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Atypical sulcal pattern in boys with attention-deficit/hyperactivity disorder

Xinwei Li[1,2] | Wei Wang[2] | Panyu Wang[3] | Chenru Hao[4] | Zhangyong Li[1,2]

[1]Chongqing Post-doctoral Research Station of Medical Electronics and Information Technology, Chongqing University of Posts and Telecommunications, Chongqing, China

[2]Chongqing Engineering Laboratory of Digital Medical Equipment and Systems, Chongqing University of Posts and Telecommunications, Chongqing, China

[3]College of Computer Science and Technology, Chongqing University of Posts and Telecommunications, Chongqing, China

[4]Department of Medical Physics, Hebei Medical University, Shijiazhuang, Hebei, China

Correspondence
Xinwei Li and Zhangyong Li, School of Bioinformatics, Chongqing University of Posts and Telecommunications, Chongqing 400065, China.
Email: lixinwei@cqupt.edu.cn (X. L.) and lizy@cqupt.edu.cn (Z. L.)

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Abstract

Neurodevelopmental disorders, such as attention-deficit/hyperactivity disorder (ADHD), are often accompanied by disrupted cortical folding. We applied a quantitative sulcal pattern analysis technique using graph structures to study the atypical cortical folding at the lobar level in ADHD brains in this study. A total of 183 ADHD patients and 167 typical developmental controls matched according to age and gender were enrolled. We first constructed sulcal graphs at the brain lobar level and then investigated their similarity to the typical sulcal patterns. The within-group variability and interhemispheric similarity in sulcal patterns were also compared between the ADHD and TDC groups. The results showed that, compared with controls, the left frontal, right parietal, and temporal lobes displayed altered similarities to the typical sulcal patterns in patients with ADHD. Moreover, the sulcal patterns in ADHD seem to be more heterogeneous than those in controls. The results also identified the disruption of the typical asymmetric sulcal patterns in the frontal lobe between the ADHD and control groups. Taken together, our results revealed the atypical sulcal pattern in boys with ADHD and provide new insights into the neuroanatomical mechanisms of ADHD.

KEYWORDS
attention-deficit/hyperactivity disorder, brain development, magnetic resonance imaging, sulcal pattern, sulcal pit

1 | INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a common childhood-onset psychiatric disorder characterized by inappropriate levels of inattention, hyperactivity, and/or impulsivity (Association, 2013). Despite its prevalence, the neuroanatomical and neurophysiological underpinnings of ADHD remain unclear. Numerous studies using magnetic resonance imaging (MRI) have revealed an increasing number of ADHD-related brain structural and functional abnormalities. For example, functional alterations in ADHD have been observed in multiple neuronal systems involved in higher-level cognitive functions and sensorimotor processes using task functional MRI (Cortese et al., 2012). Besides, altered gray matter volume, thinner cortical thickness, lower cortical surface area, and impaired gyrification in ADHD patients have been found in widespread brain regions using structural MRI (Bralten et al., 2016; Carmona et al., 2005; Hoogman et al., 2019; Shaw et al., 2012). Moreover, Shaw et al. reported that although the cortical development trajectory of ADHD patients was similar to that of the control group, the cortical thickness and surface area of ADHD patients peaked several years later than controls, which may partly explain the cortical morphological abnormalities found in ADHD (Shaw et al., 2007; Shaw et al., 2012).

Sulcus-based morphometry measures can provide additional insights into altered brain development in ADHD. So far, only a few studies have analyzed sulcal morphology in this population. Li et al. focused on the central sulcus in ADHD, and revealed that the average depth and maximum depth of the left central sulcus and the average cortical thickness of bilateral central sulci in the ADHD group were larger than those in the control group (S. Li, Wang, Li, Li, & Li, 2015). Besides, our recent analyses of the sulcal pits, which are the locally deepest points in cortical sulci, in boys with ADHD have reported reduced pits number in superficial secondary sulci and altered depth of sulcal pits in several brain regions (X. W. Li, Jiang, Wang, Liu, & Li, 2021). However, these methods cannot effectively characterize the spatial, geometric, and topological relations among multiple sulci, namely, the sulcal pattern. Studying the sulcal pattern can help us to understand the optimal organization of cortical functional areas and their underlying white matter connections (Fischl et al., 2008; Sun & Hevner, 2014). A recent review suggested that the alteration in global sulcal patterns reflects the changes in early brain development, manifested as interindividual differences in cognitive function, personality characteristics, or mental disorders (Im & Grant, 2019). Early studies on the sulcal patterns were mainly based on qualitative visual observation of the sulcal arrangement, connection, or interruption (Molko et al., 2003; Nakamura et al., 2007), which cannot quantify the intersulcal relationships and were time-consuming. In recent years, researchers have proposed to quantitatively analyze the sulcal pattern by modeling the sulcal pits in a local region as a sulcal graph (Im, Pienaar, et al., 2011; Meng, Li, Lin, Gilmore, & Shen, 2014; Takerkart, Auzias, Brun, & Coulon, 2017), successfully establishing the relationship with genetic factors (Im, Choi, et al., 2011) and describing cortical abnormalities in patients with various disorders (Im, Pienaar, et al., 2013; Im, Raschle, Smith, Ellen Grant, & Gaab, 2016; Ortinau et al., 2019).

