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META-ANALYSIS

Multimodal abnormalities of brain structures in adolescents and young adults with major depressive disorder: An activation likelihood estimation meta-analysis

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Abstract

BACKGROUND

Major depressive disorder (MDD) in adolescents and young adults contributes significantly to global morbidity, with inconsistent findings on brain structural changes from structural magnetic resonance imaging studies. Activation likelihood estimation (ALE) offers a method to synthesize these diverse findings and identify consistent brain anomalies.

AIM

To identify consistent brain structural changes in adolescents and young adults with MDD using ALE meta-analysis.

METHODS

We performed a comprehensive literature search in PubMed, Web of Science, Embase, and Chinese National Knowledge Infrastructure databases for neuroimaging studies on MDD among adolescents and young adults published up to November 19, 2023. Two independent researchers performed the study selection, quality assessment, and data extraction. The ALE technique was employed to

synthesize findings on localized brain function anomalies in MDD patients, which was supplemented by sensitivity analyses.

RESULTS

Twenty-two studies comprising fourteen diffusion tensor imaging (DTI) studies and eight voxel-based morphometry (VBM) studies, and involving 451 MDD patients and 465 healthy controls (HCs) for DTI and 664 MDD patients and 946 HCs for VBM, were included. DTI-based ALE demonstrated significant reductions in fractional anisotropy (FA) values in the right caudate head, right insula, and right lentiform nucleus putamen in adolescents and young adults with MDD compared to HCs, with no regions exhibiting increased FA values. VBM-based ALE did not demonstrate significant alterations in gray matter volume. Sensitivity analyses highlighted consistent findings in the right caudate head (11 of 14 analyses), right insula (10 of 14 analyses), and right lentiform nucleus putamen (11 of 14 analyses).

CONCLUSION

Structural alterations in the right caudate head, right insula, and right lentiform nucleus putamen in young MDD patients may contribute to its recurrent nature, offering insights for targeted therapies.

Key Words: Major depressive disorder; Adolescent; Young adults; Neuroimaging; Diffusion tensor imaging; Voxel-based morphometry; Activation likelihood estimation; Meta-analysis

Core Tip: This activation likelihood estimation (ALE) meta-analysis illuminates significant structural brain changes in adolescents and young adults with major depressive disorder (MDD), particularly in the right caudate head, right insula, and right lentiform nucleus putamen, highlighting their potential as neural markers. By employing ALE across diffusion tensor imaging and voxel-based morphometry studies, the research reveals consistent patterns of reduced fractional anisotropy, underscoring the recurrent nature of MDD. These insights provide a deeper understanding of its neuropathology and highlights the critical role of specialized neuroimaging in unraveling the complex mechanisms underlying MDD.

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INTRODUCTION

Major depressive disorder (MDD), a complex neuropsychiatric condition characterized by pervasive feelings of sadness, pessimism, heightened sensitivity, and cognitive dysregulation, significantly contributes to the global disease burden across diverse age groups, especially among adolescents and young adults[1]. In the global context, the prevalence of self-reported depressive symptoms in adolescents is approximately 34%, with regions such as the Middle East, Africa, and Asia reporting the highest prevalence of elevated depressive symptoms in this demographic group[2]. In addition, the prevalence of MDD among young people has markedly increased in the past decade[3]. This demographic variation emphasizes the critical need for age-specific research that encompasses both adolescents and young adults to effectively address and understand the nuances of MDD within these populations. Depressive symptoms during these crucial developmental periods are often underrecognized, thus potentially leading to rapid disease progression and long-term detrimental effects on educational attainment, social integration, and overall quality of life[4]. The onset of MDD during these stages of significant biological, psychological, and social transformations introduces unique challenges, thus underscoring the importance of specialized research aimed at elucidating the distinct etiology, pathophysiology, and treatment responses of MDD in adolescents and young adults[5,6].

In recent years, the rapid advancement of neuroimaging research has provided a robust foundation for investigating the neurophysiology of MDD patients. Despite decades of fundamental science, clinical neuroscience, and psychiatric research, the pathophysiology of severe MDD remains incompletely understood[7]. Neuroimaging methods offer a powerful, noninvasive avenue to study the neurobiological mechanisms underlying psychiatric disorders[8]. These neuroimaging techniques have yielded invaluable insights into the impact of depression on brain structures in adolescents and young adults, thus providing insight into the intricate interplay between neural development and psychopathology[9]. Structural magnetic resonance imaging (sMRI) is one such technique that has been pivotal in advancing our understanding of the brain's structure in the context of mental health disorders[10]. sMRI provides high-resolution images of the brain, thus enabling detailed analyses of brain morphology and structure[11]. Within the domain of sMRI, techniques such as voxel-based morphometry (VBM) and diffusion tensor imaging (DTI) have been instrumental[12].

