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Review Article

# Cognitive Dysfunction: An Important Feature of Major Depressive Disorder

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**Abstract**

Depression is a common mental illness with high prevalence, disability, and suicide rates. Most patients experience recurrent attacks, which converts depression into a chronic disease.

**Keywords:** cognitive dysfunction; major depressive disorder; physical therapy; psychotherapy; hippocampus; exercise therapy

## Introduction:

Depression is a common mental illness with high prevalence, disability, and suicide rates. Most patients experience recurrent attacks, which converts depression into a chronic disease. Major depressive disorder (MDD) is a type of emotional dysfunction caused by genetic abnormalities or great changes in the patient's environment, which can manifest as a host of symptoms such as persistent and spontaneous depression with changes in cognitive function. According to worldwide statistics, 50% of suicides each year occur during episodes of depression, and patients with MDD are 20 times more likely to commit suicide than the general population. During MDD, patients display obvious changes, such as inattention and memory loss, which are mainly manifested as deficiencies in executive function, memory, learning, language processing, and attention. Persistent symptoms seriously affect patients' social communication, family life, study, and work, as well as the prognosis of patients and the recovery of social function. However, the mechanisms underlying cognitive dysfunction remain unclear. Therefore, the etiological understanding and treatment of MDD are urgent problems to be solved, in which understanding cognitive dysfunction is an important goal for the diagnosis and treatment of patients with MDD. This review mainly expounds on the etiological and pathological changes and the treatment of cognitive function in major depressive disorder.

### Etiology of major depressive disorder

MDD is characterized by one or more severe depressive episodes with significant changes in emotional, cognitive, and autonomic functions; significant weight loss or gain; fatigue; feeling worthless or guilty; inability to concentrate; and/or recurrent suicidal thoughts lasting for at least two [Error! Reference source not found.,1]. The incidence of MDD in women is twice as high as that in men, with one in six adults suffering from the disease. The pathogenesis of MDD has not been fully elucidated because it involves the interaction between complex genetic and environmental factors; hence, its etiological mechanism has been the focus of much research.

### The main causes of MDD are as follows (Figure.1)

1)Personality traits: The negative components of personality, such as inferiority, remorse, and pessimism, can easily manifest in MDD; however, the risk of MDD can be reduced through daily psychological adjustment.

Once such a patient is diagnosed with MDD, the treatment time is prolonged, and most patients need pharmacological treatment combined with psychotherapy to completely eliminate the symptoms [1,4].

2)Genetic factors: MDD has obvious hereditary features. If someone in the family suffers from MDD, especially immediate family members, the likelihood of a person developing MDD will increase. Children whose parents have MDD have a 35–37% chance of developing depression. In addition, a genetic crossover between MDD and other mental disorders (such as schizophrenia and bipolar disorder) has been identified [1,5,6].

3)Disease factors: Studies have shown that MDD is closely associated with diabetes, heart disease, cancer, Alzheimer's disease, and stroke. If underlying conditions are present, the incidence of MDD increases. For example, about one in five patients with cardiovascular disease have MDD, and MDD is a risk factor for the incidence, severity, and poor prognosis of cardiovascular disease [7,8,9,10].

4)Environmental factors and adverse stimuli: When environmental stress is too high or patients experience adverse stimulation, the incidence of MDD increases [11,12]. MDD-related stress events usually occur one year before the onset of the disease, including unemployment, economic stress, chronic or life- threatening health problems, violence, separation, and bereavement, which often occur in adulthood [13,14]. However, Dannehl et al. found that children who experienced physical and sexual abuse, psychological injury, domestic violence, or premature separation from their parents were more likely to develop MDD later in life. The number and severity of adverse life events were positively correlated with the risk, severity, and chronic duration of MDD [14,15]. In most cases, the etiology of MDD is not singular, and different causes may exist simultaneously, augmenting each other's effect on MDD occurrence and development. MDD will, in turn, affect its etiology. For example, patients with MDD are generally less able to withstand stress and are more likely to suffer from certain diseases than healthy people, and MDD also impedes the treatment of other diseases, such as depression associated with Alzheimer's disease [16,17].

