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Comparison of Brain Function Between Medication-Naïve ADHD with and without Comorbidity in Chinese Children Using Resting-State fNIRS

ABSTRACT

Background: This study used functional near-infrared spectroscopy (fNIRS) to investigate brain activation patterns in children with attention deficit hyperactivity disorder (ADHD) with and without additional comorbidities to identify disease-related biomarkers by the neuroimaging that will facilitate to make a diagnosis decision.

Methods: In this study, 165 medication-naive children aged 7 to 15 years were recruited and categorized into four groups: ADHD, ADHD with learning disabilities (ADHD&LD), ADHD with oppositional defiant disorder (ADHD&ODD), and healthy controls. A multichannel fNIRS system was used to monitor hemodynamic changes at rest state in the prefrontal and temporal lobes of the brain. The amplitude of a low-frequency fluctuation (ALFF) matrix was calculated by summation and averaging of the square root of the signal power spectrum. One-way analysis of variance was used to identify statistical differences between channels.

Results: All ADHD children presented significantly higher ALFF values in different brain regions when compared with the healthy controls. Patients with ADHD&LD exhibited higher ALFF values in the medial prefrontal cortex ($P_{Ch38}=.01$, $P_{Ch48}=.01$), temporal cortex ($P_{Ch22}=.04$, $P_{Ch41}=.002$, $P_{Ch51}=.001$), and the left ventrolateral prefrontal cortex ($P_{Ch39}=.0009$, $P_{Ch50}=.001$), whereas ADHD&ODD children were not significantly different to those diagnosed with ADHD.

Conclusions: ADHD with learning disabilities (LD) possessed a different pathogenesis from ADHD, manifested as lower functional brain activity in the medial prefrontal cortex, temporal cortex, and the left ventrolateral prefrontal cortex, while ADHD&ODD did not present significant changes compared with ADHD. ODD-related symptoms may be part of ADHD symptoms rather than being an independent disorder.

Keywords: Attention deficit hyperactivity disorder brain imaging, children, learning disabilities, oppositional defiant disorder

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Introduction

Attention deficit hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder in children. It is characterized by persistent difficulty in maintaining attention, hyperactivity, and impulsive behaviors. There is a large gap of 2-16% or more in prevalence of ADHD in children and adolescents, related to the different assessment tools used and between self and parents-reports and clinicians and differences in epidemiological samples, countries, and even different regions of a country.[1-3] ADHD may have lifelong impacts by increasing the risk of other psychiatric disorders, accidents, addictions, criminality, educational and occupational failure, and social disability.[4] Comorbidity is highly prevalent, and it was estimated that more than half of children with ADHD may have at least one comorbid psychiatric disorder.[5] Common comorbid disorders include oppositional defiant disorders (ODD), conduct disorders (CD), learning disabilities (LD), tic disorder (TD), depression, anxiety, and autism spectrum disorder (ASD).[6] Approximately 48-67% of ADHD children suffer

from comorbid ODD or CD.[7] In total, 40-50% of children with ADHD could have comorbidity with LD, such as dyslexia, dyscalculia, and dysgraphia.[8] The presence of comorbidity poses a challenge to the diagnosis, treatment, and prognosis of ADHD.

Some theories explain comorbidity, such as the phenocopy hypothesis, the direct causation model, a mixed group theory, and a third unique entity theory.[9,10] Specifically, the phenocopy hypothesis suggests that people with ADHD and comorbidities suffer from ADHD or specific comorbidity separately, with the symptoms of ADHD a consequence of the symptoms of the comorbidity and vice versa. The direct causation model is similar to the phenocopy hypothesis. The presence of one disorder is presumed to be caused by neurophysiological deficits due to another disorder. The mixed group theory proposes that people with ADHD and comorbidity represent a mixed group whose symptoms are additive but not beyond the combination of two independent pathologies. Additionally, a third unique entity theory proposes that ADHD with its comorbidity is not a simple combination of two disorders but a third unique entity; the individual with comorbidity would exhibit different neurocognitive deficits due to the additive combination. To summarize, there may be three possible types of pathogenesis of ADHD and its comorbidity according to the above theories, i.e., (1) ADHD or comorbidity alone; (2) the combination of ADHD and a specific comorbidity; and (3) a third unique entity.

To further understand the underlying mechanism of ADHD and its comorbidity, functional neuroimaging techniques, such as functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and functional near-infrared spectroscopy (fNIRS) have been widely applied. Numerous studies on brain function exist for children with only ADHD, ODD, or LD. Children with ADHD had structural and functional deficits, mainly in the dorsolateral and ventrolateral prefrontal cortex, the anterior cingulate cortex, the supplementary motor area, and the cerebellar-frontostriatal circuitry.[11,12] These deficits were associated with attention deficit and impaired executive function, especially inhibitory control.[13,14] Currently, there have been a limited number of studies that address whether ADHD children with comorbidity exhibit different patterns of brain structure and functions compared with those with only ADHD. Langer et al used structural and functional MRI to investigate behavior, brain structure, and neural correlations in 60 children divided into four groups: children with reading disabilities (RD), ADHD, ADHD comorbid with RD (COM group), and typically developing (TYP), and found significant differences in brain structure and function between the COM and ADHD groups via whole-brain analyses of variance.[15] More specifically, the observed abnormalities in performance included reduced cortical thickness in the middle temporal gyrus in the COM group compared to the ADHD group and increased activity in the left inferior frontal gyrus in the ADHD group compared to the COM and RD groups. Additionally, whole-brain analysis of the reading fluency task showed significantly increased brain activity in the left fusiform gyrus in the TYP group compared to the RD group and stronger activation in the left superior temporal gyrus in the COM and ADHD groups compared to the RD group.[15] Perera et al. [16] distinguished two clusters in children with and without comorbidity regarding event-related potentials and psychometric profiles. The study also detected unique neurocognitive deficits in the comorbid ADHD group, suggesting that ADHD with comorbidity may act as a distinct pathological entity.