VBM allows for the investigation of focal differences in brain anatomy by comparing the concentration of gray matter across different brain regions, whereas DTI focuses on the integrity and organization of white matter tracts by measuring the diffusion of water molecules in the brain[13].

Although researchers have used sMRI techniques to analyze changes in brain structure in adolescents and young adults with MDD, the findings of these studies are inconsistent and remain controversial[14-35]. This inconsistency underscores the complexity of MDD across these age groups and the influence of individual and methodological differences. The high prevalence and distinct nature of adolescent and young adult MDD necessitate a nuanced understanding of its neural underpinnings. sMRI studies, including those utilizing DTI and VBM, have provided valuable insights into brain structural anomalies associated with MDD[36]. However, the variability in research outcomes highlights the complexity of the disease and the impact of individual and methodological differences[37]. This variability calls for a comprehensive and systematic approach to synthesize existing research, such as by utilizing activation likelihood estimation (ALE) meta-analysis. By integrating a wealth of available data, ALE meta-analysis aims to extract coherent and actionable insights, thus bridging the gap in our understanding of the neural basis of MDD among adolescents and young adults. Importantly, the ALE meta-analysis method overcomes the challenges of method diversity and result heterogeneity, thus helping to screen for credible and practically valuable research results[38]. Previously, Yuan *et al*[39] used the ALE method to conduct a meta-analysis of MDD patients; however, they did not include a young population and may not have identified the consistently vulnerable brain regions in the resting state that may differ between adolescent depression patients and adults.

In this study, we hypothesized that populations with depressive disorders among adolescents and young adults will exhibit distinct brain outcome alteration patterns compared to healthy control (HC) groups, thus potentially revealing neural damage mechanisms associated with depressive disorders. We employed ALE analysis to exclusively focus on multimodal brain structure anomalies by using methodologies from DTI and VBM studies, thus aiming for a more comprehensive understanding of consistent brain structural changes in patients with depressive disorders among adolescents and young adults.

MATERIALS AND METHODS

Literature search

In alignment with PRISMA[40], a comprehensive literature search was systematically executed across four major electronic databases up to November 19, 2023. This review was registered with PROSPERO (ID: CRD42023371521). These databases included PubMed, Web of Science, Embase, and Chinese National Knowledge Infrastructure. The search terms were as follows: (adolescent OR youngster OR young people OR youth OR childhood OR teenage OR teen OR juvenile) AND (depression OR depression neurosis OR depressive disorder OR major depression OR melancholia) AND (white matter OR white brain matter OR cerebellar white matter OR white matter integrity) AND (diffusion tensor* OR DTI OR magnetic resonance imaging OR tractography OR mean diffusivity OR axial diffusivity OR radial diffusivity OR fractional anisotropy OR structural connectivity OR structural changes OR structural MRI OR voxel-based morphometry OR VBM) AND (magnetic resonance OR MRI OR functional MRI OR fMRI OR neuroimaging). In addition, review articles and the reference lists of the included articles were also checked to identify potential omitted studies in the searches.

Inclusion and exclusion criteria

Studies were included in this analysis if they met the following criteria: (1) Had a diagnosis of depression according to the Diagnostic and Statistical Manual of Mental Disorders edition in use at the time of the study's publication; (2) included adolescent or young adult participants; (3) were right-handed; and (4) had results reported for the whole brain in stereotactic space, either in the Montreal Neurological Institute (MNI) or Talairach coordinates for DTI or VBM studies. Studies were excluded if they met at least one of the following criteria: (1) Were abstracts, case reports, systematic reviews, or meta-analyses; (2) were intervention studies; (3) used regional homogeneity or amplitude of low-frequency fluctuations (ALFF); (4) focused on brain connectivity networks or depression in combination with other diseases; or (5) were studies wherein the full text was not available or did not report of coordinates.

To prevent data duplication, when two or more studies used the same dataset, only the study with the largest sample size and most comprehensive information was selected. For longitudinal or intervention studies, only baseline data were considered.