**Cognitive Dysfunction and pathological changes in MDD**

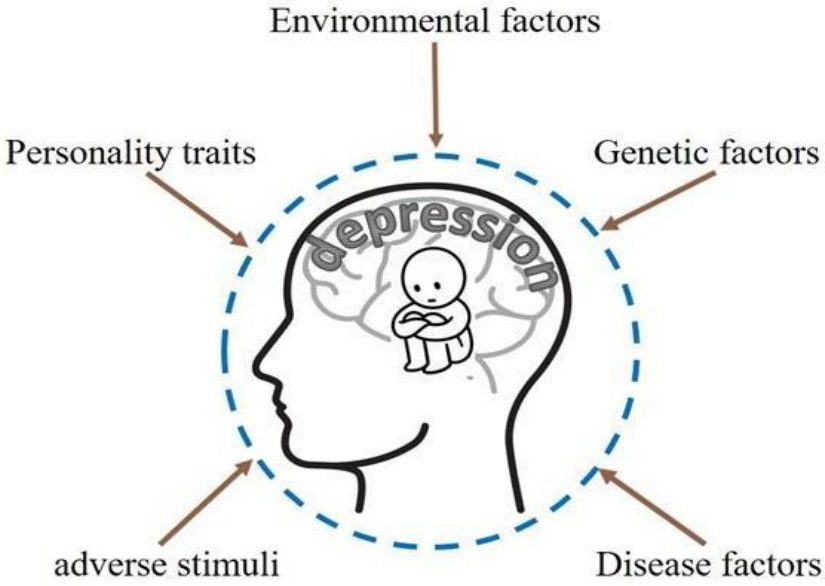


**Figure 1:** Pathogenesis of major depressive disorder

Studies have shown that patients with depression have defects in the following cognitive areas: executive function and attention transfer, memory, visual-spatial processing, and psychomotor function [18,19,20]. At present, cognitive dysfunction in depression is a primary focus of MDD research and is a potential predictor of occupational and social adaptation disorders in adult MDD patients. After the psychological symptoms of MDD are relieved, cognitive dysfunction persists and needs to be treated separately from emotional symptoms [21,22,23]. It is worth noting that patients' cognitive deficits may affect their professional and social communication abilities and lead to suicidal ideation. Additionally, the persistence of cognitive dysfunction may interact with existing depression and increase the risk of recurrence [24,25].

The brain is a complex neural network with interconnections between brain regions. Studies have found that some neural network functions change during depression, including those of the prefrontal cortex and cingulate gyrus, subcortical areas of the striatum and thalamus, and temporal cortex, including the amygdala and hippocampus [26]. Lesions in the prefrontal cortex will cause a decrease in executive function, and a decrease in hippocampal volume will lead to memory impairment, which may be the progressive result of MD

[25,26]. Therefore, restoring the function of these structures may become the basis for the treatment of depression. However, existing treatment methods are not effective for all cases, and it is necessary to further understand the relationship between cognitive dysfunction and neural markers of MDD. Therefore, research and treatment of cognitive dysfunction in MDD are very important.

Initially, depression was thought to be only a mental disorder; however, with an increase in research on depression, a number of studies have found that patients with MDD have organic lesions. The cross-sectional results of brain structural imaging showed that the main brain regions related to MDD pathogenesis were the frontal cortex, thalamus, striatum, hippocampus, and parietal cortex [27]. Magnetic resonance imaging studies found that the volume of many brain regions decreased during MDD; in particular, hippocampal volume reduction was consistently observed, but it is not clear whether hippocampal volume reduction is an early manifestation or a late phenomenon in the course of the disease [28]. The hippocampus is involved

in the memory, recall, and reward systems. There is evidence that when patients with MDD are stressed, the level of glucocorticoids in the hippocampus increases through the hypothalamus- pituitary-adrenal axis; glucocorticoids then bind to the glucocorticoid receptor in the hippocampus, resulting in hippocampal neuronal atrophy [29]. A study of antidepressant therapy and electroconvulsive therapy in patients with MDD showed that the decrease in hippocampal gray matter volume and hippocampal functional activity in patients with depression led to a decrease in negative emotion and cognitive ability, suggesting that the increase in hippocampal gray matter volume during therapy was related to the improvement of clinical symptoms[30,31,32,33].

