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META-ANALYSIS

Vulnerable brain regions in adolescent attention deficit hyperactivity disorder: An activation likelihood estimation meta-analysis

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Abstract

BACKGROUND

Attention deficit hyperactivity disorder (ADHD) is a prevalent neurodevelopmental disorder in adolescents characterized by inattention, hyperactivity, and impulsivity, which impact cognitive, behavioral, and emotional functioning. Resting-state functional magnetic resonance imaging (rs-fMRI) provides critical insights into the functional architecture of the brain in ADHD. Despite extensive research, specific brain regions consistently affected in ADHD patients during these formative years have not been comprehensively delineated.

AIM

To identify consistent vulnerable brain regions in adolescent ADHD patients using rs-fMRI and activation likelihood estimation (ALE) meta-analysis.

METHODS

We conducted a comprehensive literature search up to August 31, 2024, to identify studies investigating functional brain alterations in adolescents with ADHD. We utilized regional homogeneity (ReHo), amplitude of low-frequency fluctuations (ALFF), dynamic ALFF (dALFF) and fractional ALFF (fALFF) analyses. We compared the regions of aberrant spontaneous neural activity in adolescents with ADHD with those in healthy controls (HCs) using ALE.

RESULTS

Fifteen studies (468 adolescent ADHD patients and 466 HCs) were included. Combining the ReHo and ALFF/fALFF/dALFF data, the results revealed increased activity in the right lingual gyrus [LING, Brodmann Area (BA) 18], left LING (BA 18), and right cuneus (CUN, BA 23) in adolescent ADHD patients compared with HCs (voxel size: 592-32 mm³, $P < 0.05$). Decreased activity was observed in the left medial frontal gyrus (MFG, BA 9) and left precuneus (PCUN, BA 31) in adolescent ADHD patients compared with HCs (voxel size: 960-456 mm³, $P < 0.05$). Jackknife sensitivity analyses demonstrated robust reproducibility in 11 of the 13 tests for the right LING, left LING, and right CUN and in 11 of the 14 tests for the left MFG and left PCUN.

CONCLUSION

We identified specific brain regions with both increased and decreased activity in adolescent ADHD patients, enhancing our understanding of the neural alterations that occur during this pivotal stage of development.

Key Words: Attention deficit hyperactivity disorder; Adolescent; Resting-state functional magnetic resonance imaging; Activation likelihood estimation; Meta-analysis; Medial frontal gyrus; Precuneus; Cuneus; Lingual gyrus

Core Tip: This study used activation likelihood estimation meta-analysis to identify vulnerable brain regions in adolescents with attention deficit hyperactivity disorder (ADHD) based on resting-state functional magnetic resonance imaging. Increased activity was detected in the bilateral lingual gyrus and right cuneus, whereas decreased activity was detected in the left medial frontal gyrus and left precuneus. These findings provide novel insights into the neurophysiological mechanisms of ADHD and suggest potential targets for therapeutic interventions to improve cognitive and behavioral outcomes in affected adolescents.

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INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a complex disorder driven primarily by polygenic genetic factors; it is characterized by structural and functional deficits in the corticostriatal circuitry and is associated with cognitive impairments in attention and executive control[1]. The disorder most commonly emerges in childhood and persists through adolescence, affecting approximately 5%-7% of adolescents worldwide[2]. During these developmental stages, ADHD significantly impacts cognitive, emotional, and social maturation, leading to potential long-term consequences if unaddressed. Understanding the intricate neural underpinnings of ADHD is imperative to mitigate long-term consequences and improve outcomes.

Neuroimaging studies, particularly functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI), have revealed that ADHD is associated with structural and functional abnormalities in brain networks. These approaches have revealed abnormalities in white matter integrity and altered connectivity within key neural networks, especially those involving the frontal cortex, basal ganglia, and cerebellum[3]. By elucidating these neural mechanisms, researchers can provide more effective interventions tailored to the specific neurobiological deficits found in adolescent ADHD patients.

Resting-state fMRI (rs-fMRI) provides a noninvasive and accurate method to observe dynamic changes in brain activity when no specific cognitive tasks are performed[4]. It assesses spontaneous fluctuations in blood oxygen level-dependent signals during rest, revealing intricate patterns of connectivity and activity across distinct brain regions. Analytical approaches in rs-fMRI, such as Regional Homogeneity (ReHo), Amplitude of Low-Frequency Fluctuations (ALFF), fractional ALFF (fALFF), and dynamic ALFF (dALFF), are frequently employed to characterize intrinsic brain activity during rest[5]. ReHo is utilized to assess the local synchrony of rs-fMRI signals, aiding in the identification of neural synchronization anomalies. ALFF measures the change in the brain's local function by calculating the ALFF at each voxel. fALFF quantifies the relative contribution of low-frequency signals to the overall signal, enhancing the specificity of measurements, whereas dALFF provides insights into the dynamic variations across different brain areas, highlighting abnormal neural activity patterns in ADHD.