To better understand the mechanism of structural cortical development in ADHD, it is important to study whether and how the sulcal pattern is affected in children with ADHD. Here, we utilized the regional sulcal pattern analysis technique to study the atypical cortical folding at the lobar level in ADHD brains. We first extracted sulcal pits from individual structural MR images of 183 ADHD boys and 167 boys with typical developmental controls (TDC). Then, we constructed sulcal graphs for each brain lobe and investigated their similarity to the typical sulcal patterns. We also compared within-group variability and interhemispheric similarity in sulcal patterns between the ADHD and TDC groups.

2 | MATERIALS AND METHODS

2.1 | Subjects

Structural MRI data from 167 TDC and 183 ADHD children were obtained from the ADHD-200 public available database (http://fcon_1000.projects.nitrc.org/indi/adhd200/). The ADHD sample consists of 119 children diagnosed with the combined type and 64 with predominantly inattentive type. The subjects were selected according to a set of criteria: (a) data from sites including both TDC and ADHD subjects; (b) passed the quality control of anatomical images; (c) only male subjects were selected as this sex constitutes the majority of ADHD children (Cuffe, Moore, & McKeown, 2005); (d) ages between 7 and 14 years to minimize potential developmental effects; (e) right-handedness; (f) intelligence quotients (IQ) ≥80 to avoid the effect of low intellectual functioning on the results; (g) subjects diagnosed with predominantly hyperactive/impulsive type were excluded because of their low number in the ADHD-200 database. The resulting sample was from four contributing sites, that is, Kennedy Krieger Institute (KKI, $n = 48$), New York University (NYU, $n = 107$), Oregon Health & Science University (OHSU, $n = 56$), and Peking University (PKU, $n = 139$). The demographic information of the study sample is summarized in Table 1. More detailed inclusion/exclusion criteria and demographic information of the participants from each institution can be found at the ADHD-200 website. The same sample was used in our previous study of the geometrical properties of sulcal pits in ADHD (X. W. Li et al., 2021). All study procedures were approved by each site's local Institutional Review Board. Parental written informed consent and child assent were obtained from all participants.

2.2 | Image acquisition and preprocessing

MRI data were collected using Philips Achieva Quasar (KKI), Siemens Allegra (NYU), and Siemens Trio (OHSU and PKU) 3-Tesla MRI scanners. High-resolution T1-weighted images were acquired for each subject using a 3D magnetization-prepared rapid gradient echo sequence. Subjects stopped medications at least 24 hr before scanning. The imaging parameters for each institution were listed in Supporting Table S1.

The quality controlled and preprocessed ADHD-200 images were provided by the Preprocessed Connectomes Project (Bellec et al., 2017). Briefly, the structural MRI were preprocessed using the FreeSurfer v5.3.0 pipeline (Fischl, 2012) that includes motion correction, transformation to the Talairach space, intensity normalization, removal of nonbrain tissue, tessellation of the gray/white matter interface, cortical surface reconstruction, automated topology correction, and surface deformation to refine tissue boundaries.

2.3 | Construction of pit graphs

As described in Auzias, Brun, Deruelle, and Coulon (2015), the sulcal pits were extracted from the white matter surfaces for each individual using the BrainVISA software (version 4.6.1, http://brainvisa.info). First, a depth feature of each vertex on the white matter surface was estimated by a depth potential function (Boucher, Whitesides, & Evans, 2009). Then, a filter watershed algorithm was used to divide each surface into several sulcal basins, each with a unique label. Finally, the locally deepest point in each sulcal basin was identified as

Variable	TDC ($N = 167$)	ADHD ($N = 183$)	p-Value
Age (years)	10.698 ± 1.731	10.623 ± 1.962	.705
Subtype	n/a	119 combined, 64 inattentive	n/a
Gender	All males	All males	Matched
Handedness	All right-handed	All right-handed	Matched
Full-scale IQ	116.040 ± 13.379	106.808 ± 13.689	<.001

TABLE 1 Demographic information of the subjects in the current study

Abbreviations: ADHD, attention-deficit hyperactivity disorder; IQ, intelligence quotient; TDC, typically developing children.

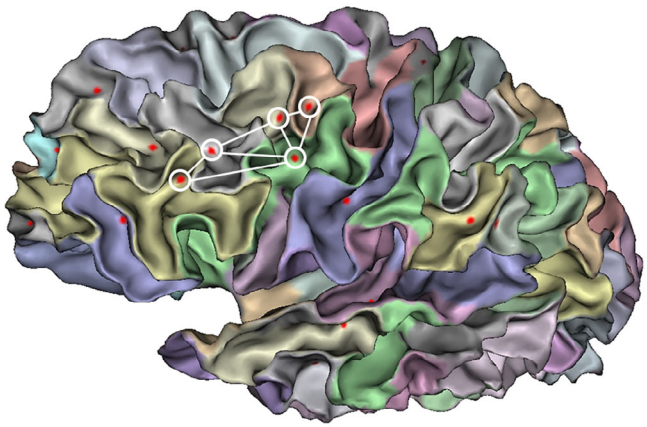

FIGURE 1 Individual sulcal pits and pit graph. Each colored patch represents a sulcal basin, and the small red dots represent sulcal pits. A schematic pit graph is shown in white, where pits are the nodes and adjacent basins are connected by edges

a sulcal pit, as shown in Figure 1. This extraction method was proved to be independent of individual brain size (Auzias et al., 2015).