The striatum is an important component of the basal ganglia. Neuroimaging studies have reported significant changes in the striatum of patients with MDD and decreased gray matter intensity in the ventral striatum of patients with MDD who committed suicide Major depressive disorder (MDD) causes great decrements in

health and quality of life with increments in healthcare costs, but the causes and pathogenesis of depression remain largely unknown, which greatly prevent its early detection and effective treatment. With the advancement of neuroimaging approaches, numerous functional and structural alterations in the brain have been detected in MDD and more recently attempts have been made to apply these findings to clinical practice. In this review, we provide an updated summary of the progress in the translational application of psycho-radiological findings in MDD with a specified focus on potential clinical usage. The foreseeable clinical applications for different MRI modalities were introduced according to their role in disorder classification, subtyping, and prediction. While evidence of cerebral structural and functional changes associated with MDD classification and subtyping was heterogeneous and/or sparse, the ACC and hippocampus have been consistently suggested to be important biomarkers in predicting treatment selection and treatment response. These findings underlined the potential utility of brain biomarkers for clinical practice. The interruption of striatal output is speculated to lead to impulsive suicidal behavior. Functional magnetic resonance imaging showed a decrease in striatal activity in the reward system, and the decrease in reward network connections was related to the severity of depression. These findings suggest that abnormal striatal activity plays an important role in the disease progression [34,35]. The literature shows that compared with healthy adults, the volume of the bilateral putamen, caudate nucleus, right amygdala, and left thalamus in MDD patients is significantly reduced [36,37,38,39]. The putamen plays a key role in emotion, cognitive processes, motivation, and motor regulation, whereas the dysfunction of the caudate nucleus may lead to the interruption of dopaminergic signals and reduce the afferent impulses of ventral tegmental dopaminergic neurons [39,40,41].

The pathological changes in different brain regions of patients with MDD may correspond to the symptoms; however, these alterations are difficult to use as the basis for treatment. At present, research on the role of each

brain region in MDD is incomplete, and it is difficult to treatone brain region alone.

Treatment of MDD

Many hypotheses have been proposed for the treatmentof MDD, including the stress-induced inflammatoryfactors hypothesis, hypothalamus-pituitary-adrenocortical axis hypertrophy hypothesis, and metabolic abnormality-induced changes in neurotransmitters and neurotrophic factors hypothesis, among others. Changes that can lead to an increase in inflammatory factors in the neural system are an imbalance between the synthesis and release of neurotransmitters, a decrease in the secretion of brain- derived nerve growth factor (BDNF), a decrease in the protective effect on nerve cells, and the loss of cortical and hippocampal neurons. These circumstances lead to a decline in hippocampal function and cognitive dysfunction. However, the detailed mechanism has not been fully clarified, and the corresponding treatment has not been developed. Currently, the main treatment methods for cognitive function are drug therapy, physiotherapy, psychotherapy, and exercise therapy **(Figure.2).**