Data extraction

Two authors (H YZ and ZQ) independently extracted data from each study by using a predefined data extraction form. Any disagreements were resolved through discussion among the authors. Information on the authors, publication year, sample size, characteristics of the study population (age and sex), age range, and MRI technical details (MRI scanner, field strength, processing software, standard stereotactic space, method, differential brain region, corrective methods, and thresholds) was obtained (Table 1). The coordinates in each study were independently extracted following the requirements of the ALE.

Quality assessment

The quality of the included studies was assessed by using the Newcastle Ottawa Quality Assessment Scale (NOS). The

Table 1 Characteristics of the included studies

Ref.	Sample size		Age, mean ± SD		Sex, M/F		MRI equipment & field strength	Processing software	Method	Differential brain region	Corrective methods	Quality
	Patient	HCs	Patient	HCs	Patient	HCs						
Cullen *et al*[14], 2010	14	14	16.79 ± 1.29	16.81 ± 1.50	4/10	6/8	Siemens Trio Tim 3.0 T	FSL	DTI	10	NA	4/1/1
Liu *et al*[15], 2010	12	16	Approximately 30.38	Approximately 29.75	4/12	4/12	Siemens 1.5 T	SPM12	DTI	14	$P_{uncor} < 0.001$	4/1/1
Henderson *et al*[16], 2013	17	16	6.80 ± 2.20	16.40 ± 1.40	9/8	6/10	Siemens Allegra 3.0 T	FSL	TBSS	4	$P_{uncor} < 0.001$	4/1/1
Bessette *et al*[17], 2014	31	31	17.10 ± 1.88	17.00 ± 2.40	7/24	12/19	Siemens Allegra MRI 3.0 T	FSL	TBSS	56	TFCE $P < 0.05$	4/1/1
Jiang *et al*[18], 2015	35	34	29.54 ± 8.57	31.91 ± 8.80	17/18	17/17	GE Milwaukee WI 3.0 T	FSL	DTI	10	$P_{uncor} < 0.001$	4/1/1
Xiao *et al*[19], 2015	22	22	20.14 ± 1.64	20.77 ± 1.41	12/10	12/10	Siemens Magnetom Symphon 1.5 T	FSL	TBSS	10	$P < 0.01$	4/1/1
Geng *et al*[20], 2016	26	31	15.60 ± 1.27	15.60 ± 1.38	7/19	14/17	GE Signa HDX 3.0 T	PANDA software	DTI	4	AlphaSim, $P < 0.05$	4/1/1
Tatham *et al*[21], 2016	55	18	36.40 ± 10.50	33.20 ± 10.20	NA	NA	GE Signa HDX 3.0 T	FSL	TBSS	3	FEW, $P < 0.05$	4/1/1
Chang *et al*[22], 2018	108	156	20.61 ± 4.91	22.25 ± 4.35	38/93	63/45	GE Signa HDX 3.0 T	SPM8	DTI/GMV	5 & 17	$P < 0.01$	4/1/1
Wu *et al*[23], 2018	23	17	19.44 ± 4.61	18.07 ± 3.85	NA	NA	GE Signa HDX 3.0 T	PANDA	DTI	6	$P < 0.05$	4/1/1
Wei *et al*[24], 2020	49	49	30.03 ± 0.91	31.12 ± 9.95	11/38	18/31	GE Signa HDX 3.0 T	SPM8	DTI	6	GRF, $P < 0.001$	4/1/1
Wang *et al*[25], 2020	18	18	15.77 ± 1.18	16.18 ± 0.95	10/8	10/8	Siemens Trio Tim 3.0 T	NIT	FOCA	3	FDR, $P < 0.05$	4/1/1
Lee *et al*[26], 2021	19	22	15.03 ± 1.45	15.96 ± 1.02	NA	NA	Siemens Trio Tim 3.0 T	FSL	TBSS	4	FWE, $P < 0.05$	4/1/1
Roelofs *et al*[27], 2022	22	21	15.93 ± 1.45	15.09 ± 1.80	2/20	4/17	Philips Achieva 3.0 T	FSL	TBSS	2	FWE, $P < 0.05$	4/1/1
Ding *et al*[28], 2010	18	18	15.78 ± 1.20	16.20 ± 0.90	10/8	10/8	Siemens Trio Tim 3.0 T	SPM5	GMV	11	$P < 0.05$	4/1/1
Shad *et al*[29], 2012	22	22	16.00 ± 2.10	15.00 ± 2.10	10/12	11/11	GE Milwaukee WI 1.5 T	SPM5	GMV	25	FWE, $P < 0.05$	4/1/1
Vulser *et al*[30], 2015	119	461	14.45 ± 0.36	14.40 ± 0.41	41/78	158/303	NA	SPM8	GMV	8	FWE, $P < 0.05$	4/1/1
Straub *et al*[31], 2019	60	43	17.30 ± 3.44	17.62 ± 3.85	12/48	5/38	Siemens Allegra 3.0 T	SPM 12	GMV	4	FWE, $P < 0.05$	4/1/1
Chen *et al*[32], 2023	95	78	18.14 ± 4.47	17.85 ± 4.30	95/0	38/40	GE 750 1.5 T	SPM12	GMV	6	GRF, $P < 0.05$	4/1/1
Vulser *et al*[33], 2023	265	128	14.41 ± 0.52	14.40 ± 0.43	NA	NA	Siemens Corp 3.0 T	SPM 12	GMV	4	FWE, $P < 0.05$	4/1/1
Deng *et al*[34], 2023	31	29	NA	NA	8/23	11/18	GE Brivo MR355 1.5 T	SPM8	GMV	4	FWE, $P < 0.05$	4/1/1
Kang *et al*[35], 2023	54	167	35.69 ± 13.47	35.82 ± 12.91	21/33	67/100	Siemens Trio Tim 3.0 T	SPM 12	GMV	18	$P_{uncor} < 0.001$	4/1/1

