe et al., 2005) (Ivanov et al., 2010; Rowe et al., 2005). ADHD is characterized by cortical hypoarousal and a lack of inhibition of irrelevant sensory input, and the research utilizing electroencephalographic (EEG) found enhancements in the delta–theta activity in the CSTC loop involved in reduced arousal and therefore manifested as cardinal symptoms in ADHD (Rowe et al., 2005). Besides, reduced activation for inhibition in the CSTC loop, especially in the thalamus area, is pronounced in patients of ADHD conducted by fMRI (Dickstein et al., 2006; Hart et al., 2013).

Except for the possible association of thalamus and ADHD symptoms demonstrated in EEG and fMRI studies, Weining et al. also detected the volume of thalamus-precentral connection in the right hemisphere negatively correlated with the ADHD symptom severity which relates well to our finding from the aspect of white matter (Wu et al., 2019). Besides, Ivanov et al. further reported the thalamic structure positively associated with inattentive symptom localizing specifically in the right medial surfaces and the pulvinar nucleus of the thalamus (Ivanov et al., 2010). These analyses all hypothesized the activation or structure of the thalamus is associated with the symptoms of ADHD, especially inattentive severity, which is consistent with our results in the iADHD group. It can be inferred the thalamus plays a prominent role in ADHD symptomatology.

Naturally, this study also comes with limitations. First, the exclusion of the hyperactive/ impulsive subtype of ADHD for its small quantity (only five after exclusion) prevents us from drawing general conclusions in volumetric alterations of three specific subtypes. Second, some data of participants in the dataset is incomplete or measured by different standards in every site (e.g. inattentive symptom severity), consequently resulting in unable to analyze thoroughly for every subject. Finally, the current study's cross-sectional design limits inferences about the direction of causality in the correlation of regional thalamic volumes with inattentive symptoms in iADHD.

5. Conclusion

Our cross-sectional findings point to increased grey matter, particularly in the bilateral thalamus in uncomorbid ADHD compared to TDC. Further analyses among subtypes showed only the iADHD subtype increased the volume in the right thalamus and precentral gyrus and the right thalamus volume correlated with inattentive severity. It implies that clinical interventions targeting the right thalamus in the iADHD subtype may prove more effective than other brain regions. Moreover,

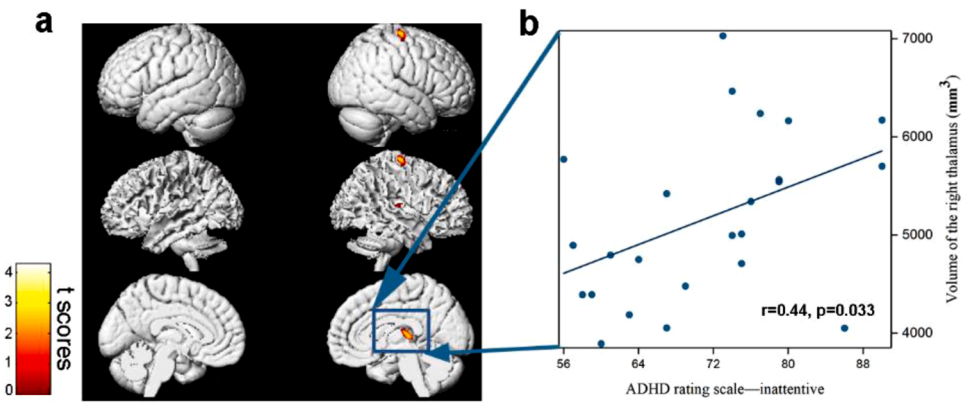

Fig 3. Greater grey matter in the inattentive ADHD subtype (iADHD) group compared to typically developmental controls (TDC) at a threshold of P< .0001 (uncorrected) and its correlation with ADHD symptoms. **a** Increased volumes were in the right thalamus and pre-central gyrus. **b** Relationships between the volume of the right thalamus and inattentive scores measured by Conners' Parent Rating Scale-Revised, Long version (CPRS-LV) in the iADHD group (Illustrated by Pearson's bivariate correlation analysis)

Table 2
Increasing brain regions of ADHD or iADHD subtype compared to Control Subjects

Region		peak-level			MNI coordinates		
	Voxel	t	Z	p	x	y	z
ADHD versus TDC							
Right thalamus	197	4.26	4.21	< .0001	15	-16	16
Left thalamus	135	4.49	4.43	< .0001	-12	-7	9
iADHD versus TDC							
Right thalamus	214	4.29	4.22	< .0001			
					11	-24	9
Right precentral gyrus	141	4.06	4.00	< .0001			
					35	-16	66

Cluster threshold set at 20 voxels using p < .0001; Brain regions are based on AAL atlas; GM = grey matter; MNI: Montreal Neurological Institute

we conclude that respective subtype may reflect different pathophysiology which needs to be treated apart in clinical.

Author Statement

M.H.W. and K.Z. contributed to the study conception and design. M. H.W. acquired the funding. C.Q.F., S.L.C., A.D.Q., R.H.Z collected the patients' data. J.J.Z and C.Y. checked the data. C.Q.F. performed statistical analyses and drafted the article. J.L.C., K.Z., and M.H.W. critically revised it. All authors reviewed the final manuscript and approved it to be submitted.

Declaration of Competing Interest

None of the authors have any financial interests or potential conflicts of interest to disclose.

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