MAIN POINTS

- *ADHD with LD possessed a different pathogenesis from ADHD only.*
- *ADHD with ODD did not present significant changes in fNIRS images when compared with ADHD.*
- *Our study suggested that ODD-related symptoms may be part of ADHD symptoms rather than being an independent disorder.*

Functional near-infrared spectroscopy (fNIRS) has recently been widely used to measure the cortical hemodynamic response with a high resolution due to its non-invasiveness, noiselessness, and portability. fNIRS allows subjects to perform tests in a relatively natural environment at a lower cost than magnetic resonance imaging (MRI). High ecological validity, reliability and reproducibility has led to fNIRS being commonly applied in ADHD research and clinical practice, particularly among children.[17-19] To the best knowledge of the authors, there are no studies of comorbidities of ADHD using fNIRS.[17] Consequently, the current study was conducted using resting-state fNIRS to acquire cerebral hemodynamic data from subjects in four groups, i.e., ADHD, ADHD comorbid with ODD, ADHD comorbid with LD, and healthy controls. The aim was to identify the specific pattern of brain function in ADHD children with and without comorbidity (i.e., ODD and LD) and further verify existing theories/hypotheses of comorbidity.

Material and Methods

Study Design and Participants

A total of 165 children were recruited for this study, including 90 (54.55%) children diagnosed with ADHD; 37 (22.42 %) had both ADHD and LD; 14 (8.48%) had ADHD and ODD, and 24 (14.55%) as healthy controls. Children with ADHD and comorbidities were recruited from the Peking University Sixth Hospital outpatient clinic between March and June 2017. The diagnosis was made by a pediatric psychiatrist or an attending physician or above, according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR); a semi-structured interview from the Clinical Diagnostic Interview Scale (CDIS) was used for further verification.[20] Inclusion criteria were children (1) diagnosed with ADHD; (2) with an intelligence quotient (IQ) ≥ 80 according to the Chinese-Wechsler Intelligence Scale for Children (C-WISC); (3) aged from seven to fifteen years old; and (4) who did not take any central stimulants, atomoxetine, antipsychotics, antidepressants or other psychiatric drugs. Exclusion criteria included children with (1) mental disorders consistent with DSM-IV Axis I diagnosis; (2) a history of head trauma, neurological illness, or other obvious physical or neurological abnormalities; and (3) unable to understand and use Mandarin.

Normal controls were students selected from the local primary and secondary schools between March and June 2017. Their normality was determined with the Schedule for Affective Disorders and Schizophrenia for School Age Children-Present and Lifetime Version (K-SADS-PL) by a pediatric psychiatrist who was an attending physician or above. Inclusion criteria were children (1) with IQ ≥ 80 according to an evaluation by the Chinese-Wechsler Intelligence Scale for Children; (2) aged between seven and fifteen years old and whose gender ratio matched the study group. Children were excluded if (1) they reported more than four items of attention deficit and/or hyperactive impulsivity on the ADHD-IV symptom

scale; (2) currently or previously had psychiatric diseases, significant physical and neurological diseases, or disorders. All the selected children in the normal group were right-handed, with either normal or corrected vision, no color weakness, glaucoma, or other ocular abnormalities.

The study was conducted according to the Declaration of Helsinki[21] and was approved by the Research Ethics Review Board of the Peking University Sixth Hospital (IRB number: 2016-15, date of approval: 2016-07-13). Written informed consent was obtained from the guardian of all children before the study.

Clinical and Neuropsychological Assessment

Parents completed the ADHD DSM-IV Symptom Questionnaire (DQ) and a Parent Symptom Questionnaire to evaluate the severity of ADHD and ODD symptoms. The Learning Disabilities Diagnostic Inventory was used to examine the presence of LD.[22-24]

Brain Imaging Data Acquisition and Processing

A multichannel fNIRS system (ETG-4000; Hitachi, Japan) was used to measure hemodynamic changes in the prefrontal and temporal lobes of the brain in the resting state. The system employed two wavelengths of near-infrared light (695 and 830 nm) at a sampling rate of 10 Hz. The setup included seventeen light sources and sixteen detectors, spaced 2 cm apart, creating 52 measurement channels. Probes were placed according to the international EEG 10-20 system, with the middle inferior probe positioned over Fpz and the inferior row of probes directed toward T3 or T4. Figure 1 illustrates the fNIRS channel arrangement on a model brain.

Children were instructed to sit quietly, maintain a steady head position, clear their minds as much as possible, and refrain from changing body positions. The measurement session lasted eight minutes. During this period, behavior and real-time signal changes were monitored for subsequent data preprocessing, with annotation of any artificial interference signals.

Statistical Analysis and Data Visualization

Firstly, we compared the clinical and neuropsychological characteristics across four groups, i.e., ADHD, ADHD&LD, ADHD&ODD, and healthy controls. Regarding the continuous variables, a one-way analysis of variance (one-way Analysis of Variance [ANOVA]) was applied, and regarding the categorical variable, the Chi-square test was used. Raw data was processed with the NIRS_KIT, a MATLAB toolbox,[25] by converting the original light intensity data to the concentration of oxyhemoglobin based on a modified Beer–Lambert law.[26] A polynomial regression model and the temporal derivative distribution method were used to remove baseline drift and motion artifacts.[27] Subsequently, a bandpass filter 0.01-0.08 Hz was applied to remove low-frequency drift and high-frequency neurophysiological noise.[28]

An amplitude of low-frequency fluctuation (ALFF) matrix was applied to the preprocessed data of each subject. The ALFF was obtained by summing and averaging the square root of the signal power spectrum.[29] Data processing used MATLAB Version R2022a. Oxyhemoglobin data were chosen for subsequent analyses due to their better signal-to-noise ratio.[30] The averages of ALFF matrixes from different groups were calculated to characterize the average level of each group. A one-sample *t*-test was performed to examine data consistency within each group. Significant differences ($P < .05$) between probe channels across groups were assessed by one-way analysis of variance.