DTI: Diffusion tensor imaging; FOCA: Four-dimensional (spatiotemporal) consistency of local neural activities; GMV: Gray matter volume; HCs: Healthy controls; M/F: Male or female; MRI: Magnetic resonance imaging; NA: Not available; TBSS: Tract-based spatial statistics.

NOS has three levels and a total of eight items: (1) Four items for subject selection; (2) one item for comparability between groups; and (3) three items for outcome measurement. The total score is 9 points. A result ≥ 5 points was included in the data analysis. Each study was independently reviewed and rated by two authors (H YZ and ZQ). If disagreements occurred, the papers were discussed by the authors' group to determine a consensus score.

ALE analysis

The ALE meta-analysis method was conducted by using GingerALE 3.0.2 software (www.brainmap.org/ale)[41]. ALE models each alteration focus as the center of a spherical Gaussian probability distribution. This approach is used to create spatial probability maps that highlight consistent brain region involvement in certain tasks or conditions[42]. For the ALE meta-analysis, our study was conducted in the MNI standard space. Hence, it was essential to utilize the Lancaster transformation within GingerALE 3.0.2 to convert the three-dimensional coordinates of brain regions in the Talairach space to the MNI space.

Subsequently, Gaussian function smoothing with a full width at half maximum (FWHM) was performed based on 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 that were reported in the study group. This process yielded three-dimensional modeling activation (MA) maps for each study group.

Afterwards, based on three-dimensional (3D)-MA maps, a 3D ALE map was generated of 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 (FWE) correction was set at $P < 0.05$, the threshold permutations were set at $P < 0.001$ with 1000 permutations, and finally, a threshold map (ALE image) was obtained. Finally, our study used Mango software (http://rii.uthscsa.edu/mango/) to check and analyze the resulting ALE images.

Sensitivity analysis

The jackknife sensitivity analysis method was employed to assess the reproducibility of the meta-analysis outcomes. In this approach, a single study was systematically excluded from the dataset, followed by ALE meta-analysis of the remaining study data using GingerALE 3.0.2 software. This procedure was repeated 14 times (each time removing one study) to verify the consistency of the results after the exclusion of a study and to compare these results with the original analysis.

RESULTS

General information of the included studies

The systematic search generated 252 related articles, 22 of which[14-35] were ultimately selected for inclusion in this meta-analysis (Figure 1). These included 14 studies utilizing DTI and 8 utilizing VBM. Notably, the study by Chang *et al*