To compare the sulcal patterns across different subjects, the sulcal pits and basins were projected to a common spherical space using a surface-based registration method provided by FreeSurfer (Fischl, 2012). Based on sulcal pits, a pit graph was built for a certain region to characterize the local folding pattern as in Im, Pienaar, et al. (2013). The pits in the region define the nodes of the graph, and the spatial adjacent relations between basins define the edges of the graph. That is, two pits are connected by an undirected edge if their corresponding sulcal basins are spatially connected on the white matter surface. A schematic pit graph is illustrated in white in Figure 1. To better characterize the folding pattern, two attributes were added to each graph node, that is, its coordinates on the common sphere and its depth in native space. For each subject, the pit depth was normalized by the maximum depth value to minimize the effect of brain size variation.

2.4 | Similarity measurement of pit graphs

The similarity between two pit graphs P and Q was computed using a graph kernel as introduced in Takerkart et al. (2017), which compares all node pairs $p_{ij} \in P$ and $q_{kl} \in Q$:

$$S(P,Q) = \sum_{\substack{i,j \in P \\ i,j=1}}^{N_P} \sum_{\substack{k,l \in Q \\ k,l=1}}^{N_Q} k_e(p_{ij},q_{kl}) \cdot k_c(p_{ij},q_{kl}) \cdot k_d(p_{ij},q_{kl}) \quad (1)$$

where N_P and N_Q are the number of nodes in P and Q; $k_e(p_{ij},q_{kl})$, $k_c(p_{ij},q_{kl})$, and $k_d(p_{ij},q_{kl})$ are three subkernels that reflect different features of the graphs. Normalization is performed to ensure the similarity between the graph and itself is equal to one:

$$\hat{S}(P,Q) = \frac{S(P,Q)}{\sqrt{S(P,P)S(Q,Q)}} \quad (2)$$

The first subkernel $k_e(p_{ij},q_{kl})$ guarantees that the graph comparison is performed only when both pairs of nodes p_{ij} and q_{kl} are connected:

$$k_e(p_{ij},q_{kl}) = e_{ij}^P \cdot e_{kl}^Q \quad (3)$$

where e_{ij}^P reflects the connection between nodes $i \in P$ and $j \in P$, and e_{kl}^Q reflects the connection between nodes $k \in Q$ and $l \in Q$ ($e = 1$ if the nodes are connected, and 0 otherwise). The second subkernel $k_c(p_{ij},q_{kl})$ compares the locations of p_{ij} and q_{kl} using Gaussian kernels:

$$k_c(p_{ij},q_{kl}) = e^{-\frac{\left\| c_i^P - c_k^Q \right\|}{2\sigma_c^2}} \cdot e^{-\frac{\left\| c_j^P - c_l^Q \right\|}{2\sigma_c^2}} \quad (4)$$

where C_i^P and C_j^P represent the spherical coordinates of nodes $i,j \in P$; C_k^Q and C_l^Q represent the spherical coordinates of nodes $k,l \in Q$; σ_c is a hyperparameter that determines the width of the Gaussian kernels that act on the coordinate features. In practice, this subkernel acts as a spatial filter that weights the comparisons of edges with their proximity, thus guaranteeing that only close edges are compared. The third subkernel $k_d(p_{ij},q_{kl})$ compares the depth features between node pairs p_{ij} and q_{kl}:

$$k_d(p_{ij},q_{kl}) = e^{-\frac{\left\| d_i^P - d_k^Q \right\|}{2\sigma_d^2}} \cdot e^{-\frac{\left\| d_j^P - d_l^Q \right\|}{2\sigma_d^2}} \quad (5)$$

where d_i^P and d_j^P represent the normalized depth of nodes $i,j \in P$; d_k^Q and d_l^Q represent the normalized depth of nodes $k,l \in Q$; σ_d is the kernel bandwidth. The two hyperparameters σ_c and σ_d were set to the

median Euclidean distances of the coordinates and depth features of all nodes in all graphs, whose effectiveness was demonstrated in Takerkart, Auzias, Thirion, and Ralaivola (2014).