Results

Demographic and Clinical Variables of the Study Population

Table 1 gives the characteristics of the study population. There were no statistically significant differences in age and gender across the four groups. IQ values were lowest in the ADHD group comorbid with the LD group when compared to the other groups. Conners' Behavior scores were significantly higher in children with ADHD and LD ($P < .05$). The Disruptive Behavior Questionnaire for Adolescents, Conners'' Abbreviated, and Child Conduct scores were significantly higher in children with ADHD&ODD ($P < .05$).

Brain Activation Performance in ALFF of the Study Population

Figure 2 illustrates the average amplitude of low-frequency fluctuation (ALFF) values across all channels for each group within the study. For healthy controls (HCs), the medial prefrontal cortex (MPC) along with the left and right temporal cortex (TC) showed significantly lower ALFF values, while the left and right posterior prefrontal cortex (PPC) demonstrated significantly higher ALFF values. In ADHD

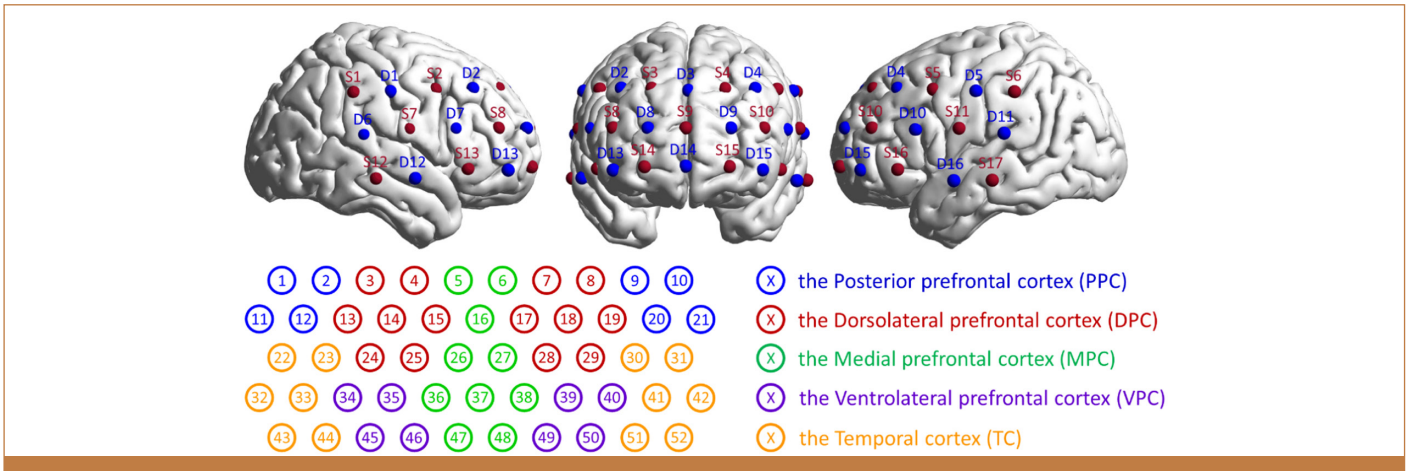

Figure 1. Arrangement of 17 light sources and 16 detectors on a model brain and the correspondence between 52 channels and ROIs. ROIs, regions of interest.

Table 1. Clinical and Neuropsychological Characteristics of the Study Population

	ADHD (n = 90)	ADHD&LD (n = 37)	ADHD&ODD (n = 14)	Healthy controls (n = 24)	*P* value
Age, years	9.24 ± 2.47	10.24 ± 2.43	9.37 ± 1.93	9.14 ± 1.99	.20
Gender					.32
Boy	75 (83.33)	28 (75.68)	11 (78.57)	16 (66.67)	
Girl	15 (16.67)	9 (24.32)	3 (21.43)	8 (33.33)	
IQ	104.77 ± 14.74	95.04 ± 13.43	111.10 ± 15.62	117.07 ± 9.80	<.001
DQA score	2.90 ± 0.43	3.12 ± 0.41	3.21 ± 0.41	NA	.02
DQH score	2.50 ± 0.76	2.36 ± 0.73	2.87 ± 0.70	NA	.21
DQI score	2.40 ± 0.77	2.22 ± 0.83	2.64 ± 0.80	NA	.35
CA score	7.12 ± 4.70	6.54 ± 3.80	10.89 ± 3.76	NA	.04
CB score	6.43 ± 2.12	7.75 ± 2.17	6.78 ± 3.11	NA	.03
CC score	1.08 ± 1.42	1.00 ± 1.30	2.33 ± 1.80	NA	.04
CD score	5.42 ± 3.02	5.14 ± 2.72	5.67 ± 2.96	NA	.87
CE score	3.18 ± 1.94	2.18 ± 1.70	3.22 ± 2.82	NA	.07
CF score	12.99 ± 4.80	12.11 ± 4.45	14.22 ± 5.63	NA	.48

ADHD, attention deficit hyperactivity disorder; CA, Conners for conduct problem; CB, Conners for learning problem; CC, Conners for psychosomatic problem; CD, Conners for impulsivity-hyperactivity; CE, Conners for anxiety; CF, Conner's for hyperactivity index; DQA, DSM-IV Symptom Questionnaire for attention; DQH, DSM-IV Symptom Questionnaire for hyperactivity; DQI, DSM-IV Symptom Questionnaire for impulsiveness; IQ, Intelligence Quotient; LD, learning disabilities; ODD, oppositional defiant disorders.