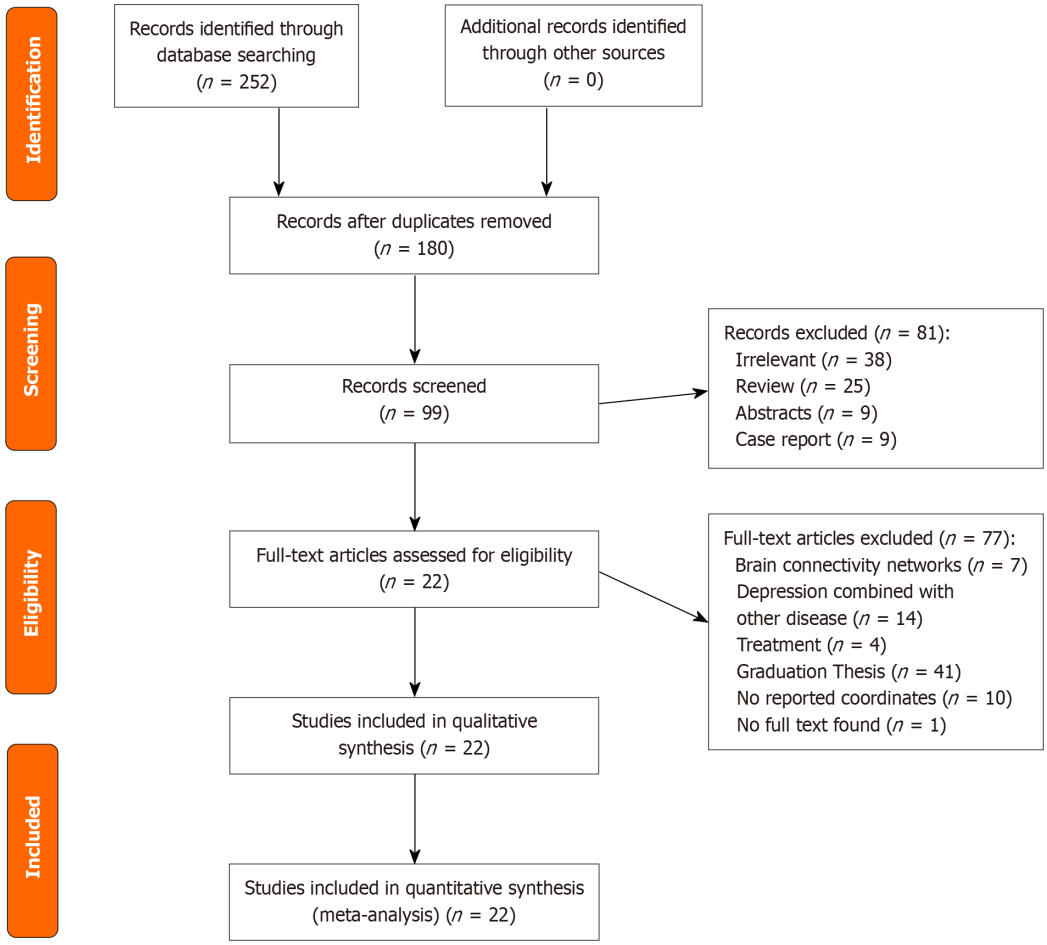

Figure 1 PRISMA flow diagram for included studies in the current meta-analysis.

[22] encompassed analyses using both DTI and VBM methodologies, thereby contributing to a total of nine VBM-based investigations. Finally, the DTI studies included 451 individuals diagnosed with MDD and 465 HCs, with the identification of alterations in 137 distinct brain areas. The VBM studies included 664 individuals diagnosed with MDD and 946 HCs and identified alterations in 80 distinct brain areas (Table 1).

The main results of changes in brain structure during adolescent and young adult MDD

ALE analysis based on DTI structural data demonstrated significant reductions in fractional anisotropy (FA) values in the right caudate head, right insula, and right lentiform nucleus putamen in adolescents and young adults with depression in comparison to HCs (Figure 2 and Table 2). However, no brain regions where FA values increased were identified. In contrast, ALE analysis based on VBM structural data did not reveal any significant changes in gray matter volume.

Sensitivity analysis

The outcomes of the sensitivity analysis demonstrated reproducibility in the findings, with the right caudate head, right insula, and right lentiform nucleus putamen showing consistent alterations in 11 of 14 analyses, 10 of 14 analyses, and 11 of 14 analyses, respectively (Table 3).