Previous studies have indicated that ADHD is associated with atypical local activations in several regions, including the basal ganglia, sensorimotor cortex, and cerebellum, as demonstrated by changes in ALFF and ReHo. Jin *et al*[6] reported that in children with ADHD, genetic variation is significantly associated with ALFF values in the right superior frontal gyrus, where increased ALFF is correlated with enhanced inhibitory function, as measured by the Stroop task. Kim *et al*[7] reported that in children with ADHD, static ReHo in the parietal lobe (PL) is reduced, and the variability in dynamic ReHo is also significantly decreased. Thus, combining ReHo, ALFF, fALFF, and dALFF can more comprehensively reflect the patterns of spontaneous local brain activity changes in youth with ADHD. Functional connectivity

(FC) measures the functional correlations between a seed point and surrounding brain areas, differing from the spontaneous neural activity reflected by ReHo, ALFF, fALFF, and dALFF[8]. Unless all studies pertain to the same network, FC is not a suitable candidate for meta-analyses. To our knowledge, although numerous previous studies have employed ReHo, ALFF, fALFF, and dALFF methods alongside rs-fMRI to explore the changes in spontaneous brain activity in youth with ADHD[9-23], the findings have been inconsistent and remain a subject of debate.

Activation likelihood estimation (ALE) is a meta-analytic technique extensively utilized in neuroimaging research. It aggregates peak activation coordinates from multiple studies to generate spatial probability maps, thus identifying consistent activation patterns[24]. By integrating results across diverse investigations, ALE employs a quantitative approach to emphasize regions of convergence, offering more robust conclusions regarding brain function in specific conditions. Previously, Lukito *et al*[25] conducted an ALE study using whole-brain voxel-based morphometry (VBM) and reported decreased gray matter (GM) volume in the ventromedial orbitofrontal cortex of individuals with ADHD compared with controls, but they did not address potential changes in brain functional activity. Tamon *et al*[26] used task-based fMRI and reported increased activity in the lingual and rectal gyri and reduced activation in the middle frontal gyrus (MFG), parahippocampal gyrus, and insula in ADHD and ASD patients. However, their study lacked rs-fMRI data, which may have overlooked FC patterns during spontaneous brain activity.

In this study, we utilized ALE analysis to focus on integrating and assessing data from brain regions with reported abnormalities in prior studies using ReHo, ALFF, fALFF, and dALFF approaches. We hypothesize that, compared with healthy controls (HCs), adolescent ADHD patients exhibit abnormal brain activity changes, potentially revealing the neural mechanisms underlying ADHD. By conducting an ALE meta-analysis, this study aims to identify vulnerable brain regions, thereby enhancing our understanding of the impact of ADHD on brain function and deepening insights into the neurofunctional dynamics of this disorder.

MATERIALS AND METHODS

Literature search

In accordance with the PRISMA guidelines[27], a comprehensive literature search was systematically conducted across four major electronic databases up to August 31, 2024. The databases included PubMed, Web of Science, Scopus, and CNKI. The search terms focused specifically on ADHD in adolescents and included the following: ("attention deficit hyperactivity disorder" OR "ADHD") AND ("youth" OR "adolescent" OR "children" OR "teenagers" OR "pediatric") AND ("resting-state functional magnetic resonance imaging" OR "rs-fMRI" OR "functional MRI" OR fMRI) AND ("amplitude of low-frequency fluctuations" OR ALFF OR "low frequency fluctuation" OR "regional homogeneity" OR ReHo OR homogeneity OR "brain activity"). In addition, review articles and reference lists of the included studies were screened to identify any potentially overlooked research. This review was registered with PROSPERO (ID: CRD42024531049).

Inclusion and exclusion criteria

Studies were included if they met the following criteria: (1) Diagnosis of ADHD according to the diagnostic and statistical manual of mental disorders edition in use at the time of the study's publication; (2) Inclusion of adolescent participants; (3) Whole-brain analysis of differences in brain functional activity between adolescents with ADHD and HCs *via* rs-fMRI; (4) ReHo or ALFF/fALFF analysis methods; and (5) Brain regions with differences between adolescents with ADHD and HCs presented as Montreal Neurological Institute (MNI) or Talairach three-dimensional peak coordinates (x, y, z). Studies were excluded if they met at least one of the following criteria: (1) Used rs-fMRI methods to assess FC, independent component analysis, degree centrality, default mode network (DMN), or other networks; (2) Used VBM, task-state fMRI or cerebral perfusion; (3) Were meta-analyses, reviews, or case reports; (4) Had incomplete three-dimensional coordinates (x, y, z); and (5) Involved subjects other than adolescents with ADHD. To avoid data duplication, when two or more studies used the same dataset, only the study with the largest sample size and most comprehensive data was selected. For longitudinal or intervention studies, only baseline data were considered.

Data extraction

Data from each study were independently extracted by two authors (Hou YZ and Zhang Q) using a standardized data extraction form. Any disagreements were resolved through discussion among the authors. The extracted data included author names, publication year, sample size, participant age, and IQ scores; rs-fMRI parameters such as the MRI scanner model, field strength, and analysis methods; statistical thresholds and methods for multiple comparison corrections; and differences in brain regions between adolescents with ADHD and HCs, including the size and central coordinates of identified discrepancies (Table 1). All coordinates were independently extracted according to the requirements for ALE meta-analysis.

