

Research progress in the brain area responsible for depression

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Abstract. Depression is one of the main types of affective disorders, which is extremely harmful to the physical and mental health of patients. The typical clinical symptoms of depression include decreased volitional activity, retardation of thinking, low spirits, and cognitive impairment. The pathogenesis of depression is very complex, including multiple factors such as biological, psychological and environmental factors. Researchers at home and abroad have carried out research on depression in many fields. In neuroscience, it has been concluded that the dysfunction of the frontal lobe, hippocampus, temporal lobe, striatum, amygdala and other brain of patients with depression can contribute to depression. Besides, the abnormal connections between these brain regions may also result in depression. Herein, we mainly introduced the current research of the above-mentioned responsible brain regions and related neural circuits for depression, and further summarized the current knowledge about the diagnosis and treatment of depression. Finally, we briefly discussed the feasibility of using rodents as animal models to explore depression.

Keywords: Depression, Brain Area, Neural Circuit.

1. Introduction

Based on previous statistics from the World Health Organization, depression has now become the fourth-highest burden of disease in the world. Low spirits, cognitive impairment, retardation of thinking, and decreased volitional activity are typical clinical symptoms of patients with depression. Besides, the number of patients with depression [1] has increased over the past decade. More than 300 million people worldwide experience depression at this time. Noticeably, this chronic mental disease has doubled the suicide rate in the population. Therefore, the exploration of the pathogenesis of depression is important for subsequent clinical diagnosis and treatment. With the advancement of neuroimaging in recent years, more imaging methods are now being used to study depression, and the mysteries of many depression-related brain regions have been gradually unmasked. Magnetic Resonance Imaging (MRI) technology has been widely employed in the field of neural science [2]. For example, diffusion tensor imaging (DTI), which is commonly used by researchers, describes the microstructure of white matter, and has now been used to assist the diagnosis of Vascular Depression (VD) [3]; functional Magnetic Resonance Imaging (fMRI) can be used to analyze neuronal dynamics describing brain regions. Besides, a high-resolution structural imaging (3D-T1) technique has been developed to observe volumetric and morphological gray matter thickness. Research has indicated that the frontal lobe, hippocampus, temporal lobe, striatum, amygdala [4] and related projection circuits in depression patients are significantly different from those of normal people, which provides important evidence for identifying these brain regions and connections as the pathogenetic clues of depression. Some scholars have proposed to explain the pathogenesis of depression from the direction of the brain network model of depression. However, the research on depression relies on long-term follow-up and treatment of patients with many limitations. In this review, we also discussed the rationality of more experiments to explore depression in animal models in the future.

2. Depression-related brain regions

2.1. Prefrontal cortex

Prefrontal-cortex is one of the depression-related brain regions. According to earlier research, patients with depression have a different volume of the frontal lobe than healthy individuals. A portion of the anterior cingulate cortex, the orbitofrontal cortex, the middle prefrontal cortex, the dorsolateral prefrontal cortex (DLPFC), and other regions are all affected by prefrontal cortex (PFC) lesions [5, 6, 7, and 9]. It is well known that the anterior cingulate cortex (ACC), the dorsal neocortex, and the ventral paralimbic region are all connected anatomically. However, their connection is not limited to anatomy, which plays an important role in emotion regulation [10]. Recent secondary measurements have also revealed evidence for some structural alterations in the prefrontal cortex associated with depression. A recent positron emission tomography study found reduced PFC synapse numbers and reported reduced levels of synaptic vesicle glycoprotein 2A (SV2A) ligand binding in patients with depression [11]. SV2A, a protein found in presynaptic vesicles, was found to be reduced in the brains of those who had serious depression, and this reduction was connected to altered PFC connection, according to this phenomenon. In post-mortem studies of depressed patients [12], additionally, direct proof of synapse loss has been discovered., including reductions in synaptic markers and synapse numbers in the PFC. Some researchers did a review from the perspective of the asymmetry of the left and right cerebral hemispheres in patients with depression [13]. They used data from behavioral, EEG, neuroimaging studies and event-related potentials as evidence to assume decreased activity and function of the left frontal lobe of patients with depression and bring fresh insight into the neural network underlying this laterality change. As an illustration, patients with depression who also have anxiety problems are more likely to have left frontal brain activity that is lower than right frontal lobe activity. The relevance of this left-right asymmetry to assessing the risk of developing depression, diagnostic subtypes, and clinical response to medication and further research on cognitive-behavioral treatment is required.