DISCUSSION

To the best of our knowledge, this meta-analysis represents the inaugural exploration of multimodal brain structural abnormalities in adolescents and young adults with depression by employing the ALE methodology, with the utilization of both DTI and VBM. The findings of this meta-analysis underscore the nuanced neurobiological underpinnings of MDD among adolescents and young adults, thus revealing significant alterations in brain structure and function. The observed reductions in FA within specific brain regions, such as the right caudate head, right insula, and right lentiform nucleus putamen, align with literature suggesting the pivotal role that these areas play in emotional regulation, cognitive processing, and the reward system[43,44]. Notably, no regions exhibited augmented FA values, thus suggesting a pervasive trend toward decreased white matter integrity across the affected neural domains. Alterations in white matter microstructure, particularly in the uncinate fasciculus, are associated with emotional dysregulation[45]. Additionally, a

Table 2 Decreased fractional anisotropy values in brain regions of adolescents and young adults with major depressive disorder

Research methods	Anatomical label	Peak MNI coordinate			ALE value	Volume in mm^3
		X	Y	Z		
FA decrease	Right caudate head	24	28	-4	0.015717618	1096
	Right insula	32	26	-8	0.012060626	656
	Right lentiform nucleus putamen	24	24	-12	0.010999768	696

ALE: Activation likelihood estimation; FA: Fractional anisotropy; MDD: Major depressive disorder; MNI: Montreal Neurological Institute.

Table 3 Jackknife sensitivity analyses

Discarded article	Right caudate head	Right insula	Right lentiform nucleus putamen
Cullen *et al*[14], 2010	N	N	N
Liu *et al*[15], 2010	Y	Y	Y
Henderson *et al*[16], 2013	Y	Y	Y
Bessette *et al*[17], 2014	N	N	N
Jiang *et al*[18], 2015	Y	Y	Y
Xiao *et al*[19], 2015	Y	Y	Y
Geng *et al*[20], 2016	Y	N	Y
Tatham *et al*[21], 2016	Y	Y	Y
Chang *et al*[22], 2018	Y	Y	Y
Wu *et al*[23], 2018	N	N	N
Wei *et al*[24], 2020	Y	Y	Y
Wang *et al*[25], 2020	Y	Y	Y
Lee *et al*[26], 2021	Y	Y	Y
Roelofs *et al*[27], 2022	Y	Y	Y

N: No; Y: Yes.

study on sex incongruence revealed lower FA in the inferior fronto-occipital fasciculus, thus emphasizing the role of white matter organization in sex identity[46]. Furthermore, findings in adolescents at high risk for bipolar disorder (BD) suggest decreased FA in various brain areas, thus emphasizing the potential role of FA as an endophenotype for BD[47]. The insula, which is a component of the limbic system, plays a pivotal role in memory and emotion processing[48]. The lack of areas showing increased FA values further emphasizes the potential of these structural changes as being neural markers of MDD, thus being potentially indicative of disrupted white matter integrity and altered neural connectivity.

However, contrary to the alterations observed in white matter through DTI analysis, this study did not identify any regions exhibiting significant changes in gray matter volume among adolescents and young adults with depression. This indicates a more consistent pattern of brain structural changes characterized by reduced integrity, particularly in regions such as the right caudate head, right insula, and right lentiform nucleus putamen, compared to HCs. The absence of significant gray matter volume changes further underscores the potential of these structural alterations as being neurobiomarkers for MDD, thus being potentially indicative of impaired white matter integrity and altered neural connectivity. These findings provide objective neuroimaging evidence, which enriches our understanding of the neurobiological mechanisms underlying depression in adolescents and young adults.

Role of the striatum in adolescent and young adult MDD patients

The putamen and globus pallidus together form the lentiform nucleus, which, along with the caudate nucleus, constitutes the striatum. The striatum, which is a subcortical structure, is divided into the ventral and dorsal striatum. The dorsal striatum includes the caudate nucleus and putamen, whereas the ventral striatum comprises the nucleus accumbens[49]. The caudate nucleus is believed to control cognitive aspects within the striatum, thus playing a role in emotional processing, motor control, and particularly in regulating cognitive functions[50,51]. The putamen, which is a critical component of the basal ganglia, is involved in learning, controlling bodily movements, and processing visual information and is associated with emotional processing, cognitive processes, motivation, and motor regulation, thus playing a key