Quality assessment

The quality of each included study was evaluated independently by two authors (Hou YZ and Zhang Q) using the Newcastle-Ottawa Quality Assessment Scale (NOS). The NOS evaluates three key areas across eight items: Four items assess subject selection, one item evaluates comparability between groups, and three items measure the outcome. Studies can achieve a maximum score of nine points, with studies scoring five or more points deemed suitable for data analysis. In cases of disagreements, a consensus was reached through discussion among the authors' group.

Table 1 Characteristics of the included studies

Ref.	Sample size		Age, mean ± SD		IQ score, mean ± SD		MRI equipment and field strength	Method	Differential brain region	Corrective methods	Quality
	ADHD	HCs	Patient	HCs	Patient	HCs					
Cao *et al* [9], 2006	29	27	13.34 ± 1.44	13.08 ± 0.93	101.22 ± 10.10	115.83 ± 11.58	Siemens Trio Tim 3.0T	ReHo	14	Alphasim	4/1/1
Zang *et al*[10], 2007	13	12	13.0 ± 1.4	13.1 ± 0.6	99.0 ± 11.6	118 ± 11.7	Siemens Trio 3.0T	ALFF	11	$P^{uncor} < 0.01$	4/1/1
Cao *et al* [11], 2008	12	13	13.40 ± 1.70	13.20 ± 1.20	102.70 ± 9.00	112.70 ± 13.80	Siemens Trio Tim 3.0T	N/A	10	N/A	4/1/1
Yang *et al*[12], 2011	30	33	9.20 ± 1.9	9.4 ± 1.2	101.30 ± 3.20	104.90 ± 10.10	Siemens Trio Tim 3.0T	fALFF	11	$P^{uncor} < 0.01$	4/1/1
Wu *et al* [13], 2012	32	30	9.20 ± 1.70	9.40 ± 1.20	≥ 80	≥ 80	Siemens Trio Tim 3.0T	ALFF	10	N/A	4/1/1
An *et al* [14], 2013	19	23	13.30 ± 1.40	13.20 ± 1.00	102.70 ± 10.40	113.50 ± 12.80	Siemens Trio Tim 3.0T	ALFF/ReHo	11/18	Alphasim	4/1/1
Wang *et al*[15], 2014	57	59	11.70 ± 2.60	12.20 ± 2.90	106.40 ± 15.50	113.70 ± 14.60	Siemens Allegra 30T	ALFF	7	Alphasim	4/1/1
Yang *et al*[16], 2013	18	18	8.80 ± 0.70	9.90 ± 0.90	95.77 ± 10.79	100.93 ± 8.33	GE Discovery MR750 3.0T	ALFF/ReHo	4/8	Alphasim	4/1/1
Li *et al* [17], 2014	33	32	10.10 ± 2.60	10.90 ± 2.60	N/A	N/A	N/A	N/A	5	FWE	4/1/1
Yu *et al* [18], 2016	30	30	10.30 ± 1.70	10.20 ± 1.70	106.20 ± 14.50	121. 10 ± 13.90	N/A	ReHo	5	Alphasim	4/1/1
Xie *et al* [19], 2016	10	10	10.40 ± 2.60	10.40 ± 2.60	≥ 80	≥ 80	GE 1.5T	ALFF	5	N/A	4/1/1
Wang *et al*[20], 2017	38	42	11.00 ± 2.00	11.00 ± 2.00	≥ 80	≥ 80	SIEMENS TRIO 3.0T	fALFF	6	Alphasim	4/1/1
Zhou *et al*[21], 2018	45	26	8.49 ± 1.87	9.04 ± 1.56	114.00 ± 13.27	121.00 ± 13.87	GE Signa HDX 3.0T	ReHo	1	FWE	4/1/1
Lou *et al* [22], 2021	50	28	8.26 ± 1.93	8.93 ± 1.46	116.94 ± 17.45	122.43 ± 13.84	GE Signa HDX 3.0T	dALFF	2	GRF	4/1/1
Feng *et al* [23], 2023	52	51	10.17 ± 1.81	10.64 ± 1.85	105.38 ± 13.57	123.81 ± 16.32	GE Discovery MR750 3.0T	ALFF/ReHo	3/1	GRF	4/1/1

HCs: Healthy controls; IQ: Intelligence quotient; MRI: Magnetic resonance imaging; ReHo: Regional homogeneity; ALFF: Amplitude of low-frequency fluctuation; dALFF: Dynamic amplitude of low-frequency fluctuation; fALFF: Fractional amplitude of low-frequency fluctuation; FWE: Familywise error; GRF: Gaussian random field; N/A: Not available.

ALE analysis

ALE meta-analysis was performed using GingerALE 3.0.2 software (http://www.brainmap.org/ale)[28]. For the ALE meta-analysis, our study was conducted in the MNI standard space. Hence, we utilized the Lancaster transformation in GingerALE 3.0.2 to convert the three-dimensional coordinates of brain regions in the Talairach space to MNI space.