2.5 | Sulcal pattern analyses

In this study, we examined the sulcal pattern similarity at the lobular level within and between groups, as illustrated in Figure 2. Specifically, for each lobe of the left and right hemispheres, we used Equation (6) to calculate the mean similarity of each ADHD subject with all TDC subjects, Equation (7) to calculate the mean similarity of each TDC subject with other TDC subjects, and Equation (8) to calculate the mean similarity of each ADHD subject with other ADHD subjects.

$$\hat{S}'_{A,T}(m) = \frac{1}{N_T}\sum\nolimits_{n \in TDC} \hat{S}_{A,T}(m,n), \quad \forall m \in ADHD, \forall n \in TDC \tag{6}$$

$$\hat{S}'_{T}(m) = \frac{1}{N_T - 1}\sum\nolimits_{n \in TDC, m \neq n} \hat{S}_{T}(m,n), \quad \forall m \in TDC \tag{7}$$

$$\hat{S}'_{A}(m) = \frac{1}{N_A - 1}\sum\nolimits_{n \in ADHD, m \neq n} \hat{S}_{A}(m,n), \quad \forall m \in ADHD \tag{8}$$

where $\hat{S}(m,n)$ is the similarity between pit graphs of two subjects calculated using Equation (2), N_T and N_A are the number of TDC and ADHD subjects, respectively. Notably, we observed that the sulcal patterns of a few subjects differed significantly from those of the rest, as shown in Figure 2b–d. These outliers were identified as being more than three standard deviations from the mean. We visually examined all white matter surfaces and found that these outliers contained some very different brains and all poor-quality surfaces. These outliers were excluded in the subsequent analyses to avoid the possibility that our findings were driven by them. This procedure of removing outliers also has an advantage of excluding only those subjects with an abnormal cortical surface in the region of interest. Indeed, FreeSurfer's cortical surface quality varies among lobes, as reported in Makropoulos et al. (2018).

Three comparative analyses were conducted. First, we examined whether the similarity between the ADHD and TDC groups ($\hat{S}'_{A,T}$, Equation (6)) was significantly different from the similarity within the TDC group ($\hat{S}'_{T}$, Equation (7)). Second, we investigated the sulcal pattern variability in ADHD by comparing the sulcal pattern similarity within the ADHD group ($\hat{S}'_{A}$, Equation (8)) and the similarity within the TDC group ($\hat{S}'_{T}$, Equation (7)). Third, we tested whether the inter-hemispheric sulcal pattern similarity was different between the TDC and ADHD groups. For each brain lobe, the interhemispheric similarity between the left and right pit graphs of each subject was calculated using Equation (2). It is worth noting that in the first two analyses, the common spherical space was based on the FreeSurfer nonsymmetric template (fsaverage), while in the third analysis, the common spherical space was based on the FreeSurfer unbiased symmetric template (fsaverage-sym).

Permutation tests were used to explore the group differences of the above sulcal pattern similarities as follows. First, we used multiple linear regression models with sulcal pattern similarities as the responses and confounding covariates as explanatory variables to calculate the residuals. Then, we permuted the residuals of the two comparison groups to estimate the null distribution, where the number of permutations was set at 10000. Next, the actual difference between groups was positioned in this distribution to calculate the *p*-value. Considering the priori one-tailed hypothesis that ADHD leads to decreased sulcal pattern similarities, we conducted one-tailed

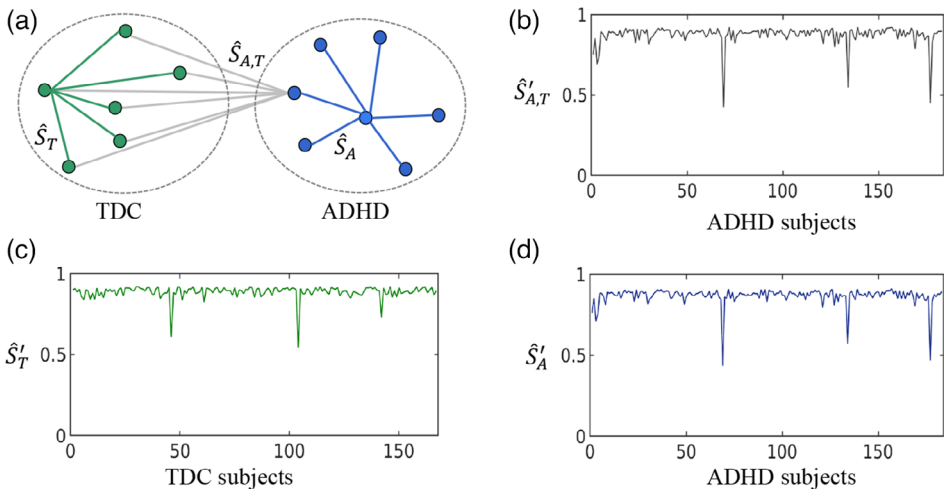

FIGURE 2 Sulcal pattern similarity analyses. (a) schematic diagram for calculating sulcal pattern similarity, each point represents a subject, and the line between two points represent the pit graph similarity between them, where $\hat{S}_T$ is the similarity between two typical developmental control (TDC) subjects, $\hat{S}_A$ is the similarity between two attention-deficit/hyperactivity disorder (ADHD) subjects and $\hat{S}_{A,T}$ is the similarity between one ADHD and one TDC subjects. (b) Mean sulcal pattern similarity of each ADHD subject with all TDC subjects ($\hat{S}'_{A,T}$) in the left frontal lobe. (c) Mean sulcal pattern similarity of each TDC subject with other TDC subjects ($\hat{S}'_{T}$) in the left frontal lobe. (d) Mean sulcal pattern similarity of each ADHD subject with other ADHD subjects ($\hat{S}'_{A}$) in the left frontal lobe

