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•Review•

Neuroimaging studies of depressive disorders in China since 2000

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Summary: This paper reviews neuroimaging studies of depressive disorders conducted in Chinese populations since 2000. Both cross-sectional and longitudinal studies using structural and functional imaging techniques have compared different types of depressed individuals, with and without specific genotypes, and the characteristics of depressed individuals before and after treatment with antidepressants. Many of the findings are unstable – probably because most of the studies are underpowered – but there have been some important contributions to the international literature. Future studies in China need to use standardized methods, longitudinal designs, and joint application of both structural and functional MRI.

Key words: neuroimaging, structural imaging, functional imaging, depressive disorder, China, review

1. Introduction

Depressive disorders are highly prevalent, frequently recurrent, and associated with increased risk of death by suicide. The estimated lifetime occurrence of depressive disorder is between 10 and 20% and the estimated suicide rate among individuals with depression varies from 15 to 20%.[1] It is associated with a substantial decrease in social functioning that both diminishes the quality of life of the individual and results in serious economic consequences for the community. A recent large-scale epidemiological survey in China found a current prevalence of 6.1% for depressive disorder, which translates into 26 million individuals.[2] Effectively preventing and managing depression requires a detailed understanding of the etiological mechanisms that increase the risk of depression and that sustain the condition after it has started.

One relatively recent method of researching the onset and course of depression is via neuroimaging techniques. There has been an explosion of this type of research in China in the last two decades as the new technology has become increasingly available. The current review summarizes this work. We searched scientific literature databases in English (PubMed, Medline, Elsevier, Springer, and Wiley-Blackwell) and in Chinese (China Biology Medicine disc, Chongqing VIP database for Chinese Technical Periodicals, Chinese National Knowledge Infrastructure and WANFANG) using the terms 'depressive disorder AND neuroimaging AND Chinese' and found 53 studies published after 2000 with subjects of Han Chinese ethnicity (the majority of which were conducted at institutions in mainland China).

2. Structural imaging studies

Structural imaging studies of depressive disorders focus on structural changes of the neural circuits controlling emotions, primarily the thalamus-limbic system circuit in the frontal lobe. Many such studies in China report decreased volume or decreased density of the prefrontal cortex and the orbitofrontal cortex inindividuals with major depressive disorder (MDD)[3,4] and increased volume of the inner prefrontal white matter (a change that has been associated with cognitive decline).[5] Bai and colleagues[6] were the first to document anomalous prefrontal white matter connections in both geriatric depression and mild cognitive impairment. However, there have been many conflicting reports about

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structural changes in other brain regions. Some studies[7] report increased volume of grey matter in the cingulated gyrus in depression while other studies[3] report decreased density. Most studies on the hippocampus[8] find decreased volume in depressed individuals but one study[9] failed to identify any volume difference. Some studies on structural changes in the amygdala with depression report increased volume[10,11] or increased density of gray matter,[3] while other studies report decreased volume.[12,13]

3. Functional imaging studies

In China, resting-state functional magnetic resonance imaging (fMRI) and, to a lesser extent, event-related fMRI have been widely used to identify functional changes in different regions of the brain.[14]Most event-related fMRI studies in China with depressed patients assess their cognitive deficits when performing different types of memory tests. Deficiencies of verbal working memory were associated with changes in the phonological loop;[15] decreased spatial working memory was related to dysfunctions in bilateral BA9/46, BA6 and BA7/40 brain regions;[16] and deficits in autobiographical memory tasks were associated with decreased activation in the left middle temporal gyrus (BA 21), putamen, right fusiform gyrus (BA 37) and cuneus (BA 18) and with over-activation in the right superior parietal lobule (BA 7).[17]Another study that compared event-related fMRI results in depressed and normal subjects found that the activity of the brain regions related to emotional regulation was not significantly different when processing positive emotions but it was significantly decreased in depressed subjects when processing negative emotions.[18]

Most resting-state fMRI studies in China involve the analysis of functional connectivity (FC) in different regions of interest (ROIs), including the prefrontal cortex, limbic system (mainly the hippocampus and amygdala), default mode network (DMN), thalamus and cerebellum. The main changes reported among depressed individuals[19,20] are attenuated FC between the hippocampus and other brain regions including the prefrontal cortex, anterior cingulum (in DMN), insula, parahippocampal gyrus, inferior parietal cortex (in DMN), and cerebellum. Studies on the amygdala found weakened FC between the bilateral amygdalas[21] and between the amygdale and the ventral prefrontal cortex and dorsolateral prefrontal cortex;[22] however a study of late-onset depression (LOD) reported increased FC between the amygdala and the right post-central gyrus.[23] A study focusing on the DMN showed decreased FC between the medial prefrontal cortex and the anterior and posterior cingulated cortex and the precuneus; it also showed decreased FC between the posterior cingulated cortex and the precuneus.[24] Peng and colleagues[25] found increased FC between the pregenual anterior cingulated cortex (ACC) and the parahippocampal gyrus, parietal lobe and frontal lobe. Another study using independent component analysis in depressed patients[26] found increased FC in the anterior medial cortex region (associated with rumination) and decreased FC in the posterior medial cortex region (associated with excessive autobiographical memory).