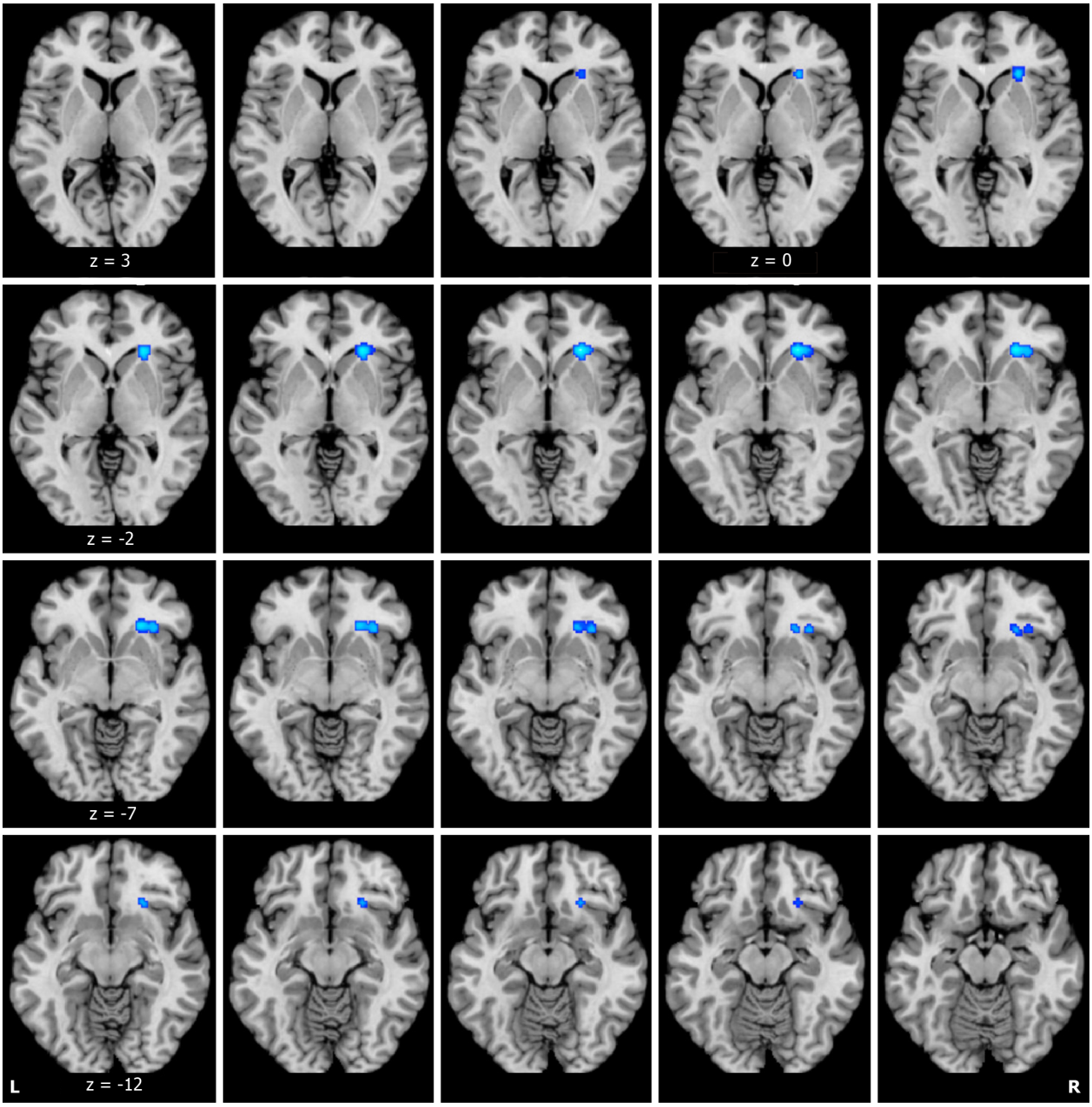

Figure 2 Brain structure alterations in adolescents and young adults with major depressive disorder compared to healthy controls.

role in action selection[52,53].

Recent research has elucidated the structural abnormalities within the striatum in MDD patients, particularly in adolescents and young adults. For instance, studies have reported of lower FA values in the right caudate nucleus among MDD patients than among HCs, thus highlighting white matter integrity impairment[54]. Furthermore, Ding *et al*[55] reported that individuals with MDD exhibit reduced FA values across the striatum bilaterally, thus suggesting widespread structural changes within this brain region. Moreover, volumetric studies have noted a reduction in the size of the striatum among MDD patients, with one study demonstrating volume reductions in the ventral striatum and putamen even before the onset of the disorder in adolescents at risk due to parental MDD history[56,57]. This familial predisposition is further evidenced by findings of increased right striatum gray matter volume among first-degree relatives of MDD patients, thus suggesting that striatal structural abnormalities may be a risk factor for developing MDD [58].