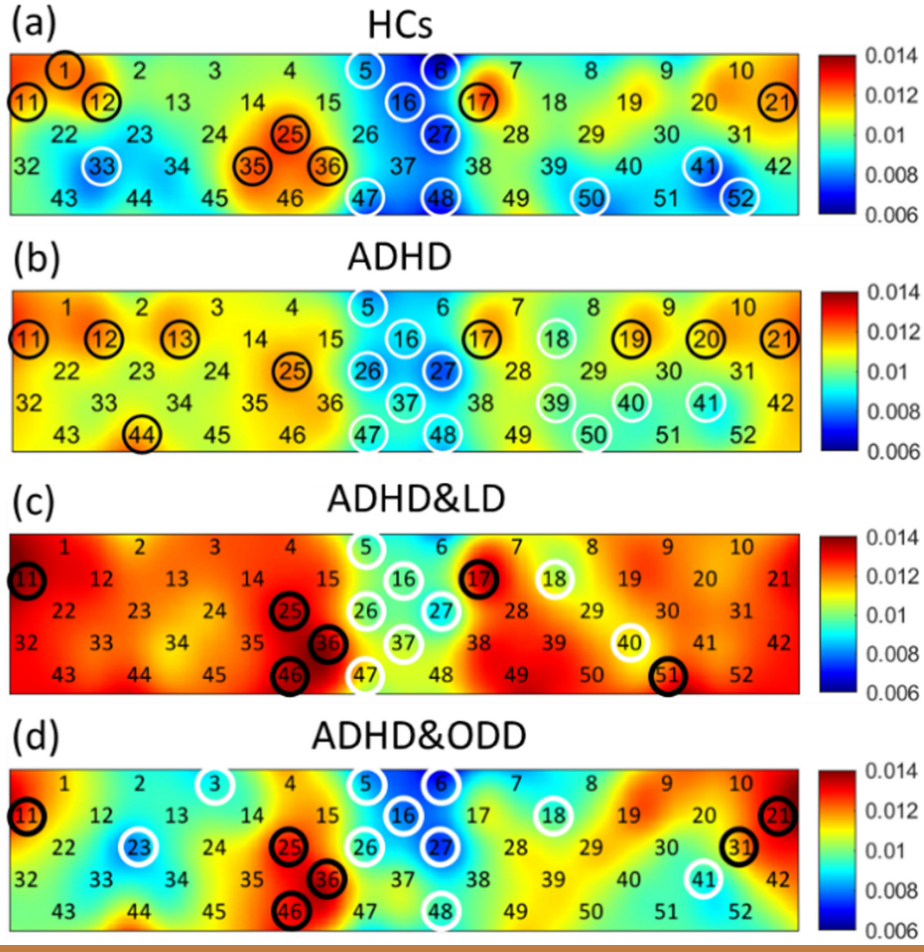

Figure 2. The activation pattern of 52 channels. (a) Healthy controls; (b) ADHD children; (c) ADHD&LD children; and (d) ADHD&ODD children. ADHD, attention deficit hyperactivity disorder; HCs: healthy controls; LD, learning disabilities; ODD, oppositional defiant disorders. The color bar indicates different amplitude of low-frequency fluctuation (ALFF) values. Circles indicate channels with significantly higher (black) and lower ALFF values (white), respectively (*P* < .05).

children, notable reductions in ALFF values were observed in the MPC and the left ventral prefrontal cortex (VPC). In contrast, increased ALFF values were seen in both the left and right PPC and the right dorsolateral prefrontal cortex (DPC). For children with ADHD&LD, the MPC exhibited significantly lower ALFF values when compared to the ADHD group alone. Significant findings were also noted in the right PPC, the left and right DPC, the left and right VPC, and the left TC, although these did not reach significance in the region of interest (ROI) analysis. For children with ADHD&ODD, the ALFF value in the MPC was significantly lower and the left PPC showed a significantly higher ALFF value compared to the average of the 52 channels. Significant findings in the right PPC, both the left and right DPC, the right VPC, and both the left and right TC were observed but did not reach significance in the ROI analysis. Specific analysis results were presented in Supplementary Table 1.

Statistical Difference in ALFF of the Study Population

Figure 3 visualizes the subtraction of ALFF values across the four groups to indicate differences better. Channels with significant differences in the two-sample *t*-test analysis are circled. Compared with HCs, ADHD children had higher ALFF values in the right TC (Ch-33) and the left VPC (Ch-50). For children with ADHD&LD, the MPC (Ch-38, 48), the left (Ch-41, 51, 52) and right (Ch-22, 23, 33) TC and the left VPC (Ch-39, 50) had significantly higher ALFF values. ADHD&ODD children had a significantly higher ALFF value in the MPC (Ch-48) than HCs. Furthermore, compared to children with only ADHD, those with ADHD&ODD exhibited significantly increased ALFF values in the MPC (Ch-38, 48), in the left (Ch-41, 51) and right (Ch-22) TC, and in the left VPC (Ch-39, 50).

ADHD&ODD children showed no significant difference when compared with ADHD children. ADHD&LD children exhibited significantly increased ALFF values in the left (Ch-51, 52) and right TC (Ch-23) when compared with ADHD&ODD children.