permutation tests in this study. For the confounding covariates, we used the intracranial volume and age. In addition, although a previous study has demonstrated the extraction of sulcal pits is highly reliable across scanner type and scan session (Im, Lee, et al., 2013), we still controlled the site in our statistical analyses to remove their potential impact. Specifically, these four sites were included in the statistical models as three dummy variables. We also tested whether the pits number and average similarity measures of each lobe different across sites via ANOVA, which details can be found in the Supporting Information 1. Moreover, since our ADHD sample consisted of two subtypes, we conducted all the above comparisons for these two subtypes. If they showed significant differences, the disease subtype was treated as a nuisance covariate in that statistical analysis. Additionally, as suggested by Dennis et al. (2009), we did not treat IQ scores as nuisance covariates in our main statistical analyses. However, we also conducted statistical analyses with IQ controlled, which details are presented in the Supporting Information 2. The significance level was set at $p < .05$ for all statistical tests in this study, and Bonferroni correction was used for multiple comparison corrections: considering the four lobes that make up each hemisphere, the significance level was set at 0.0125. We also calculated Cohen's d to estimate the effect sizes. With 183 ADHD patients and 167 controls, we were able to detect the differences in sulcal pattern similarities as small as Cohen's $d = 0.3$ at a significance level $p = .05$ and 80% power, which was determined by the G*power software (version 3.1).

3 | RESULTS

3.1 | Cohort

Our study includes 167 subjects with TDC and 183 subjects with ADHD. The age was not significantly different between the ADHD group and control groups (TDC: 10.689 ± 1.731 years, ADHD: 10.623 ± 1.962 years; $p = .705$). The two groups matched in gender and handedness. Moreover, the ADHD group had a significant lower full-scale IQ than the TDC group (TDC: 116.040 ± 13.379, ADHD: 106.808 ± 13.689; $p < .001$).

3.2 | Comparisons of similarity to the typical sulcal pattern

Figure 3a shows the four brain lobes of interest in this study, including the frontal, parietal, temporal, and occipital lobes, which were obtained by the lobe mapping provided by FreeSurfer. It is worth