Subsequently, Gaussian function smoothing with a full width at half maximum (FWHM) was performed on the basis of the sample size of each test group. Using the FWHM values, Gaussian functions were simulated on the three-dimensional brain mask of coordinates for a set of aberrantly activated brain regions reported in the study group. This process yielded three-dimensional modeling activation (MA) maps for each study group.

Then, on the basis of the 3D-MA maps, a 3D ALE map was generated from the Gaussian probability distribution of the activated brain regions between different study groups, and the P value of the activation probability of the brain regions was calculated according to the Gaussian model to construct a 3D-P value distribution map. Moreover, the statistical test threshold was set by a 3D-P value distribution plot. The main parameters were as follows: The cluster-level familywise error correction was set at $P < 0.05$, the threshold permutations were set at $P < 0.001$ with 1000 permutations, and a threshold map (ALE image) was obtained[29]. Finally, Mango software (http://rii.uthscsa.edu/mango/) was used to analyze the resulting ALE images.

Sensitivity analysis

To assess the reproducibility of our findings, a jackknife sensitivity analysis was implemented. Each study was sequentially removed from the dataset, and the ALE meta-analysis was rerun on the remaining studies using GingerALE 3.0.2. This process was repeated 15 times, each with a different study excluded, to verify the consistency of the findings and compare them with the initial results.

RESULTS

General information of the included studies

The systematic search generated 1431 related articles, 15 of which[9-23] were ultimately selected for inclusion in this meta-analysis (Figure 1). These studies, published between 2006 and 2023, included participants from the pediatric age group, specifically children and adolescents aged approximately 8-13 years. The selected studies featured matched average ages and IQ scores between ADHD patients and HCs. They employed various rs-fMRI analysis methods, such as ReHo, ALFF, fALFF, and dALFF. Altogether, 468 youths with ADHD and 466 HCs were included, with a total of 132 distinct brain regions subjected to ALE meta-analysis (Table 1). According to the NOS, all included studies showed low publication bias and met the quality criteria for data analysis.

ALE meta-analysis results

The ALE meta-analysis revealed significant alterations in brain activity in adolescents with ADHD compared with HCs (Table 2). Increased activity was observed in the right lingual gyrus [LING, Brodmann Area (BA) 18], left LING (BA 18), and right cuneus (CUN, BA 23) (Figure 2A) in adolescent ADHD patients compared with HCs (voxel size: 592-32 mm^3, $P < 0.05$). Decreased activity was found in the left MFG (BA 9) and left precuneus (PCUN, BA 31) (Figure 2B) in adolescent ADHD patients compared with HCs (voxel size: 960-456 mm^3, $P < 0.05$).

Sensitivity analysis

The sensitivity analysis confirmed the robustness and reproducibility of the findings. In the jackknife analysis of increased brain activity in adolescent ADHD patients, the right LING, left LING, and right CUN were consistently observed in 11 out of 13 iterations (Table 3). Similarly, in the analysis of decreased brain activity, the left MFG and left PCUN were consistently identified in 11 out of 14 iterations. This high level of consistency across analyses underscores the reliability of the identified alterations in brain activity (Table 4).

DISCUSSION

Abnormalities in intrinsic brain activity are closely associated with ADHD, which prompted us to employ the ALE method to integrate multiple previous neuroimaging studies on brain function and explore dynamic changes in resting-state brain activity in adolescents with ADHD. Specifically, we combined findings from studies utilizing ReHo, ALFF, fALFF, and dALFF approaches to identify brain regions with significant differences in activity between ADHD patients and HCs. The results revealed that increased brain activity in adolescent ADHD patients was primarily distributed in the right and left LING and the right CUN, whereas decreased activity was observed in the left MFG and left PCUN. This convergence of evidence underscores the robustness of our findings. Jackknife sensitivity analyses further confirmed the reproducibility and reliability of these results, confirming the validity of the observed differences. These findings may help identify potential therapeutic targets for adolescent ADHD patients.

Brain regions with increased spontaneous neural activity in adolescents with ADHD

The regions with increased activity, particularly in the right and left LING (BA 18) and the right CUN (BA 23), belong primarily to the visual network (VN) and are key components of the visual processing and spatial attention systems[30]. The LING, which is part of the occipital lobe, is responsible for visual perception, memory encoding, and sensory processing and plays a central role in interpreting stimuli from the environment[31,32].