Supplementary Tables 2 and 3 present the results of specific analysis (i.e., *t* value, F value, and *P* value) underlying analysis used for Figure 3.

Discussion

This study compared brain function across subgroups of healthy children, children with only ADHD, children of ADHD comorbid with LD, and children of ADHD comorbid with ODD using resting state fNIRS and found different patterns of low-frequency amplitude in each group. Compared with healthy controls, the main abnormal brain areas in children with ADHD and comorbidities are the medial prefrontal cortex, the ventrolateral prefrontal cortex, and TC. Compared with ADHD children, children with ADHD&LD had higher ALFF values in the medial prefrontal cortex, TC, and the left ventrolateral prefrontal cortex. In contrast, children with ADHD&ODD did not show significant changes when compared to children with only ADHD.

A higher or lower ALFF value indicates an increased or decreased level of spontaneous brain activity and suggests inefficiency of the requisite brain area function, which results in obvious functional abnormalities. The findings of ALFF patterns were consistent with several previous studies. For instance, Li et al. [31] found that the ALFF value in the left orbitofrontal cortex and superior frontal gyrus decreased in their ADHD group, while the ALFF value in the right pallidum and right dorsal superior frontal gyrus increased compared with the healthy control group. Yang et al[32] showed that the ALFF value of children with ADHD increased in the left sensorimotor and superior frontal gyrus when compared with healthy controls. Both studies showed hyperactivity in regions of the prefrontal cortex and TC in children with ADHD compared with healthy controls, and children with either ADHD&ODD or ADHD&LD had significantly stronger spontaneous neural activity in the prefrontal cortex. A compensatory

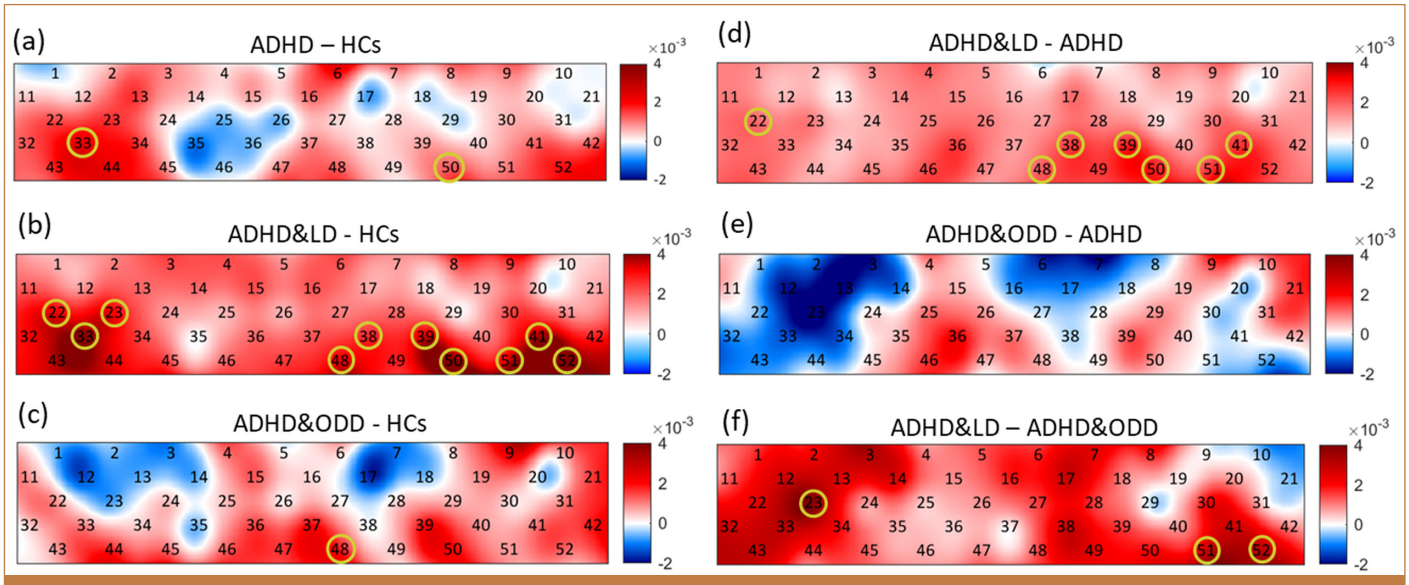

Figure 3. Subtraction of ALFF values in each channel between groups. ALFF, amplitude of low-frequency fluctuation. Notes: The color bar indicates different ALFF subtractions. The circles highlight the channels with significant differences in the two-sample *t*-test between groups ($P < .05$). (a) Substraction of ALFF values in each channel between ADHD and healthy control group; (b) Substraction of ALFF values in each channel between ADHD&LD and healthy control group; (c) Substraction of ALFF values in each channel between ADHD&ODD and healthy control group; (d) Substraction of ALFF values in each channel between ADHD&LD and ADHD group; (e) Substraction of ALFF values in each channel between ADHD&ODD and ADHD group; (f) Substraction of ALFF values in each channel between ADHD&LD and ADHD&ODD group.

mechanism could explain these results.[33] There was an inefficiency in neural processing in the prefrontal cortex of children with ADHD that made interference control challenging.[18,32] To compensate for this deficit, specific regions of the cortex, particularly those involved in attention, must become hyperactive.[33]