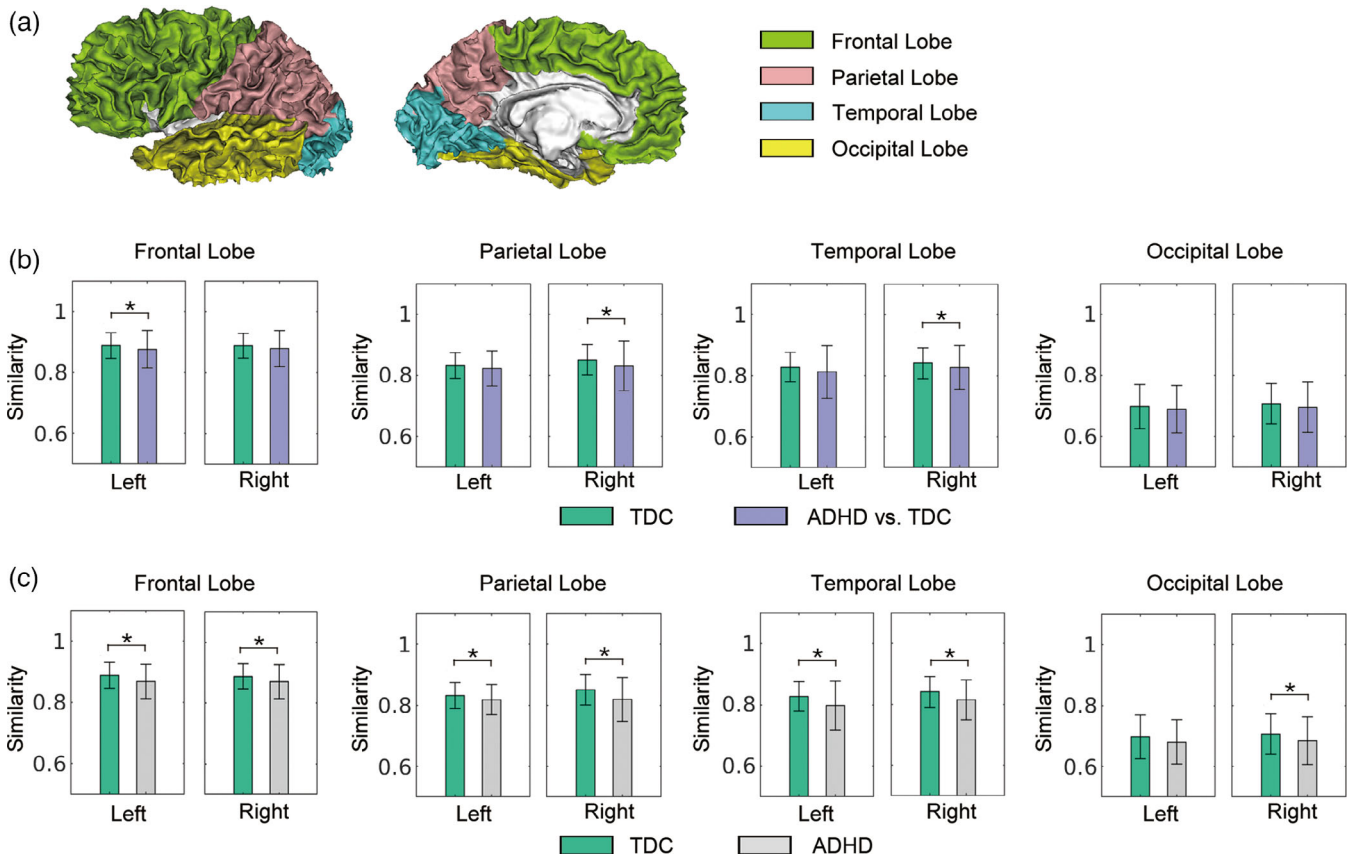

FIGURE 3 Results for the analyses of sulcal patterns. (a) Brain lobes are defined as ROIs for analyses. (b) Bar charts of the sulcal pattern similarity within the typical developmental control (TDC) group and the similarity between the attention-deficit/hyperactivity disorder (ADHD) and TDC groups. (c) Bar charts of the sulcal pattern similarity within the TDC and ADHD groups. *$p < .05$, Bonferroni corrected

noting that FreeSurfer's definition of the lobes does not include the insula and cingulate cortex (Klein & Tourville, 2012), so these two regions were not included in the lobe-level sulcal pattern analysis in this study. The bar charts shown in Figure 3a illustrate the sulcal pattern similarity within the TDC groups and the similarity between the ADHD and TDC groups. Table 2 provided additional statistical information. The results showed that the sulcal pattern similarity between the ADHD and TDC groups were lower than those within the TDC group. Significant differences were found in the left frontal lobe ($p = .005$, Cohen's $d = 0.356$), right parietal lobe ($p = .002$, Cohen's $d = 0.399$) and temporal lobe ($p = .009$, Cohen's $d = 0.312$). Moreover, no significant differences were found between ADHD subtypes ($p > .05$). Comparisons results with IQ controlled are shown in Supporting Table S3.

3.3 | Comparisons of within-group sulcal pattern similarity

The comparison results of the within-group sulcal pattern similarity between the TDC and ADHD groups are shown in Figure 3c and Table 3. The ADHD group revealed significantly lower within-group similarity than the TDC group in all lobes ($p < .05$ with Bonferroni correction, all Cohen's $d > 0.3$) except for the left occipital lobe ($p = .065$). We also observed that the sulcal pattern similarity varies with different brain lobes, with the most similar in the frontal lobe (about 88%) and the lowest in the occipital lobe (about 69%) in both groups. Moreover, there were no significant differences between ADHD subtypes ($p > .05$). Comparisons results with IQ controlled are shown in Supporting Table S4.

3.4 | Comparisons of interhemispheric sulcal pattern similarity

All four lobes showed high interhemispheric sulcal pattern similarity, with about 92% in the frontal lobe, about 89% in the temporal lobe, and about 86% in the parietal and occipital lobes, see Table 4. Significant difference in the interhemispheric sulcal pattern similarity between the ADHD-inattention subtype and the ADHD-combined subtype was found in the frontal lobe (inattention: 0.927 ± 0.028, combined 0.911 ± 0.036, $p = .004$). We also observed significant

TABLE 2 Statistical results for the comparisons of the sulcal pattern similarity within the TDC group and the similarity between the ADHD and TDC groups

	TDC	ADHD vs. TDC	Cohen's *d*	*p*-Value
Left				
Frontal lobe	0.893 ± 0.020	0.883 ± 0.032	0.356	.005*
Parietal lobe	0.835 ± 0.033	0.829 ± 0.038	0.163	.181
Temporal lobe	0.832 ± 0.035	0.821 ± 0.048	0.279	.028
Occipital lobe	0.703 ± 0.063	0.695 ± 0.063	0.121	.412
Right				
Frontal lobe	0.892 ± 0.020	0.885 ± 0.035	0.258	.064
Parietal lobe	0.855 ± 0.027	0.841 ± 0.045	0.399	.002*
Temporal lobe	0.848 ± 0.033	0.835 ± 0.046	0.312	.009*
Occipital lobe	0.712 ± 0.052	0.704 ± 0.061	0.126	.386

Note: p-Value was controlled for age, intracranial volume, and site. *$p < .05$, Bonferroni corrected.
Abbreviations: ADHD, attention-deficit/hyperactivity disorder; TDC, typically developing children.