The observed increase in activity in adolescents with ADHD suggests an abnormal engagement of sensory processing pathways, potentially as a compensatory response to attentional and executive function deficits commonly observed in ADHD. In a study by Dibbets *et al*[33], task switching in adults with ADHD resulted in increased activation in the right LING, indicating altered visual processing pathways to manage cognitive demands. Another DTI study in ADHD patients revealed increased fractional anisotropy in the left LING, suggesting atypical white matter development, possibly linked to attention, executive function, and processing speed deficits[34]. Wu *et al*[35] utilized network motif analysis and reported that the reduced ability to receive information in the right LING of ADHD patients may lead to difficulties in processing visual information promptly, contributing to inattention. Visual processing impairments are often associated with deficits in working memory (WM), as observed in adolescents with anxiety disorders, where impaired WM is attributed to reduced cognitive resources[36]. Mattfeld *et al*[37] employed fMRI to examine the dissociation between WM impairments and ADHD and reported that ADHD patients with impaired WM exhibited significantly reduced activation, particularly in the LING, compared with both unimpaired ADHD and control groups. Despite the increased spontaneous neural activity in the LING observed in our ALE meta-analysis, it may reflect a compensatory mechanism rather than effective functional engagement. This increased activity suggests that although the

Table 2 Applying the activation likelihood estimation method to study changes in brain function activity in adolescent attention deficit hyperactivity disorder

Research methods	Anatomical label	Brodmann areas	Peak MNI coordinate			ALE value	Volume in mm³
			X	Y	Z		
ReHo & ALFF/dALFF/fALFF Increase	LING_R	BA 18	16	-82	-4	0.006502583	592
	LING_L	BA 18	-12	-92	-8	0.005300413	160
	CUN_R	BA 23	12	-74	16	0.004788109	32
ReHo & ALFF/dALFF/fALFF decrease	MFG_L	BA 9	2	48	8	0.006200704	960
	PCUN_L	BA 31	-4	-46	36	0.00574992	456

ALE: Activation likelihood estimation; ReHo: Regional homogeneity; ALFF: Amplitude of low-frequency fluctuation; dALFF: Dynamic ALFF; fALFF: Fractional ALFF; BA: Brodmann Area; MNI: Montreal Neurological Institute; LING: Lingual gyrus; CUN: Cuneus; MFG: Medial frontal gyrus; PCUN: Precuneus; R: Right; L: Left.

Table 3 Jackknife sensitivity analyses

Discarded article	Adolescent ADHD > HC		
	LING_R	LING_L	CUN_R
Cao *et al*[9], 2006	No	No	No
Zang *et al*[10], 2007	Yes	Yes	Yes
Yang *et al*[12], 2011	yes	yes	yes
Wu *et al*[13], 2012	Yes	Yes	Yes
An *et al*[14], 2013	No	No	No
Wang *et al*[15], 2014	Yes	Yes	Yes
Yang *et al*[16], 2013	Yes	Yes	Yes
Li *et al*[17], 2014	Yes	Yes	Yes
Yu *et al*[18], 2016	Yes	Yes	Yes
Xie *et al*[19], 2016	Yes	Yes	Yes
Wang *et al*[20], 2017	Yes	Yes	Yes
Lou *et al*[22], 2021	Yes	Yes	Yes
Feng *et al*[23], 2023	Yes	Yes	Yes
Total	11 out of 13	11 out of 13	11 out of 13

ADHD: Attention deficit hyperactivity disorder; HC: Healthy control; LING: Lingual gyrus; CUN: Cuneus; R: Right; L: Left.

brain attempts to maintain basic visual perception, higher-order functions such as attention and WM remain compromised, as this spontaneous activity does not translate into improved performance. This aligns with Ko *et al*'s findings[38], where heightened activation in the left lingual area during dual-tasking in adults with ADHD was interpreted as a need for greater attentional resources, underscoring a compensatory rather than efficient neural response.

Additionally, WM impairments may further exacerbate visual processing difficulties. For example, in multiple sclerosis, reduced activation in prefrontal networks during WM tasks is correlated with decreased accuracy in visual processing, indicating that WM deficits directly affect visual attention and encoding[39]. A possible explanation is that, in ADHD patients, visual information requires rapid storage, processing, and retrieval, but impaired visual processing disrupts efficient information transfer, directly affecting WM performance. This disruption likely contributes to cognitive impairment in ADHD patients.

Moreover, our study revealed increased activity in the right CUN. Situated within the VN, the CUN, as part of the posterior visual pathway, is crucial for visuospatial processing[40]. It integrates sensory information with attention and memory systems, playing a pivotal role in visual perception and spatial orientation.

Wang *et al*[41] reported a significant positive correlation between inattentive scores and increased ReHo in the bilateral CUN, highlighting the role of the CUN in the inattentive symptoms associated with ADHD. In addition, Su *et al*[42] reported increased CBF-fALFF coupling in the left CUN in ADHD children, with a negative correlation with the attention

Table 4 Jackknife sensitivity analyses

Discarded article	Adolescent ADHD < HC	
	MFG_L	PCUN_L
Cao *et al*[9], 2006	Yes	Yes
Zang *et al*[10], 2007	Yes	Yes
Cao *et al*[11], 2008	Yes	Yes
Yang *et al*[12], 2011	No	No
Wu *et al*[13], 2012	No	No
An *et al*[14], 2013	No	Yes
Wang *et al*[15], 2014	Yes	Yes
Yang *et al*[16], 2013	Yes	Yes
Li *et al*[17], 2014	Yes	Yes
Yu *et al*[18], 2016	Yes	No
Wang *et al*[20], 2017	Yes	Yes
Zhou *et al*[21], 2018	Yes	Yes
Lou *et al*[22], 2021	Yes	Yes
Feng *et al*[23], 2023	Yes	Yes
Total	11 out of 14	11 out of 14