Combining structural MRI and fMRI, Ye and colleagues[27] were the first to document decreased density of the right dorsolateral prefrontal grey matter among patients with depression; they also observed decreased FC between the right dorsolateral prefrontal cortex and right parietal lobe and increased FC between the right dorsolateral prefrontal cortex and the left dorsal cingulate cortex, left parahippocampal gyrus, thalamus and precentral gyrus. Research using the thalamus as the seed region found increased FC between the thalamus and the DMN region among patients with major depressive disorder.[25] Studies focused on the cerebellum found decreased FC between the cerebellum and the DMN (medial prefrontal cortex and cingulated cortex), decreased FC between the cerebellum and the executive control network (mainly the dorsolateral prefrontal cortex), and increased FC between the cerebellum and the temporal lobe.[28,29] Studies applying other methods also observed abnormal FC in the prefrontal cortex, DMN and limbic system in individuals with major depressive disorder.[30-33]

Studies on regional homogeneity have consistently found decreased homogeneity in the left dorsolateral prefrontal cortex, thalamus, temporal lobe, occipital lobe and right DMN region[23,34-36] and increased homogeneity in the cerebellum and basal ganglia region.[34,36] One study[37] reported lower homogeneity in the left thalamus, left temporal lobe, left cerebellar posterior lobe and the bilateral occipital lobe. Research on the amplitude of low frequency fluctuation among depressed patients (ALFF) found increased amplitude in the cerebellum and right dorsal frontal lobe[38-40] and decreased amplitudein the DMN region.[38] Another study of depressed adolescents reported increased amplitude of low frequency fluctuation in the frontal cortex compared to that in the subcortical system.[41]

4. Imaging studies on antidepressant treatment

Chinese researchers have conducted both cross-sectional and longitudinal imaging studies on the effects of antidepressant medications in patients with depression. The cross-sectional studies mainly focus on the structural and functional brain differences between depressed individuals who are treatment-resistant (TRD) versus those who are treatment-sensitive (TSD). For example, a study using resting-state functional connectivity MRI found that patients with TRD showed reduced FC in bilateral prefrontal areas and the thalamus areas, while patients with TSD showed reduced FC in bilateral hippocampus, amygdale and insula.[42] Using similar methods, another study focused on the cerebellum as the region of interest found that, compared to healthy controls, patients with TRD or TSD had decreased cerebellar-cerebral FC in the prefrontal cortex and the DMN; the difference in the prefrontal

cortex was more pronounced in patients with TSD while that in the DMN was more pronounced in patients with TRD.[43] Using structural MRI to compare healthy controls and patients with TRD and TSD, researchers have reported decreased gray matter volume in the right middle temporal cortex among patients with TRD or TSD and reduced gray matter volume in the bilateral caudate among patients with TRD.[44]

Longitudinal imaging studies by Chinese investigators have reported that the pre-treatment heightened activity in the anterior cingulate cortex of depressed patients when experiencing sadness disappears with antidepressant treatment.[45] Another study with DMN as the region of interest found increased FC in both the anterior subnetwork and posterior subnetwork in patients with depression prior to treatment; after antidepressant treatment the abnormalities in the posterior subnetwork disappeared whereas the ones in the anterior subnetwork persisted.[46] A structural MRI study found that patients with first-episode depression had reduced bilateral hippocampal volume before treatment and that increased significantly after treatment.[47] Mild increase in the right hippocampal volume has also been reported in patients with geriatric depression after treatment, and this increase was associated with improvement in cognitive functioning.[48] However, the high regional homogeneity of the hippocampus of patients with depression has not been found to be responsive to antidepressant treatment.[49]