2.2. Hippocampus

Hippocampus is also crucial for the research of depression. The hippocampus, which is a component of the limbic system, is engaged in memory and reward circuits and is crucial for the development of emotionally charged long-term memories. In an earlier study, some researchers found that the structural imaging of the hippocampal volume in Major Depressive Disorder (MDD) patients was significantly opposed to what was shown in the control group, and the hippocampal volume in the patient group was considerably reduced. Across groups, age was inversely correlated with uncorrected hippocampal volume, hippocampal volume was negatively correlated with disease duration, and a trend toward increased hippocampal volume was observed in those patients whose cortisol levels subsequently declined under medication [14]. In the following year, other researchers also reported the result that the hippocampus of patients with depression was reduced in volume compared with normal people [15]. In recent years, some studies have further conducted controlled experiments and concluded that the correlation between Tardive Depression and hippocampal volume was stronger than that of early-onset depression, and the smaller hippocampus volume is associated with higher levels of cortisol [16]. Besides, stress-related FKBP5 was related to hippocampal characteristics [17]. After analyzing a sample of a certain number of identical twins, it was concluded that the right hippocampus of patients with depression has decreased connection strength and increased network centrality, thereby revealing the manner in which the hippocampus communicates with the rest of the brain in those who are depressed.

2.3. Temporal lobe

The temporal lobe, which is also responsible for processing sensory input like auditory information, language understanding, and naming, is intricately tied to memory functions, including the preservation of short-term and long-term memory. Moreover, the temporal lobe triggers emotional

reactions and regulates biological urges like aggression and sexuality. In 2014, some researchers applied the method of calculating fractional amplitude of low frequency fluctuation (fALFF) to study the changes of spontaneous neural activity in MDD. In order to measure the fALFF, they used a group of MDD patients and another group of healthy people as control group to perform fMRI scans at rest. In the left middle temporal gyrus, right angular gyrus, left superior temporal gyrus, right putamen, right precuneus, and right superior temporal gyrus, patients with MDD showed decreased fALFF [18].

2.4. Striatum

A crucial component of the basal ganglia is the striatum, which receives projections from the entire cerebral cortex [19]. Based on existing neuroimaging studies, there are significant changes in the striatum in patients with depression. FMRI showed a reduction in striatal activity in the deficits of the reward system. [20]. It was later found that the severity of the depression was related to a decrease in reward network connectivity [21], revealing a brain profile related with depression severity in bipolar and unipolar depression is lower reward system activation and resting-state connectivity. Therefore, decreased striatal activity in patients with depression can be expected to be one of the biomarkers for predicting the severity of depression.

2.5. Amygdala

The amygdala is a little almond-shaped structure that resides in the left and right temporal lobes of the brain. The amygdala, often known as the brain's emotional center, is involved in determining how emotionally charged a situation is (e.g., happiness, sadness, fear). In addition to emotion, the amygdala has long been linked to motivation and plays a crucial part in the neural mechanisms that process fear and reward. The amygdala includes the basolateral complex (Basolateral Amygdala, BLA: composed of lateral cells (Lateral Amygdala, LA), basal cells (Basal Amygdala, BA) and basomedial cells (BM)) and the central nucleus of the amygdala. Three distinct complexes of basolateral amygdala (BLA) neurons project to the PFC, the ventral prefrontal cortex (vHPC), or the nucleus accumbens (NAc). Depending on the varying projection strengths of these three brain regions, they are in charge of guiding responsive actions to both internal and external inputs [22].

3. Important circuits in the brain area responsible for depression

3.1. The prefrontal cortex-basolateral amygdala circuit

An increasing number of studies including fMRI images and the biological mechanisms of the above-mentioned brain regions suggest that there are many critical neural circuits changes in brain regions of patients with depression. An important role which is played by the medial prefrontal cortex-basolateral amygdala (mPFC-BLA) circuit in the production of emotions like depression, anxiety and fear. In earlier studies, researchers explored and determined how the mPFC affects the amygdala by analyzing functional imaging evidence of reduced mPFC activity in subjects with PTSD and data on mPFC-BLA interaction in conditioned fear extinction [23]. In recent years, researchers have tried to explore this circuit from different perspectives, including stereotaxic injection of retrograde tracers of different colors, etc. With the help of imaging technology and data analysis, it is concluded that the input of the prefrontal cortex to the BLA specifically drives three different projection neurons in the BLA, which is mainly determined by different synaptic connections generated on different cell types [22].

3.2. Prefrontal cortex-hippocampal circuit

According to a DTI study [24], the prefrontal hippocampal circuit originated from the fornix and output fibers, projected to the mammillary body and the anterior nucleus of the thalamus, and ultimately returned to the prefrontal lobe brain. The fornix, which includes the main fibers travelling through the hippocampus, has also been linked to a decrease in hippocampal volume, according to an

MRI study [25]. 2016 saw the collection of DTI and resting-state fMRI data from 26 teenagers with first-episode MDD and 31 healthy controls. The fractional anisotropy (FA) values of the functional connection between the fornix and the prefrontal hippocampus were calculated and compared between the two groups. They concluded that there were substantial differences between the two groups based on the correlation between the FA values of the fornix and the level of functional connectivity in the prefrontal cortex (PFC) region. Additionally, they demonstrated that the PFC-hippocampal neural pathways may be aberrant in the early stages of MDD, contributing significantly to the neuropathology of the disorder.

