Research Progress of Magnetic Resonance Imaging in Adolescent Depression

Xueyou Feng*, Hui Wang, Zhenyang Gao, Yuchen Zhong
Psychological Center, Hainan Vocational University of Science and Technology, Haikou 570100, China

Abstract: Depression is a major cause of disability and death among adolescents. The pathogenesis of depression is still unclear, and in recent years, the application of magnetic resonance imaging technology has allowed us to gain insight into the changes in depression at the neurological level; In order to further reveal the complexity of adolescent depression, this paper aims to collect the literature on adolescent depression by applying functional magnetic resonance imaging and structural magnetic resonance imaging methods, and to briefly discuss the relevant research results.

***Keywords*:** adolescent depression; magnetic resonance imaging; functional magnetic resonance; structural magnetic resonance; review

1. Introduction

Depression is a common and serious mental health disorder, with core symptoms including persistent and significant low mood, loss of interest, and anhedonia[1]. This condition has widespread and profound effects on patients' quality of life and social functioning. According to predictions by the World Health Organization, depression will become one of the three leading contributors to the global burden of disease by 2030[2]. Adolescence is a critical period for brain development as well as neurological and cognitive maturation[3]. At the same time, adolescents face a series of complex interpersonal and social challenges, making this developmental stage a high-risk period for the first onset of depression.

A meta-analysis of depression among children and adolescents in China reported that the prevalence of depression in this population is 19.85%[4]. Another national statistical study showed that the overall prevalence of depression among Chinese adolescents is 23.0%[5]. These findings indicate that depression is a widespread phenomenon among minors in China and poses a serious threat to their physical and mental health as well as their safety. A study examining the severity of depressive symptoms in children and adolescents and their predictive effect on adult depression found that individuals following a high-symptom trajectory were more likely to develop depressive symptoms and disorders in adulthood[6]. Therefore, effective interventions targeting adolescents with moderate to high levels of depressive symptoms may help prevent depression in early adulthood. Consequently, early screening, identification, and diagnosis of depression are essential.

Magnetic resonance imaging (MRI) is one of the most widely used non-invasive techniques for investigating the pathophysiological mechanisms of neuropsychiatric disorders. MRI offers several advantages, including multiparametric imaging capability, high soft-tissue resolution, absence of ionizing radiation, multi-planar imaging, and functional imaging capability. In recent years, MRI has played an increasingly important role in exploring the pathogenesis of depression. This article reviews recent studies on the application of MRI in depression, aiming to provide a reference for future research and clinical practice in the field of depression.

2. Functional Magnetic Resonance Imaging in Adolescent Depression

2.1 BOLD-fMRI in Adolescent Depression

Functional magnetic resonance imaging based on the blood oxygen level dependent (BOLD) effect, commonly referred to as BOLD-fMRI, measures fluctuations in blood oxygen signals in brain regions and has been demonstrated to be a powerful tool for investigating the functional organization of the brain[7]. BOLD-fMRI has been widely used in studies of human brain function in vivo, and it has several advantages, including being non-invasive, having high spatial and temporal resolution, strong reproducibility, and precise localization capability[8]. The working paradigms of BOLD-fMRI are mainly divided into two modes: resting-state fMRI and task-based fMRI.

Resting-state fMRI (rs-fMRI) is a technique that investigates spontaneous BOLD signal activity in the brain while participants are awake but not performing any specific task. rs-fMRI collects brain activity under resting conditions to examine intrinsic neural activity and functional organization. Several analytical approaches are commonly used in rs-fMRI studies, including regional signal variation analyses (such as regional homogeneity and amplitude of low-frequency

fluctuations), seed-based correlation analysis, and independent component analysis. Some studies have found that adolescents with depression primarily exhibit abnormal local activity in the anterior cingulate cortex[9]. Using seed-based correlation analysis with the amygdala, anterior cingulate cortex, insula, hippocampus, and dorsolateral prefrontal cortex as seed regions [10,11], researchers observed increased resting-state functional connectivity within fronto-limbic circuits in adolescents with depression compared with healthy controls. However, another study using similar seed regions reported decreased resting-state functional connectivity within a network centered on the anterior cingulate cortex in depressed adolescents[12]. This network included the anterior cingulate cortex, right prefrontal cortex, left inferior frontal cortex, superior frontal cortex, superior temporal gyrus, and insular cortex. In addition, a study that used the limbic network, salience network, and default mode network as seed regions found that adolescents with depression showed either increased or decreased resting-state functional connectivity within the limbic and salience networks compared with healthy controls, whereas no abnormalities were observed in the default mode network[13]. In contrast, another rs-fMRI study using independent component analysis reported increased functional connectivity within the default mode network in adolescents with depression[14]. Similar abnormalities in default mode network connectivity have also been observed in adults with depression[15]. These inconsistencies across studies may be related to differences in sample size, imaging equipment, and analytical methods.