ADHD&LD children were found to have higher ALFF values in the MPC, TC, and left VPC than children with only ADHD. LD is related to a complex neural reading network consisting of a predominantly left–hemisphere system encompassing the inferior frontal, temporoparietal and occipitotemporal cortical regions.[34] A previous study found that activating the right occipital-temporal region was related to poorer reading skills.[35] Patients with LD primarily have a reduced volume of the inferior frontal gyrus, temporal lobe, striatum and cerebellum,[36] which impacts speech processing.[37] Additionally, disruption in the left posterior hemisphere, the inferior frontal gyrus and right occipital-temporal neural network was associated with phonological information processing.[38] Impaired speech and information processing are core pathological disruptions of LD. Numerous functional MRI studies on dyslexia have identified a higher concentration of abnormal blood oxygenation level dependent (BOLD) signals in regions of the temporoparietal cortex associated with phonological processing, and in the ventral occipitotemporal cortex involved in the visual representation of words.[39] Moreover, a comprehensive analysis of brain imaging research on dyslexia revealed several instances of abnormal BOLD activation, such as decreased activity in the inferior frontal and inferior parietal regions, and the superior temporal, middle temporal, and inferior temporal gyrus of the left hemisphere. Additionally, over-activation was observed in the primary motor cortex and anterior insula of the left hemisphere.[40] For several decades, it has been believed that LD was caused by attention deficits, which could be explained by either the phenocopy hypothesis model or the direct causation model. However, the findings of this study did not support either of those models;instead, the results support both the mixed group and third unique entity theories.

The present study also found that from the perspective of functional brain imaging, ADHD&ODD children exhibited no significant changes in ALFF values when compared to ADHD children. This suggests that ODD may be a symptom of ADHD rather than being an independent disorder. Such results support the direct causation model and that ADHD-related symptoms of impulsive behavior may cause the ODD-related symptoms of defiant and disobedient behavior. Previous studies by Reiff and Stein[40] have made similar conclusions that mild to moderate oppositional behaviors were components of ADHD.

The prevalence of comorbidity of ADHD is relatively high around the world. In Sweden, 87% of children with ADHD had at least one comorbidity, and 67% had two or more comorbidities.[41] LD and ODD are the most common psychiatric comorbidities in children with ADHD.[42] ODD occurs in 60% of ADHD patients, and 30-40% of ADHD patients had comorbidity of LD.[43] Although the comorbidity of ADHD is an essential issue, the boundary between ADHD and its comorbidity was not so clear. The intrinsic pathogenesis of ADHD with comorbidity could not be discriminated only by observing external symptoms, which would affect clinical judgment of the condition and the choice of treatment plan. Biomarkers identified by neuroimaging should also be considered when making a diagnostic decision.

Strengths and Limitations

This study is one of few that has used resting-state fNIRS to identify specific patterns of brain function in ADHD children with and without comorbidity such as ODD and LD. Evidence is provided regarding neuroimaging and a strengthened understanding of ADHD and its comorbidities. Additionally, when compared with fMRI, fNIRS is less susceptible to movement and is therefore well-suited to study children with ADHD. At the same time, machine learning has the potential to utilize the high temporal resolution of fNIRS and overcome its low spatial resolution.[44] However, there were several limitations warranting attention. First, the sample size should be expanded to increase the accuracy and reliability of such studies. Second, children with only ODD or LD were not recruited further to discriminate the pathogenesis of ADHD with these comorbidities. Third, although numerous neuroimaging studies have demonstrated significant differences in children with ADHD when compared with HCs, no meta-analysis of neuroimaging studies has shown clear differences between individuals with ADHD and HCs. No form of neuroimaging can be clinically used for the diagnosis of ADHD until such issues are resolved. Therefore, future studies should focus more on the difference between the subjects and HCs at the individual level. Further, correlations between abnormal brain function and the severity of comorbidity symptoms are also needed. Finally, the current study was restricted to the prefrontal cortex and temporal lobe because the equipment and analysis of the whole brain should be considered.

Conclusion

The study found that ADHD with LD possessed a different pathogenesis from ADHD, mainly manifested as even less functional brain activity in the medial prefrontal cortex, temporal cortex, and the left ventrolateral prefrontal cortex. Still, children with ADHD&ODD did not show significant changes when statistically compared with children with only ADHD. It is suggested that ODD-related symptoms may be part of ADHD symptoms rather than an independent disorder. This study provides novel insights into the explanation of the pathogenesis of ADHD comorbidities.

Availability of Data and Materials: *The datasets used and/or analyzed during the current study are available from the first author, Dr. Wenjing Liao (Email: 6521023@zjue.edu.cn) on reasonable request.*

Ethics Committee Approval: *This study was approved by Ethics Committee of Peking University Sixth Hospital, (Approval No: 2016-15, Date: 2016-07-13).*

Informed Consent: *Written informed consent was obtained from the guardians of all children who agreed to take part in the study.*

Peer-Review: *Externally peer-reviewed.*

Author Contributions: *W.L., H.L., L.L., J.Y., Q.Q., and G.B were involved in the study conceptualization and study design. W.L., H.L., and N.L. collected data. Q.L. and L.C. carried out statistical analyses. W.L., H.L., and G.B. wrote the first draft of the article. Q.Q. and G.B. supervised the whole project. All authors provided critical revisions of the article for important intellectual content. All the authors contributed to the interpretation of the data and approved the final version of the article.*

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Supplementary Table 1. Brain Activation Performance in ALFF of the Study Population