These findings, although predominantly cross-sectional, provide a foundational basis for future longitudinal studies aimed at elucidating the causal relationships between striatal volume abnormalities and the progression of MDD. The consistent observation of striatal volume reductions in MDD patients compared to HCs across various studies underlines the potential of the striatum as being a key neural substrate in the pathophysiology of depression.

Role of the insula in adolescent and young adult MDD patients

This meta-analysis demonstrated a decrease in FA values within the right insula among adolescents and young adults

with MDD. The insula, which is a cortical structure with extensive connections to various cortical and limbic regions, plays a critical role in diverse cognitive, emotional, and regulatory functions, including interoceptive awareness, emotional responses, and empathic processes[59]. Several meta-analyses based on structural MRI studies have reported of bilateral reductions in insular gray matter volume in individuals with MDD[60,61]. Lu *et al*[62] observed a decrease in the gray matter volume of the right insula with the progression of MDD. Furthermore, functional MRI studies have identified alterations in functional connectivity within significant networks centered on the insula, such as the salience network, default mode network (DMN), and central executive network (CEN), in MDD patients[63,64]. The insula's mediation of dynamic switches between the DMN and CEN facilitates the allocation of cognitive resources, such as attention and working memory. Hence, alterations in the connectivity strength within these networks in affective disorders can lead to cognitive impairments[65].

Task-based functional MRI studies have demonstrated atypical insula activity during executive function and emotional processing tasks in individuals with MDD, thus potentially revealing the difficulties in cognitive-emotional integration observed in individuals with adolescent depression[66]. Positron emission tomography studies, such as those conducted by Delaveau *et al*[67], have also noted reduced insula activation in MDD patients. Moreover, changes in insula activity have been observed following various MDD treatments, including pharmacotherapy, deep brain stimulation, and cognitive behavioral therapy, which suggests that the region has a broader role in mediating antidepressant responses and remission[68].

Collectively, these findings, which are derived from diverse neuroimaging methodologies, consistently underscore the critical role of the insula in the neuropathology of depression[69]. These findings further highlight functional and structural abnormalities in the insula as being key neurobiological features of affective disorders.

Reason for the lack of positive findings in the VBM data in this meta-analysis

This meta-analysis did not identify changes in gray matter volume in the brains of adolescents or young adults with depression, which may be attributed to the relatively small number of reported brain regions with altered gray matter volume in the included studies. Among the eight studies that were analyzed, all of them reported regions of reduced gray matter volume, yet five of these studies had fewer than ten central coordinates for the reported areas of abnormal activity. The ALE meta-analysis, which functions as a probability distribution, is more influenced by studies reporting of a greater number of activation points. The scarcity of coordinates may fail to meet the threshold criteria, or the spatial information of these activity regions may be too dispersed to allow for the consolidation of results in areas proximal to the activation points. This dispersion could also explain the absence of increased activity findings in the DTI-based meta-analysis[70]. Therefore, whether there are specific brain regions in adolescents and young adults with depression that exhibit reduced gray matter volume relative to HCs and whether isolated DTI meta-analyses can demonstrate regions of increased activity warrant further exploration.

Limitations

First, the adoption of stringent exclusion criteria, particularly the exclusion of studies involving pharmacological or acupuncture treatments, has resulted in a smaller amount of literature for analysis. Second, although the ALE methodology effectively mitigates the risk of false-positives, it is less adept at circumventing false-negatives, thus posing a challenge to the robustness of the findings. Last, the number of studies employing VBM was limited to nine, thus culminating in a smaller aggregate of differential brain regions, which did not yield results of significant increases or decreases. However, ALE meta-analysis for brain imaging has the advantage of integrating locational information across diverse studies, thus offering a promising avenue for future explorations into consistent brain activity changes in specific disorders.

CONCLUSION

In conclusion, the structural alterations observed in the striatum and insula among adolescents and young adults with MDD may be indicative of the recurrent nature of the disorder. These findings underscore the potential of these structural changes as being neural markers for MDD, thus offering insights into the neuropathology of this disorder. Future research should aim to elucidate the longitudinal implications of these structural alterations.

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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; Liang S, Zheng ZL, Li JL, and Wu G contributed to critical revisions that significantly improved the intellectual content of the manuscript. Wu G and Hou YZ contributed equally to this manuscript and are therefore listed as co-corresponding authors. This

designation as co-corresponding authors underscores our shared responsibilities in handling correspondence, communicating with peers, and providing essential guidance throughout the research process.

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