Task-state fMRI (ts-fMRI) requires participants to perform specific tasks or receive external stimuli while changes in brain activity are measured. Common paradigms include facial emotion stimuli and reward-related tasks. Brent et al.[16] used a monetary reward task and found that, in adolescents currently experiencing depression, the severity of depressive symptoms was associated with reduced focal responsiveness in the nucleus accumbens. In contrast, among adolescents with a history of depression who were not currently in a depressive state, depressive severity was associated with reduced responsiveness in the corticostriatal circuitry. These findings suggest differences in reward system neural circuitry between individuals with a history of depression and those currently experiencing depressive episodes. In addition, some studies have reported that activation in cortical and subcortical regions during reward-related stimuli is positively correlated with the severity of anxiety and depressive symptoms[17,18]. In a study using facial emotion stimuli, Henje et al.[19] found that patients with major depressive disorder (MDD) exhibited significantly reduced connectivity of the insular cortex when processing both sad and happy facial expressions. Meanwhile, the connectivity between the insular cortex and the right fusiform gyrus, left middle frontal gyrus, right amygdala, and parahippocampal gyrus was increased. In a study of adolescents with depression, Liu Qi et al.[20] found that activation of the angular gyrus within the default mode network was associated with depressive symptoms. These findings reveal the neural basis of adolescent depression and highlight the complexity of its neural mechanisms, indicating that abnormalities in BOLD signals occur in both resting-state and task-based conditions.

2.2 MRS in Adolescent Depression

Magnetic resonance spectroscopy (MRS) is a non-invasive imaging technique used to study the chemical composition and metabolic processes within biological tissues. In studies of brain function and neurological disorders, proton magnetic resonance spectroscopy (1H-MRS) is commonly used to measure various metabolites, such as N-acetylaspartate, γ-aminobutyric acid, glutamate, creatine, and choline. Both depression and antidepressant treatment may lead to abnormalities in metabolites in the brain and peripheral tissues[21,22]. One study reported that adolescents with a family history of depression showed increased concentrations of creatine and choline in the left dorsolateral prefrontal cortex, and choline levels were positively correlated with the severity of depressive symptoms[23]. Bradley et al.[24] found that adolescents with depression exhibited elevated levels of γ-aminobutyric acid in the striatum, which differs from previous findings showing decreased γ-aminobutyric acid levels in the anterior cingulate cortex. A study examining the relationship between facial emotion processing and metabolic abnormalities in depressed adolescents found that, in adolescent patients with major depressive disorder (MDD), the ratio of N-acetylaspartate to creatine in the right thalamus was negatively correlated with reaction time to happy faces and positively correlated with the perceived intensity of sad, angry, and fearful emotions. In addition, the choline/creatine ratio in the right caudate nucleus was positively correlated with reaction time to fearful faces[25]. Another study on adolescents with depression who had experienced childhood adversity found that the ratio of N-acetylaspartate to glutamate complex in the anterior cingulate cortex was reduced in these individuals, whereas no such change was observed in the overall sample or in healthy controls[26]. Furthermore, a study investigating adolescents with depression and suicidal ideation reported that the mean ratio of N-acetylaspartate to glutamate complex in adolescents with suicidal ideation was significantly lower than that in both healthy controls and depressed adolescents without suicidal ideation[27]. Studies by Sonmez[28] and Chabert[29] also suggested that N-acetylaspartate and glutamine complexes may serve as potential biomarkers for bipolar traits in both healthy and depressed adolescents. Measurements of glutamate metabolic abnormalities using 1H-MRS may help identify adolescents with depression who exhibit mixed symptoms or are at risk for bipolar disorder. In summary, these findings suggest that increases or decreases in brain metabolites may

provide useful evidence for the early diagnosis or screening of adolescent depression and offer important insights into the neurobiological basis of the disorder, thereby further enhancing our understanding of adolescent depression.