ADHD: Attention deficit hyperactivity disorder; HC: Healthy control; CUN: Cuneus; PCUN: Precuneus; MFG: Medial frontal gyrus; R: Right; L: Left.

concentration index, suggesting that heightened activity in this region may contribute to attention deficits through maladaptive neurovascular mechanisms. We speculate that the CUN is involved in attention regulation deficits, and the increased functional activity in the right CUN among adolescents with ADHD suggests heightened engagement of the visuospatial processing pathway, potentially reflecting an adaptive yet inefficient compensatory mechanism for deficits in attention regulation and executive function. Zhou *et al*'s study[43] on drug-naïve boys with ADHD supports this observation, as they reported decreased FC between the superior occipital lobe and CUN, indicating disruptions within the dorsal attention network and suggesting impaired coordination between visual processing and attention regulation systems. In addition, sex differences may also play a role in the functionality of the CUN. Park *et al*[44] emphasized that male and female ADHD patients exhibit different connectivity patterns in the CUN, suggesting that this region may function differently depending on sex. In adolescent ADHD patients, GM volume alterations have also been observed in the CUN. Zhao *et al*[45] reported a significant reduction in GM volume in the left CUN of adolescent ADHD patients compared with typically developing controls. Additionally, FC analysis revealed altered connectivity between the left CUN and other brain regions, particularly with weakened connections to visual-related areas.

Therefore, structural and functional abnormalities in the CUN may contribute to deficits in visual processing and attention regulation in ADHD patients. This further supports the notion that disruptions in visual and attention-related networks, particularly within the VN, play a central role in core ADHD symptoms, such as inattention, underscoring the critical involvement of the LING and CUN in ADHD. Further research is needed to explore the potential of targeting these neural circuits in interventions aimed at improving attention and cognitive function in ADHD patients.

Brain regions with decreased spontaneous neural activity in adolescents with ADHD

In this study, we observed decreased spontaneous neural activity in the left medial frontal gyrus (MFG, BA 9) and the left precuneus (PCUN, BA 31) in adolescents with ADHD. The MFG, which is part of the executive control network (ECN), is essential for executive functions such as WM, decision-making, and attentional control. The PCUN, a core region of the DMN, is involved in self-referential thinking and memory retrieval. The ECN and DMN are thought to interact, with dysfunctions in one network potentially influencing the other[46]. In ADHD, the dysregulation of these networks can impair the ability to shift focus between internal and external stimuli[47,48]. The decreased activity in the left MFG and PCUN found in this study likely reflects disruptions in the balance between these two networks, contributing to attentional and cognitive challenges.

Multiple studies have highlighted the critical role of MFG dysfunction in ADHD. Lee *et al*[49] utilized electroencephalography to demonstrate increased theta activity in the MFG in children with ADHD, suggesting impairments in attention regulation and WM functions in this population. Similarly, Zhu *et al*[50] used functional near-infrared spectroscopy to investigate prefrontal cortex activity, including the MFG, during response inhibition tasks. Their study revealed reduced activation of the right MFG in children with ADHD, particularly in the predominantly inattentive subtype (ADHD-PI), further supporting the notion that MFG dysfunction contributes to deficits in response inhibition and attentional control.