3.3. The dorsolateral-ventromedial prefrontal cortex circuit

A previous study found that the activity of the dorsolateral prefrontal cortex (dlPFC) in patients with depression was reduced, while the activity of the ventromedial prefrontal cortex (vmPFC) was increased [26] and confirmed that the roles of dlPFC and vmPFC are equally critical in the occurrence of depression, indicating that the roles of dlPFC and vmPFC are equally critical in the occurrence of depression. It was also speculated that these two brain regions and the connection between them may be important structures in the occurrence of depression, and the dlPFC-vmPFC circuit needs to be further studied. Nevertheless, in the early studies, the majority of researchers observed the activity of two brain regions from a static perspective without the assumption of activating or inhibiting the activity of one or several brain regions to observe the changes in activity in other brain regions in patients with depression. This study proposed that in order to observe the interaction more intuitively between dlPFC and vmPFC during cognitive-emotional processing in patients with depression, the activities of dlPFC and vmPFC could be adjusted. Therefore, in 2018 [27], the researcher team continued to study the dynamic interaction mechanism of the dorsolateral-ventromedial prefrontal cortex pathway, and they used the combination of event-related potential (ERP) and functional magnetic resonance (fMRI) to dynamically reflect the brain structure and functional characteristics of self-processing time course in patients with depression with intuitive results. This study suggested that the joint effects of dlPFC and vmPFC will lead to negative self-processing bias in patients with depression.

4. Existing diagnosis and treatment methods for depression

4.1. Spatiotemporal dynamic network coding predicting depressive behavior

Local field potential oscillations in the brain fluctuate because of sudden network-level signals that control behaviors. Fundamental understanding of how the neural communicates emotional diseases will come from deciphering the code by which these oscillations are coordinated in time and place (spatiotemporal dynamics) to express complex behaviors. In recent years, researchers have found that brain activity patterns predict susceptibility and resilience to depression in response to stress [28]. In mice experiencing persistent social frustration, they found a spatiotemporal dynamic network that predicted the formation of behavioral abnormalities associated with MDD. This network's activity pattern originated in the ventral striatum and prefrontal cortex, travelled through the amygdala and ventral tegmental area, and finally converged on the ventral hippocampus. Acute threats were added to this network, and three different MDD vulnerability models were improved. The study's conclusion showed that this susceptibility network was biologically separate from the network that codifies malfunction following stress. These results suggest a convergent neural mechanism mediating MDD susceptibility.

4.2. Existing treatments of depression and their limitations

Current treatments for depression that modify neural activity, including the use of electrical stimulation, are currently being researched to transiently manipulate neuronal activity without invasive techniques. Alternatively, an invasive treatment, deep brain stimulation (DBS), generates site-specific alteration of neural activity with the aid of implanted electrodes. Several of these treatments, which

often include numerous treatment cycles, seem to operate as a component of an antidepressant response via influencing prefrontal cortical circuits. However, after the use of DBS methods, the symptoms of depression can be relieved immediately. Notably, the PFC responds to the antidepressant ketamine, which appears to transiently increase PFC activity even in the setting of medication resistance, suggesting that the circuit produces a level effect immediately after administration [29]. Within hours, ketamine considerably reduced depressed symptoms, indicating that therapies with adequate PFC levels could quickly have antidepressant effects. Although the effectiveness of the aforementioned therapeutic strategies for the clinical treatment of depression has been established and is well recognized, these methods still have many drawbacks, such as a lack of cell and area specificity.

5. Application prospects of animal models

Whether the PFC of rodents is similar to that of primates, including humans, remains unclear. In recent years, for the exploration of depression, the identification of important lesions often depends on ongoing monitoring and cross-sectional comparison of treated patients and untreated patients, which has many limitations, including a small number of experimental samples and a long experimental period. Therefore, the use of animal experiments can help to solve the above limitations. The use of chronic unpredictable mild stimulation to prepare a depressed rat model, and behavioral analysis such as open field behavioral analysis to study the brain mechanism of depression or other neural mechanisms is drawing increasing attention, because its stimulation mechanism is similar to the etiology and symptoms of depression in patients. A growing number of experiments have also shown that the use of animal models to validate neuroimaging findings and apply their results to humans will contribute to better clinical applications of neuroimaging techniques.

6. Conclusions

In this review, we summarized research on the neural mechanism of depression, and the focus of this article is on the responsible brain regions and the circuits between them. Researchers have used neuroimaging techniques including fMRI to statically obtain the data on the significant changes in the responsible brain regions and circuits of the above-mentioned depression patients that are different from healthy people. However, the biomarkers that can represent depression remain unknown. Herein, we found that the neural mechanism of depression is relatively complex since there are many subtypes of depression, and the research on the comprehensive comparison of the subtle differences in their respective pathogenesis is not enough. Due to the direct use of patients as the experimental group, the identification of important lesions often depends on long-term monitoring and cross-sectional comparison with untreated patients (control group), which has many limitations such as fewer experimental samples and longer experimental periods. Therefore, the application of rodent models to study the brain mechanism of depression or other neural mechanisms will provide feasibility of more in-depth research in the future, including exploration on how the depression-responsible brain circuit is composed and the molecular mechanism, etc., thereby to find more effective methods for preventing, diagnosing and treating depression in the clinical field, to provide protection for the physical and mental health of all human beings.

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