2.3 ASL in Adolescent Depression

Arterial spin labeling (ASL)[30,31] is a completely non-invasive magnetic resonance imaging technique that uses magnetically labeled blood as an endogenous tracer to generate images of cerebral blood flow. It can be considered similar to other perfusion imaging techniques that use diffusible tracers. Compared with traditional contrast agents (such as contrast media), ASL does not require the injection of any substances and is therefore safer and non-invasive[32]. ASL has been more widely applied in studies of adult depression and is relatively well established. Research on adult patients with major depressive disorder (MDD) has shown reduced regional cerebral blood flow in the right parahippocampal gyrus, thalamus, fusiform gyrus, middle temporal gyrus, and bilateral insula[33]. However, studies of cerebral blood flow in adolescents with depression have reported somewhat different findings. For example, one study found that adolescents with MDD showed decreased regional cerebral blood flow in the inferior frontal gyrus but increased cerebral blood flow in the right prefrontal gyrus[34]. In addition, a study investigating healthy young individuals with a familial risk of depression found that cerebral blood flow in the amygdala gradually decreased with age in healthy individuals, whereas those with increased amygdala blood flow were more likely to develop depression[35]. Furthermore, ASL has also been used to evaluate cerebral blood flow in adolescents with MDD before treatment, and changes in cerebral blood flow after treatment have been reported[36]. By examining differences in cerebral blood flow across brain regions, ASL can provide insight into functional abnormalities in patients with depression and may offer useful biomarkers for early intervention and treatment. Although ASL has shown promising potential in depression research, its clinical application is still under development. Moreover, studies using arterial spin labeling in adolescent depression remain limited. Future research should focus more on adolescents with depression and utilize ASL to explore the characteristics of brain functional abnormalities in this population, thereby promoting the application and development of ASL techniques in the field of adolescent depression.

3. Structural Magnetic Resonance Imaging in Adolescent Depression

3.1 VBM in Adolescent Depression

Voxel-based morphometry (VBM) is a neuroimaging technique used to detect structural brain changes by measuring alterations in gray matter and white matter density or volume. VBM provides an objective, comprehensive, and automated method for analyzing brain structure. By quantitatively calculating changes in the density and volume of gray and white matter in specific brain regions, VBM enables precise morphological analysis[37]. In a study using VBM to examine whole-brain gray matter volume (GMV) in adolescents with depression and suicidal ideation, decreased GMV was observed in the left middle temporal gyrus, right superior temporal gyrus, right middle temporal gyrus, superior frontal gyrus, and left occipital lobe in depressed adolescent[38]. However, another study combining VBM with seed-based correlation analysis of emotion-related brain regions found that adolescents with major depressive disorder (MDD) showed increased GMV in the right middle frontal gyrus, decreased GMV in the left caudate nucleus, and reduced volume of the right putamen[39]. Reduced volume of the right putamen has also been observed in adolescents at high risk for depression[40]. Johannah et al.[41] reported that depressive symptoms in adolescents were associated with reduced GMV in the prefrontal cortex, cingulate gyrus, insula, and hippocampus. Fu Yujia et al.[42] analyzed brain structural and functional changes in adolescents with depression using VBM and cerebral blood flow analysis and found increased brain volume in the cerebellum, frontal lobe, cingulate gyrus, globus pallidus, angular gyrus, thalamus, precentral gyrus, temporal gyrus, and supplementary motor area. In addition, other studies have reported significant reductions in overall cortical and white matter indices in adolescents with depression, mainly involving regional decreases in the frontal, limbic, and temporal lobes[43]. These findings suggest that abnormal brain activity and structural alterations in adolescents with depression are primarily concentrated within the fronto-limbic system. This indicates that structural abnormalities in these regions may occur during the development and progression of depression, providing important evidence for understanding the neuropathological mechanisms of depression as well as its clinical diagnosis and treatment.

3.2 SBM in Adolescent Depression

Surface-based morphometry (SBM) is a structural neuroimaging analysis method that uses magnetic resonance imaging data to reconstruct and analyze the highly folded cortical surface of the brain in three dimensions. Through SBM, multiple cortical features can be precisely measured, including cortical thickness, surface area, curvature, and sulcal depth across the whole brain or in specific regions. This capability represents a major advantage of SBM compared with VBM[37].

A large-sample meta-analysis reported that adolescents with depression showed reductions in both cortical thickness and surface area in the hippocampus and the basolateral amygdala[44]. Moreover, compared with individuals experiencing a first episode of depression, those with recurrent depression exhibited further reductions in the thickness and surface area of the hippocampus and the basolateral amygdala. Nielsen et al.[45] conducted a longitudinal study and found that over time the orbitofrontal cortex thickness decreased in male adolescents but increased in female adolescents, and these changes were associated with worsening depressive symptoms. In an earlier developmental stage, a study of preschool children with depression reported that depressed preschoolers exhibited a reduction in total cortical surface area, particularly in the lateral orbitofrontal cortex. The reduction in cortical surface area in this region was positively associated with depressive symptoms, whereas cortical thickness did not show a significant association with depression. These findings may represent a neural correlate of depressive symptoms in preschool children[46]. Overall, these results suggest that SBM is an important method for investigating structural brain changes in depression. However, studies applying SBM to adolescent depression remain relatively limited. Further research is needed to confirm these findings and to explore the relationship between structural brain alterations and the pathophysiological mechanisms of depression.