TABLE 3 Statistical results for the comparisons of the sulcal pattern similarity within the TDC group and the similarity within the ADHD group

	TDC	ADHD	Cohen's *d*	*p*-Value
Left				
Frontal lobe	0.893 ± 0.020	0.874 ± 0.028	0.757	<.001*
Parietal lobe	0.835 ± 0.033	0.824 ± 0.032	0.324	.007*
Temporal lobe	0.832 ± 0.035	0.806 ± 0.044	0.672	<.001*
Occipital lobe	0.703 ± 0.063	0.686 ± 0.058	0.277	.065
Right				
Frontal lobe	0.892 ± 0.020	0.876 ± 0.031	0.600	<.001*
Parietal lobe	0.855 ± 0.027	0.825 ± 0.043	0.842	<.001*
Temporal lobe	0.848 ± 0.033	0.822 ± 0.042	0.691	<.001*
Occipital lobe	0.712 ± 0.052	0.691 ± 0.061	0.358	.010*

Note: p-Value was controlled for age, intracranial volume, and site. *$p < .05$, Bonferroni corrected.
Abbreviations: ADHD, attention-deficit/hyperactivity disorder; TDC, typically developing children.

	TDC	ADHD	Cohen's *d*	*p*-Value
Frontal lobe	0.927 ± 0.026	0.917 ± 0.034	0.343	<.001[a,*]
Parietal lobe	0.868 ± 0.044	0.865 ± 0.049	0.046	.494[b]
Temporal lobe	0.903 ± 0.042	0.893 ± 0.047	0.221	.055[b]
Occipital lobe	0.869 ± 0.063	0.853 ± 0.079	0.220	.082[b]

TABLE 4 Statistical results for the comparisons of the interhemispheric sulcal pattern similarity of the TDC and ADHD groups

Note: *$p < .05$, Bonferroni corrected.
Abbreviations: ADHD, attention-deficit/hyperactivity disorder; TDC, typically developing children.
[a]*p*-Value was controlled for age, intracranial volume, site, and ADHD subtype.
[b]*p*-Value was controlled for age, intracranial volume, and site.

difference between the ADHD group and TDC group in the frontal lobe ($p < .001$, Cohen's $d = 0.343$).

4 | DISCUSSION

In this study, we used sulcal pit graphs to quantitatively analyze the sulcal pattern of 183 boys with ADHD. Compared to matched controls, ADHD children revealed significantly reduced similarity with the typical sulcal pattern in the left frontal, right parietal, and temporal lobes. Moreover, ADHD children showed greater within-group variability of the sulcal pattern than TDC children in all lobes except for the left occipital lobe. Additionally, a reduced interhemispheric similarity of the frontal lobe was observed in the ADHD group relative to controls.

The quantitative comparisons of the similarity with the typical sulcal patterns indicated that ADHD patients had atypical sulcal patterns in the temporal, frontal, and parietal lobes. Moreover, the correlation analyses of the similarity to the typical sulcal pattern between lobe pairs showed that it is a global dissimilarity in the sulcal patterns of ADHD (see Supporting Information 3). The current findings are broadly consistent with previous studies assessing different morphological measures. Specifically, numerous studies have consistently reported cortical thinning across the entire cortex in ADHD, especially in the frontal, parietal, and temporal regions (Bralten et al., 2016; Carmona et al., 2005; Hoogman et al., 2019; Shaw et al., 2012). In terms of surface area, Shaw et al. detected abnormalities in these lobes with a cortical maturation delay in patients with ADHD (Shaw et al., 2012). Recently, a large-scale study from the ENIGMA-ADHD consortium (2,246 cases and 1,934 controls) found that ADHD children have widespread lower surface area, mainly in the frontal, cingulate, and temporal regions, as well as lower cortical thickness in the temporal regions (Hoogman et al., 2019). Additionally, Jacobson et al. reported volume reductions in the bilateral frontal, parietal, and temporal lobes in preschool children with ADHD, suggesting that structural abnormalities in ADHD appear very early in development (Jacobson et al., 2018). The cortical volume, thickness, and surface area reflect different brain attributes. Further research using more sophisticated analyses will allow us to examine their contribution to the disorganized sulcal patterns. Moreover, recent reviews of functional neuroimaging studies have demonstrated that the default mode and frontoparietal networks are among the most abnormal neural circuits implicated in ADHD (Castellanos & Aoki, 2016; Posner, Park, & Wang, 2014), which supports our results to some extent, as the core regions of these two networks are mainly located in the temporal, frontal, and parietal lobes (Yeo et al., 2011). Besides, a unified feature of the temporal, frontal, and parietal lobes is the involvement of the heteromodal association cortex, which forms a distributed nervous system supporting attention maintenance and behavioral inhibition (M.-M. Mesulam, 1998; Sowell et al., 2003). Thus, the atypical sulcal patterns found in this system may account for deficits in attention and inhibition in ADHD.