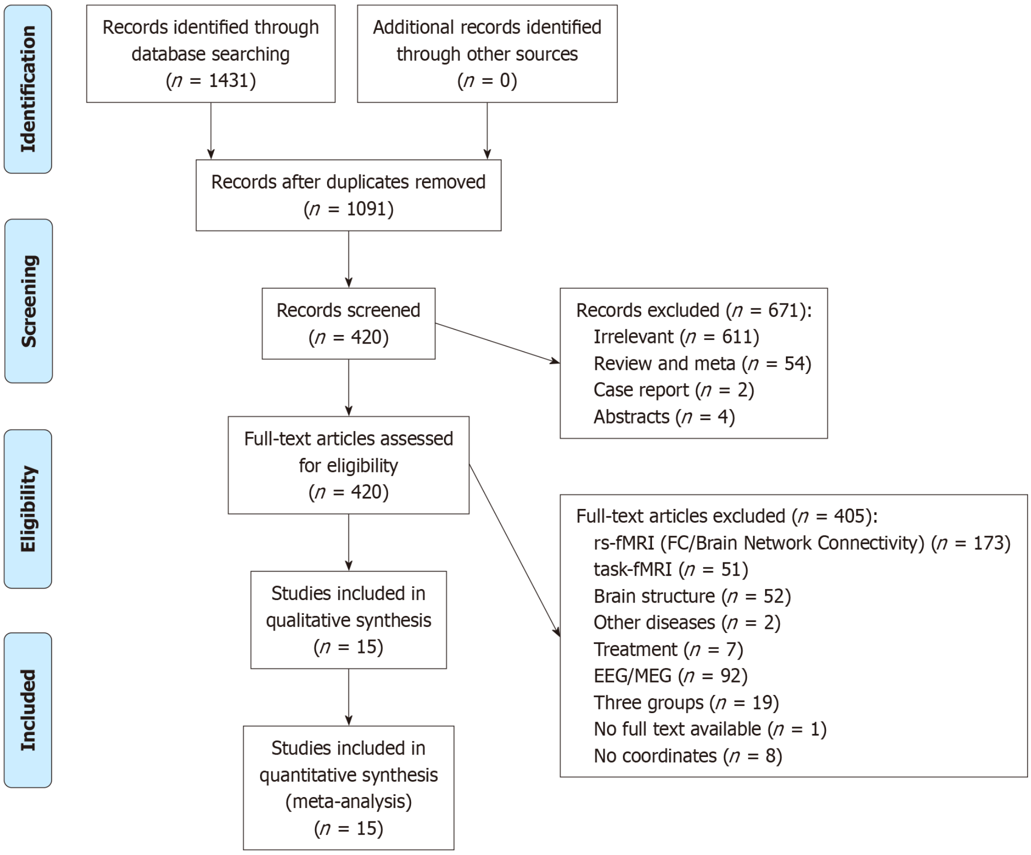

Figure 1 PRISMA flow diagram for studies included in the current meta-analysis. rs-fMRI: Resting-state functional magnetic resonance imaging; FC: Functional connectivity; fMRI: Functional magnetic resonance imaging; EEG: Electroencephalogram.

In adult ADHD patients, Tan *et al*[51] reported weaker negative FC between the left amygdala and the left MFG, indicating that functional abnormalities may contribute to altered brain connectivity and cognitive impairments. Zhao *et al*[45] similarly reported significant reductions in GM volume and decreased FC in the right MFG of adolescents with ADHD. These structural and functional abnormalities provide further evidence of the critical involvement of the MFG in the executive deficits observed in ADHD patients[45]. Additionally, the neuroimaging findings of Cao *et al*[52] highlight the potential therapeutic value of targeting the MFG in ADHD treatment. As a critical site of dysfunction, MFG-focused interventions, such as transcranial magnetic stimulation or transcranial direct current stimulation, may improve cognitive and behavioral outcomes by modulating activity within this key region responsible for executive functions.

The PCUN, another region with decreased activity observed in our study, plays a crucial role in integrating visuospatial information, coordinating mental imagery, and facilitating aspects of consciousness[53]. Previous research has reported decreased ReHo in the PCUN of adults with ADHD, with a positive correlation between inattentive symptoms and ReHo, indicating a strong association between PCUN dysfunction and inattention[41]. Similarly, our findings of decreased activity in the left PCUN in adolescent ADHD patients further extend these observations to younger populations, demonstrating consistent alterations in the PCUN across different developmental stages. In line with these findings, Kumar *et al*[54] reported abnormal connectivity in the left PCUN during a cognitive control task in children with ADHD, highlighting the improper integration of this region into broader neural networks. In adult ADHD patients, Zhao *et al*[55] reported abnormal FC between the anterior insula and the PCUN. Disruptions in this connectivity may underlie executive function deficits, particularly impaired WM and attentional control in individuals with ADHD. Additionally, Soman *et al*[56] conducted a longitudinal neuroimaging study that revealed an increased rate of structure-function coupling in the PCUN among children with ADHD, suggesting inefficient neural integration or compensatory mechanisms that may contribute to the attention deficits typical of ADHD.

Taken together, the decreased spontaneous neural activity in both the PCUN and MFG may indicate dysfunctions in the DMN and ECN, respectively. Identifying these vulnerable regions provides insights into the neurobiological underpinnings of ADHD. These findings can guide targeted interventions to improve outcomes for affected adolescents.

Limitations and prospects

Although this ALE meta-analysis offers valuable insights into spontaneous neural activity changes in adolescents with ADHD, several limitations should be noted. First, the ALE method does not account for variability in activation intensity across studies, which may lead to the exclusion of regions with low activation intensity. Second, as our analysis exclusively included studies conducted in Asian countries, caution should be exercised in extending these findings to other populations, particularly Caucasians, given the potential cultural and genetic variations that can impact neural patterns. Third, the predominance of male participants in the included studies limits our understanding of potential sex