3.3 DTI in Adolescent Depression

Diffusion tensor imaging (DTI) is a technique commonly used to investigate the structure of brain white matter. As an emerging neuroimaging method, DTI primarily reconstructs the trajectories of white matter fiber tracts by measuring the diffusion of water molecules within tissues, thereby enabling the assessment of microstructural changes in white matter[47]. The most widely used evaluation index is fractional anisotropy (fractional anisotropy, FA). Higher FA values indicate a more consistent orientation of white matter fibers, whereas lower FA values suggest microstructural damage to neural fibers[47]. A lifespan study of white matter development reported that FA values generally increase while mean diffusivity decreases during childhood, adolescence, and early adulthood[48]. Meta-analyses of DTI studies have shown that adolescents with depression exhibit significantly reduced FA values in several brain regions[49,50]. Similar findings have also been reported in studies of adults with first-episode, untreated depression[51]. Jiang et al.[52] found that young patients with first-episode, drug-naïve depression had lower FA values in the body and genu of the corpus callosum, the left superior and posterior corona radiata, and the bilateral anterior corona radiata compared with healthy controls. However, a prospective study by Lee et al.[46] involving adolescents with first-episode, untreated major depressive disorder reported significantly higher FA values in the body and genu of the corpus callosum and the right anterior corona radiata compared with healthy controls. Another study examining white matter structure in adolescents with depression found reduced FA values in the cingulum bundle, uncinate fasciculus, and superior longitudinal fasciculus. Moreover, reduced FA in the cingulum bundle was associated with lifetime diagnosis of depression and the severity of depressive symptoms[53]. In summary, although current findings are not entirely consistent, they generally support the hypothesis that early-stage depression is associated with white matter abnormalities. These results suggest that individuals at high risk for depression may already exhibit microstructural alterations in specific white matter regions during adolescence. Such findings further emphasize the neurobiological basis of depression and contribute to a better understanding of the early development of the disorder.

4. Conclusion and Future Perspectives

Neuroimaging research on adolescent depression has made significant progress in recent years. Through techniques such as resting-state fMRI and task-based fMRI, researchers have revealed differences in brain activity between patients with depression and healthy controls. These findings indicate abnormalities in the neural mechanisms underlying emotional processing, cognitive control, and emotion regulation in individuals with depression. In terms of magnetic resonance spectroscopy, adolescents with depression show alterations in the concentrations of metabolites in different brain regions, including choline, creatine, and glutamate. These changes may reflect metabolic disturbances or pathophysiological processes in specific brain regions. However, further research is still required to clarify the consistency of findings across studies and to better interpret these results. Arterial spin labeling techniques provide images of cerebral blood flow and have revealed abnormalities in blood flow in multiple brain regions in patients with depression. These abnormalities involve functional regions such as the cortico-striatal-thalamic circuit as well as networks related to executive, emotional, and motor functions. Studies using arterial spin labeling have also shown that the risk of depression may be associated with changes in amygdala blood flow. Structural magnetic resonance imaging has also played an important role in the study of adolescent depression. Using analytical methods such as VBM, SBM, and DTI, researchers have identified structural alterations including reduced gray matter volume, decreased cortical thickness, and microstructural changes in white matter in adolescents with depression. Despite these important findings, neuroimaging research on adolescent depression still faces several challenges and areas that require further investigation. First, many studies have relatively small sample sizes, and larger-scale studies are needed

to validate and replicate existing findings. Adolescence is a critical stage of brain development, and longitudinal studies could help track changes in brain structure over time and examine their associations with disease progression and treatment outcomes. Second, longitudinal research is crucial for understanding the development and course of depression, requiring continuous monitoring of neuroimaging changes in adolescents with depression and linking these changes to clinical symptoms and disease progression. In addition, the application of multimodal neuroimaging techniques will help provide a more comprehensive understanding of the complex neural mechanisms underlying depression, for example through the combined analysis of structural MRI, functional MRI, and electroencephalography. Furthermore, integrating neuroimaging findings with other biological and psychological indicators, such as genomics, biomarkers, and cognitive tasks, may provide deeper insights into depression. Neuroimaging research on adolescent depression has revealed important aspects of the neural basis of this disorder and has provided new clues for diagnosis and treatment. Future studies will continue to explore the neural mechanisms of depression and contribute to the development of personalized diagnostic and therapeutic strategies.

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Author Bio

Xueyou Feng designed the overall direction and framework of this review and revised important content of the manuscript. Xueyou Feng drafted and wrote the manuscript and was responsible for obtaining, analyzing, and interpreting the data/literature used in this study. Hui Wang, Zhenyang Gao, and Yuchen Zhong obtained, analyzed, or interpreted the data/literature and revised important content of the manuscript. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work, ensuring the accuracy and integrity of the study.