	Channel	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
ADHD	t-value	1.69	-1.03	0.81	-0.12	-6.07	-1.54	0.15	-0.83	-0.96	0.96	3.69	3.28	2.60	1.03	1.14	-4.04	2.24	-2.32	2.44	2.52	3.31	0.69	-0.12	-0.08	3.28	-5.84
	P-value	.10	.31	.42	.90	< .001	.13	.88	.41	.34	.34	< .001	.001	.01	.31	.26	< .001	.03	.02	.02	.01	< .001	.49	.91	.94	.001	< .001
HC	t-value	2.54	-0.06	0.14	0.51	-2.19	-7.20	-0.52	-1.44	-1.88	1.78	2.73	2.31	0.54	0.75	0.86	-3.32	2.71	0.23	1.78	1.93	2.70	-0.62	-1.49	0.49	3.36	-1.97
	P-value	.02	.95	.89	.62	.04	< .001	.61	.16	.07	.09	.01	.03	.59	.46	.40	.003	.01	.82	.09	.07	.01	.54	.15	.63	.003	.06
LD	t-value	1.59	-1.27	0.31	0.65	-4.03	-5.51	-1.63	-0.27	-0.16	-0.50	2.93	1.53	0.13	0.64	0.76	-2.51	2.18	-3.39	0.59	-0.64	1.65	1.13	0.24	-1.04	2.20	-3.50
	P-value	.12	.21	.76	.52	< .001	< .001	.11	.79	.87	.62	.01	.14	.90	.53	.45	.02	.04	.002	.56	.53	.11	.27	.81	.31	.04	.001
ODD	t-value	0.96	-0.98	-2.42	0.93	-3.79	-5.12	-1.56	-0.88	0.96	1.98	3.04	0.01	-0.75	-1.19	0.96	-3.78	0.43	-2.45	2.14	0.79	4.08	0.07	-2.25	0.30	3.78	-2.41
	P-value	.36	.34	.03	.37	.002	< .001	.14	.39	.35	.07	.01	.99	.46	.26	.35	.002	.68	.03	.05	.44	.001	.95	.04	.77	.002	.03

Supplementary Table 1. Brain Activation Performance in ALFF of the Study Population

	Channel	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52
ADHD	t-value	-8.75	0.75	-0.01	-0.62	0.92	1.78	-0.29	-0.18	1.17	1.58	-2.13	-0.36	-2.15	-2.52	-3.52	1.62	0.73	2.34	-0.02	1.41	-2.94	-4.86	1.20	-2.43	-0.62	0.82
	P-value	< .001	.46	.99	.54	.36	.08	.77	.86	.25	.12	.04	.72	.03	.01	.001	.11	.47	.02	.98	.16	.004	< .001	.23	.02	.53	.42
HC	t-value	-4.99	1.15	1.47	-0.29	1.38	0.46	-3.20	-1.95	2.66	3.09	-1.97	0.29	-1.67	-1.46	-4.86	-0.31	-0.18	-0.02	-1.03	1.64	-3.45	-4.69	1.10	-3.09	-1.32	-2.08
	P-value	.00	.26	.15	.78	.18	.65	.004	.06	.01	.01	.06	.78	.11	.16	< .001	.76	.86	.99	.31	.11	.002	< .001	.28	.01	.20	.05
LD	t-value	-5.72	0.60	-1.79	0.14	0.48	1.60	0.14	-1.14	0.31	2.70	-2.16	1.09	0.94	-2.36	-0.32	1.19	1.17	1.16	0.16	2.55	-2.61	-1.89	1.99	0.71	2.07	1.32
	P-value	< .001	.55	.08	.89	.64	.12	.89	.26	.76	.01	.04	.29	.35	.02	.75	.24	.25	.26	.88	.02	.01	.07	.06	.48	.05	.20
ODD	t-value	-4.80	1.16	1.69	-1.17	2.29	-0.63	-1.67	-1.12	1.25	2.73	0.20	-0.65	0.92	-0.80	-2.43	1.62	-0.66	1.32	0.54	2.76	-2.05	-2.17	1.05	-0.74	-0.55	-1.13
	P-value	< .001	.27	.11	.26	.04	.54	.12	.28	.23	.02	.84	.53	.38	.44	.03	.13	.52	.21	.60	.02	.06	.05	.31	.47	.59	.28

Supplementary Table 2. Results of *t*-tests by Comparing ALFF Values in Each Channel Between Groups

	Channel	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
ADHD-HC	t-value	-0.51	0.29	1.01	0.23	-0.09	1.11	0.65	1.25	1.16	-0.03	0.22	0.22	1.50	0.47	0.90	1.36	-0.65	-0.41	0.40	-0.05	0.00	1.42	1.35	0.37	-0.73	-0.85
	P-value	.61	.77	.32	.82	.92	.27	.51	.22	.25	.97	.83	.82	.14	.64	.37	.18	.52	.68	.69	.96	1.00	.16	.18	.71	.47	.40
LD-HC	t-value	0.73	1.05	1.63	1.75	0.94	2.18	1.14	1.86	2.45	0.39	1.23	0.98	1.41	1.58	2.45	1.84	0.72	0.35	0.83	-0.11	0.68	2.95	3.20	1.25	0.72	1.19
	P-value	.47	.30	.11	.09	.35	.03	.26	.07	.02	.70	.22	.33	.16	.12	.02	.07	.47	.73	.41	.91	.50	.005	.002	.22	.47	.24
ODD-HC	t-value	-0.23	-0.25	-0.90	0.95	-0.15	0.86	-0.83	0.58	1.89	1.03	0.62	-0.92	-0.54	-0.52	1.20	0.29	-1.29	-0.58	0.84	-0.35	1.17	0.95	-0.67	0.46	0.34	0.23
	P-value	.82	.80	.38	.35	.88	.40	.41	.56	.07	.31	.54	.37	.59	.60	.24	.78	.20	.57	.41	.73	.25	.35	.51	.65	.73	.82
LD-ADHD	t-value	1.42	1.17	1.49	2.10	1.46	-0.18	0.08	1.48	1.77	0.47	1.37	0.86	0.31	1.53	1.66	1.10	1.66	0.89	0.80	-0.10	0.98	2.04	1.59	1.24	1.79	2.25
	P-value	.16	.24	.14	.04	.15	.86	.93	.14	.08	.64	.17	.39	.76	.13	.10	.27	.10	.37	.43	.92	.33	.04	.11	.22	.08	.03
ODD-ADHD	t-value	0.14	-0.53	-1.83	0.89	-0.09	-0.62	-0.93	-0.42	1.35	0.94	0.48	-1.22	-1.72	-0.97	0.41	-0.85	-0.73	-0.22	0.56	-0.41	1.24	-0.23	-1.52	0.21	0.99	0.83
	P-value	.89	.60	.07	.37	.93	.54	.36	.67	.18	.35	.63	.23	.09	.34	.68	.40	.47	.83	.58	.69	.22	.82	.13	.84	.32	.41
LD-ODD	t-value	0.79	1.06	2.01	0.51	0.89	1.20	1.60	1.08	-0.12	-0.58	0.43	1.93	1.57	2.01	0.69	1.35	1.83	0.82	0.06	0.25	-0.32	1.47	3.18	0.62	0.27	0.71
	P-value	.43	.29	.05	.61	.38	.24	.12	.29	.90	.57	.67	.06	.12	.05	.50	.18	.07	.42	.95	.80	.75	.15	.00	.54	.79	.48