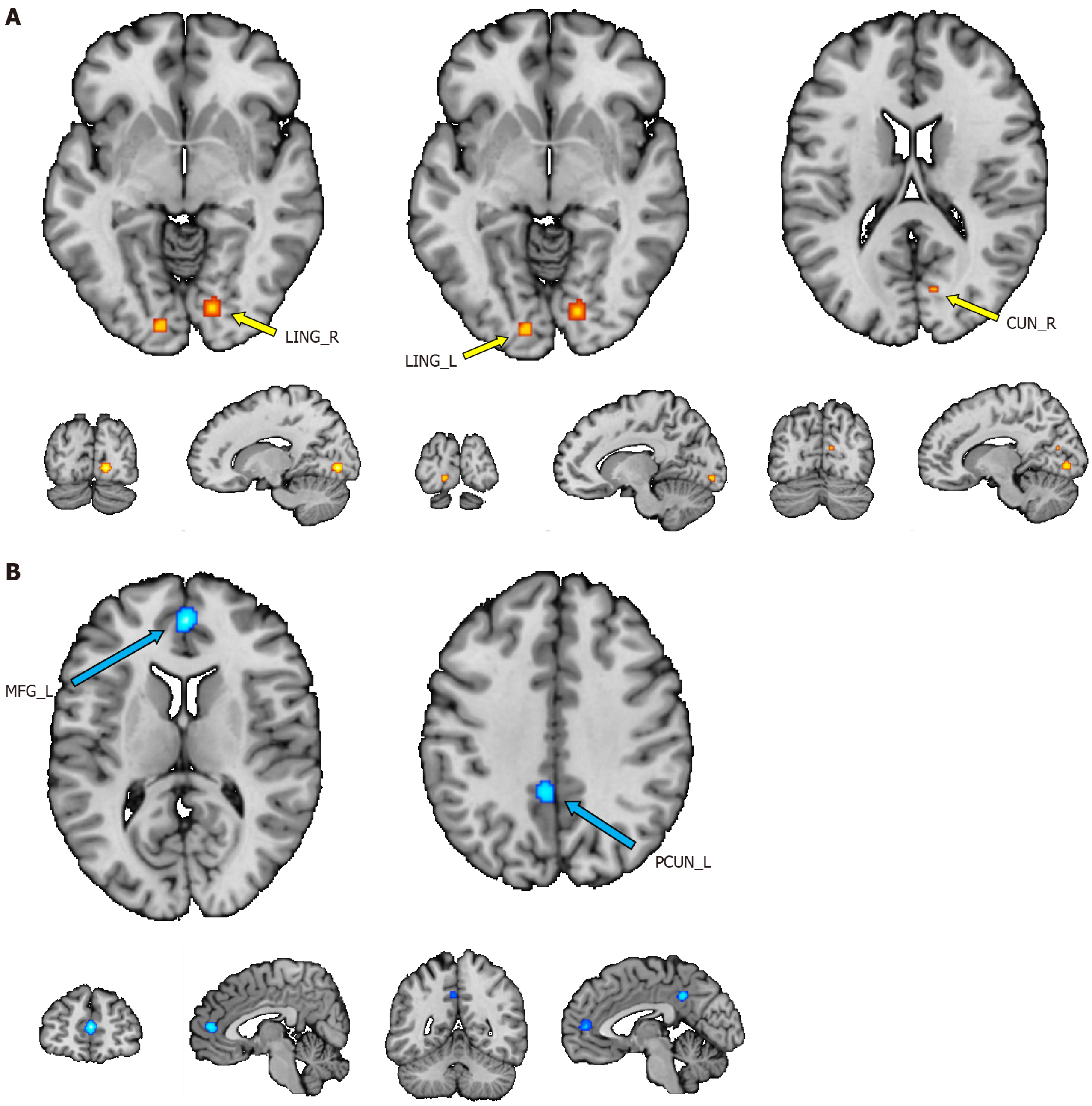

Figure 2 Brain activity. A: Increased brain activity in the right lingual gyrus, left lingual gyrus, and right cuneus in adolescents with attention deficit hyperactivity disorder (ADHD) compared with healthy controls (HCs) [cluster-level familywise error (FWE); correction at P < 0.05]; B: Decreased brain activity in the left medial frontal gyrus and left precuneus in adolescents with ADHD compared with HCs (cluster-level FWE correction at P < 0.05). MFG: Medial frontal gyrus; PCUN: Precuneus; R: Right; L: Left.

differences in ADHD-related neural activity, which may affect the applicability of the findings to female populations.

However, the ALE meta-analysis for brain imaging provides a robust framework for integrating locational information across diverse studies, offering a promising avenue for future investigations into consistent brain activity changes in ADHD.

CONCLUSION

In conclusion, our ALE meta-analysis revealed consistent alterations in the bilateral LING, right CUN, left MFG, and left PCUN among adolescents with ADHD compared with HCs. These findings may help further the understanding of the neurophysiological mechanisms underlying adolescent ADHD and contribute to the development of more targeted interventions.

FOOTNOTES

Author contributions: Shu YP conceptualized and designed the research framework. Hou YZ and Zhang Q were responsible for conducting the literature search, carrying out the initial screening, extracting relevant data, and performing the analytical computations. Li D, Liu JY, Wang XM, and He Q contributed to critical revisions that significantly improved the intellectual content of the manuscript. Zhang Q, He Q, and Hou YZ have played important and indispensable roles in the experimental design, data interpretation, and manuscript preparation as co-corresponding authors. Zhang Q designed the overall experiment, planned the specific workflow, and, together with Hou YZ, conducted the literature search, screening, and extraction of key data. Zhang Q also provided significant assistance in data analysis and offered guidance on the software used. Hou YZ and He Q reviewed and revised early drafts of the manuscript. In addition, He Q contributed to clarifying the neuroimaging associations related to ADHD. Hou YZ, as the lead corresponding author, was primarily responsible for manuscript submission, peer review, and communication with the journal throughout the publication process. Zhang Q, He Q, and Hou YZ contributed equally to this manuscript and are therefore listed as co-corresponding authors.

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