Regarding hemispheric laterality, our results of disrupted sulcal pattern in the left but not right frontal lobe is consistent with a previous volumetric analysis (Hesslinger et al., 2002). However, some studies suggested that ADHD pathology is more associated with abnormalities in the right frontal lobe (Almeida et al., 2010; Clark et al., 2007). Moreover, several studies have reported reductions in the cortical thickness and volume of both the left and right frontal lobes in ADHD patients (Makris et al., 2007; Shaw et al., 2007; Silk, Beare, et al., 2016). These inconsistencies may be due to differences in research methods or sample characteristics. Additionally, for the parietal lobe, we found atypical sulcal patterns on the right side. The right parietal lobe is thought to play a greater role in sensory processing, and ADHD patients showed similar inattention and hyperarousal symptoms as patients with right parietal lobe damage (Aman, Roberts Jr, & Pennington, 1998; M. M. Mesulam, 1981). Our results further support the right parietal lobe theories of ADHD. We also observed the sulcal pattern of the temporal lobe was abnormal on the right side. In line with our study, many previous studies have reported abnormalities in the right temporal lobe in ADHD (Fernández-Jaén et al., 2014; Kobel et al., 2010; Vilgis, Sun, Chen, Silk, & Vance, 2016). For example, Kobel et al. confirmed that the right temporal lobe is a highly affected locus in ADHD using several structural and functional imaging techniques (Kobel et al., 2010). Our findings further corroborate that the right temporal lobe is involved in the pathophysiology of ADHD.

Besides, compared with the TDC group, the ADHD group showed lower within-group similarity of the sulcal patterns in almost all lobes, which indicates that the sulcal patterns of ADHD are more heterogeneous than controls. The cortical development of ADHD may be affected by multiple genetic and environmental risk factors and their interactions (Bonvicini, Faraone, & Scassellati, 2018; Nigg, Nikolas, & Burt, 2010), which could lead to higher variability in sulcal patterns.

In fact, previous studies have consistently demonstrated that ADHD is a heterogeneous disorder on multiple levels, such as varied developmental trajectories, abnormal brain structure, and function (see review in Luo, Weibman, Halperin, & Li, 2019). It is worth noting that our ADHD sample contains two subtypes, which may partly contribute to the observed heterogeneous sulcal pattern. However, we did not observe any significant differences between the two subtypes in terms of within-group similarity and similarity to the typical sulcal patterns. In the future, it would be interesting to investigate whether ADHD can be divided into distinct anatomical subtypes based on the sulcal pattern, which may enable a better understanding of the neurobiology of ADHD and facilitate the development of interventions.

Finally, our results showed that ADHD boys have a reduced interhemispheric sulcal pattern similarity (i.e., increased asymmetry) in the frontal lobe relative to TDC boys. Indeed, atypical frontal asymmetry is among the most consistent findings in ADHD research, which may play a role in the pathogenesis of this disorder. For instance, structural MRI studies have shown changes in asymmetrical patterns of frontal cortical thickness and volume in ADHD patients (Castellanos et al., 1996; Shaw et al., 2009). Moreover, several resting-state electroencephalogram studies have reported the disruption of typical frontal alpha asymmetry in ADHD, which may support a motivational dysfunction hypothesis of this disorder (Hale et al., 2009; Keune, Wiedemann, Schneidt, & Schönenberg, 2015). Abnormal hemispheric asymmetry of the frontostriatal white-matter tract volume and underlying white-matter microstructure were also observed in children with ADHD (Silk, Vilgis, et al., 2016). It is worth noting that our recent asymmetric analyses of sulcal pit depth using the same sample did not show any significant differences between the ADHD and TDC groups (X. W. Li et al., 2021). This may indicate that the graph structure of sulcal pits is more sensitive to characterize brain morphological abnormalities than the direct analyses of sulcal pits.

The current study has several limitations. First, our sample only included boys; it is not clear whether our results could generalize to girls with ADHD. Second, the unmatched IQ between subjects with and without ADHD may introduce biases into the results, given an association between sulcal pits and human intelligence (Im, Choi, et al., 2011). However, the intelligence tests of ADHD patients can be affected by their inattention deficits, and their IQ values are generally lower than that of controls (Bridgett & Walker, 2006). Thus, according to the suggestions of Dennis et al. (2009), we did not match the IQ of ADHD and TDC groups, nor did we take IQ as a covariate in our main statistical analyses. However, we also reported and discussed the findings controlling for IQ in the Supporting Information 2. Finally, the atypical sulcal patterns in ADHD were derived cross-sectionally in the present study; however, it will be important to track the dynamical development of sulcal patterns using a longitudinal design in the future.

5 | CONCLUSIONS

In summary, the current study revealed abnormal sulcal patterns in the left frontal, right parietal, and temporal lobes of ADHD boys. Furthermore, the ADHD group showed widespread higher heterogeneous sulcal patterns than the TDC group. The results also confirmed the disruption of the typical asymmetric sulcal patterns in the frontal lobe. To the best of our knowledge, this is the first study to examine the sulcal pattern in ADHD. Our findings provide novel evidence to the growing literature reporting cortical morphological abnormalities in boys with ADHD.

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CONFLICT OF INTERESTS

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Xinwei Li and **Zhangyong Li**: Designed this research. **Xinwei Li**: Analyzed the data. **Xinwei Li**, **Wei Wang**, **Panyu Wang**, and **Chenru Hao**: Interpreted the data. **Xinwei Li** and **Panyu Wang**: Drafted the first version of the manuscript. All authors contributed to the preparation of the final manuscript and have approved its submission.

DATA AVAILABILITY STATEMENT

The derived data and code supporting the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Xinwei Li https://orcid.org/0000-0003-0713-9366

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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