Supplementary Table 2. Results of *t*-tests by Comparing ALFF Values in Each Channel Between Groups

	Channel	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52
ADHD-HC	t-value	0.45	0.36	-0.43	0.78	-0.10	1.22	2.35	1.72	-1.15	-0.49	1.05	0.31	0.93	0.64	1.70	1.54	1.13	1.62	1.34	-0.09	1.42	1.77	0.17	2.00	1.17	1.81
	P-value	.65	.72	.67	.44	.92	.23	.02	.09	.25	.63	.30	.76	.35	.52	.09	.13	.26	.11	.18	.93	.16	.08	.87	.05	.24	.07
LD-HC	t-value	2.11	1.93	0.22	1.89	0.95	2.34	3.46	2.06	0.02	1.78	2.06	2.11	2.94	1.95	3.94	2.51	2.37	1.94	1.82	1.68	2.73	3.46	1.72	3.44	3.58	3.59
	P-value	.04	.06	.83	.06	.35	.02	.001	.04	.99	.08	.04	.04	.005	.06	.00	.01	.02	.06	.07	.10	.01	.001	.09	.001	.001	.001
ODD-HC	t-value	0.09	0.46	0.56	0.18	0.96	-0.05	1.21	0.49	-0.39	1.16	1.78	0.01	1.93	0.63	1.67	2.02	0.33	1.39	1.51	1.06	1.34	2.03	0.22	1.80	0.47	0.75
	P-value	.93	.65	.58	.86	.34	.96	.23	.62	.70	.25	.08	.99	.06	.53	.10	.05	.74	.17	.14	.30	.19	.05	.83	.08	.64	.46
LD-ADHD	t-value	2.05	1.95	0.78	2.09	1.42	1.76	1.73	0.75	1.23	2.47	1.27	2.58	3.41	1.73	3.18	1.20	1.95	0.70	1.41	2.40	1.36	2.57	2.32	3.28	3.33	1.73
	P-value	.04	.05	.44	.04	.16	.08	.09	.45	.22	.01	.21	.01	.00	.09	.00	.23	.05	.48	.16	.02	.18	.01	.02	.001	.001	.09
ODD-ADHD	t-value	-0.28	0.15	1.01	-0.45	1.14	-1.00	-0.88	-0.91	0.47	1.46	0.88	-0.24	1.36	0.20	0.00	0.27	-0.61	-0.01	0.30	1.26	0.03	0.57	0.13	0.40	-0.35	-0.94
	P-value	.78	.88	.31	.65	.26	.32	.38	.37	.64	.15	.38	.81	.18	.84	1.00	.79	.54	.99	.76	.21	.97	.57	.90	.69	.73	.35
LD-ODD	t-value	1.73	1.14	-0.34	1.45	-0.05	1.90	1.88	1.23	0.36	0.23	0.02	1.71	0.88	0.84	1.95	0.56	1.67	0.46	0.57	0.43	0.97	1.12	1.25	1.43	2.08	2.23
	P-value	.09	.26	.74	.15	.96	.06	.07	.23	.72	.82	.98	.09	.38	.41	.06	.58	.10	.65	.57	.67	.34	.27	.22	.16	.04	.03

Supplementary Table 3. Results of One Way ANOVA Tests

Channel	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
F value	0.87	1.24	2.98	1.81	0.89	1.64	1.18	0.97	2.64	0.47	1.49	1.58	2.22	2.31	2.12	1.23	1.52	0.66	0.57	0.15	0.98	1.75	1.96	1.26	1.91	2.20
P value	.46	.30	.03	.15	.45	.18	.32	.41	.05	.71	.22	.20	.09	.08	.10	.30	.21	.58	.64	.93	.40	.16	.12	.29	.13	.09

Supplementary Table 3. Results of One Way ANOVA Tests

Channel	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52
F value	1.33	1.56	0.82	0.97	0.74	2.06	1.70	0.34	1.34	2.25	0.62	1.20	4.03	1.07	3.08	0.56	1.08	0.21	0.45	1.68	0.58	1.56	0.74	2.52	2.76	0.94
P value	.27	.20	.49	.41	.53	.11	.17	.80	.26	.08	.60	.31	.01	.37	.03	.64	.36	.89	.72	.17	.63	.20	.53	.06	.04	.42