5. Genetic imaging studies

Imaging genetics refers to the application of neuroimaging techniques to the measurement of brain activities across populations with different genotypes.[50] Studying geriatric patients who had recovered from depression, Yuan and colleagues[51] found that compared to non-carriers, those who were carriers of the epsilon4 (ε4) allele of the apolipoprotein E (ApoE) gene had reduced grey matter volume in the frontal gyrus and the inferior occipital gyrus. A study among elderly persons who had recovered from depression by Wu and colleagues[52] found decreased FC in the posterior cingulated cortex and temporal lobe when performing episodic memory tasks (compared to the resting-state FC) that was more pronounced among ε4 allele carriers – supporting hypotheses about the role of ApoE ε4 in brain functions related to episodic memories. Another study[53] investigating the association between angiotensin-converting enzyme (ACE) insertion/deletion polymorphisms and cognitive functioning among patients with LOD found that, compared to the I-allele, the D-allele was associated with significantly smaller volumes of white matter in the superior frontal gyrus and anterior cingulated gyrus,and with significantly larger volumes in the middle temporal gyrus and middle occipital gyrus. Moreover this study found a correlation between decline of cognitive functioning and the changes in the white matter volume in the middle temporal gyrus and the anterior cingulated gyrus. Following this line of research, Wang and colleagues[54] found associations between the ACE insertion/deletion genotypes and the FC of the posterior cingulated cortex and the temporal gyrus in patients with LOD. In addition, Chen and colleagues[55] explored the association between D-amino acid oxidase activator (DAOA) gene and brain regional homogeneity among patients with major depressive disorder. A gene by depression status interaction was found for the regional homogeneity of the cerebellum and the temporal gyrus; this suggests that the DAOA gene moderates the association between depression and the homogeneity of these brain areas.

6. Summary and future directions

The current review summarizes neuroimaging studies conducted by Chinese researchers since 2000. These studies assessed the structural and functional changes in the brain among individuals with depression, as evaluated by the effect of antidepressants on these changes. The findings are generally similar to those observed in Western populations but there have been a few unique findings, which need to be confirmed in further studies with larger samples. (a) The decreased volumes in the prefrontal cortex, orbital frontal cortex, and the hippocampus observed in depressed patients are more obvious among females.[5,8] (b) The increased volume of the medial prefrontal cortex among individuals with depression is associated with cognitive decline.[4] (c) Previous studies in the West have documented decreased volume of the ACC in depression; however, *increased* volume was reported in elderly individuals with depression in China.[7] (d) Studies from Western countries report that abnormalities in the functioning of the cerebellum are an indicator of relapse[56] while studies in China report that decreased connectivity in the DMN is associated with treatment-resistant depression,[43,46] which suggests that the dysfunctions in the DMN is more important in the relapse of depression relapse.

Neuroimaging techniques have been used in China to explore the underlying mechanisms of depressive disorders, but a number of limitations in these studies have resulted in frequent reports of contradictory results. There has been no standard protocol for conducting neuroimaging studies, and most studies are cross-sectional studies with small sample sizes. Depression is an umbrella term for several etiologically heterogeneous conditions that may have different underlying mechanisms. Most imaging studies in China focus on selected brain areas without assessing all the inter-related neuropathways in the network of interest. The many types of antidepressants used in the drug studies using imaging techniques affect brain activity via different mechanisms. Genetic imaging studies have been limited to single-gene studies at a few loci; some important genes (e.g., 5-hydroxytryptamine transporter length polymorphism [5-HTTLPR] or brain-

derived neurotrophic factor [BDNF] gene [57]) have not been studied and gene-gene or gene-environment interactions have not been assessed.

Resolving these limitations in current neuroimaging studies of depression in China will require a re-focusing of the research effort. It would be better to have fewer studies with larger samples than many studies with small samples. There should be fewer cross-sectional studies and more longitudinal studies, allowing for assessment of the temporal relationships between episodes of depression and changes in the structure and functioning of the brain. More studies should integrate structural and functional assessments of brain regions of interest, increasing the ability of the studies to identify biological markers that help confirm the diagnosis, that identify individuals who will be treatment resistant or treatment sensitive, or that are associated with high rates of relapse. Finally, to increase the ability to compare and combine the results of the various studies, there needs to be standardization of the methods employed in the studies.

Conflict of interest

The authors report no conflict of interest related to this manuscript.

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中国 2000 年以来抑郁症的神经影像学研究

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概述：本文回顾了自 2000 年以来在中国人群中有关抑郁症的神经影像学研究。利用结构成像和功能成像技术的横断面研究和纵向研究比较了不同类型的抑郁症患者、有无特定基因型的抑郁症患者、和抗抑郁药治疗前后抑郁症患者的特征。许多研究结果不稳定 -- 可能是因为大部分的研究的检验效能较低 -- 但对国际文献仍做出了重要的贡献。中国未来的研究需要使用标准化的方法、纵向设计、以及结构和功能性磁共振成像的联合应用。

关键词：神经影像学，结构成像，功能成像，抑郁症，中国，综述

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