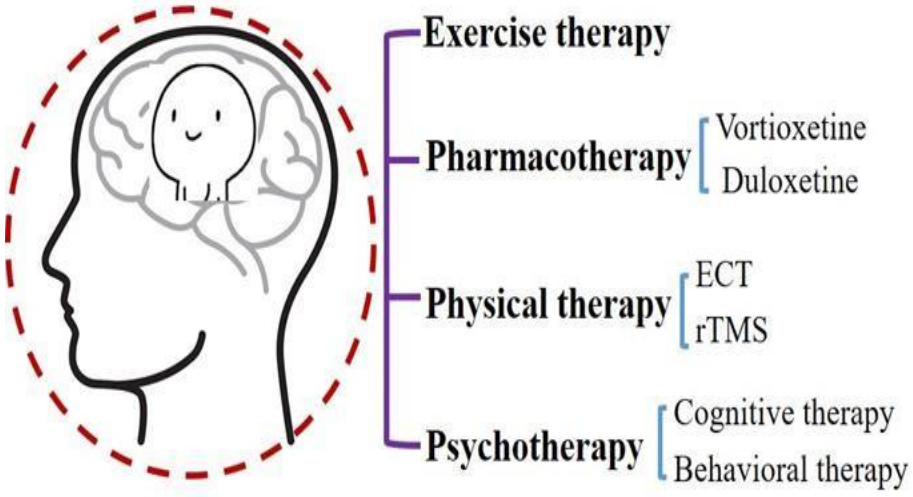


**Figure 2:** The main treatment of major depressive disorder

**Pharmacotherapy for MDD**

Many MDD patients have improved moods after antidepressant treatment, but the improvement in cognitive function is not necessarily consistent. It has been proven that persistent cognitive dysfunction after the remission of depressive symptoms is the reason whypatients cannot fully recover, and vice versa; dysfunctioncan also lead to the persistence of cognitive symptoms inMDD. To date, two antidepressants, vortioxetine, and

duloxetine, have been shown to cause direct,independent, and clinically related changes in cognitive dysfunction in patients with MDD [42,43]. Vortioxetine seems to have the greatest effect on psychomotor speed, executive control, and cognitive control, whereas duloxetine has the greatest effect on delayed recall [23,44,45].

Among the antidepressants, vortioxetine is the most widely studied [44.45,46]. It is an effective and well-tolerated antidepressant that inhibits serotonin (5-HT or 5-hydroxytryptamine) transporters and regulates a variety of 5-HT receptors [48,49]. Antidepressants administered through multiple pathways affect multiple neurotransmitter systems, including serotonin, norepinephrine, dopamine, gamma-aminobutyric acid, glutamic acid, histamine, and the cholinergic system [50,51,52]. Previous clinical studies have shown that vortioxetine is an antagonist of 5-HT1D, 5-HT3, and 5- HT7 receptors and an inhibitor of some, but not all, 5- HT1A and 5-HT1B receptor agonists and 5-HT transporters [1]. The inhibition of the serotonin transporter 5-HTT and the activation of 5-HT1A receptors induces a rapid and powerful antidepressant response, and theaction of 5-HT3 receptors can increase the release of norepinephrine and acetylcholine in the forebrain and improve cognitive dysfunction in MDD [53]. Vortioxetine can increase extracellular 5-HT levels and induce adult hippocampal neurogenesis, which is a candidate mechanism for mediating antidepressant responses in rodents [54]. Acute administration of vortioxetine canreverse the memory impairment caused by a 5-HT loss inrats in a dose-dependent manner, and long-term treatment can reverse the memory impairment caused bya 5-HT loss in rats. Recent studies have shown that acute and subchronic intermittent administration of vortioxetinecan improve the reversal of learning disorder induced by4-chloro-DL-phenylalanine methyl ester hydrochloride, used to reduce serotonin in rats [545556]. In addition, the long-term use of vortioxetine can revert the reversal of learning impairment caused by chronic intermittent cold stress in normal animals. Therefore, based on the available data, vortioxetine is a useful treatment option for patients with MDD and significant cognitive dysfunction.

**Physical Therapy for MDD**

Physiotherapy for MDD mainly includes electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS). ECT is an effective and safe treatment with proven success in the treatment of MDD [57]. However, the exact underlying mechanism remains unclear. Its antidepressant effect on changing the level of neurotransmitters, improving neuroplasticity, and increasing functional connectivity is related to BDNF levels [58]. ECT is usually recommended as a second- line treatment for depression because of its potential side effects such as transient memory impairment, disturbance of consciousness, headache, and nausea [59,60].

rTMS was approved by the United States Food and Drug Administration in 2008 for the treatment of major depression. It has been increasingly used clinically worldwide [61]. Experiments have shown that cranial magnetic stimulation can change the excitability of the stimulated areas of the brain, which lasts longer than the stimulation itself. From a therapeutic perspective, this feature of rTMS is particularly beneficial. Depending on the frequency of stimulation, the activity of the cortex becomes excitatory or inhibitory. When repetitive pulses stimulate the primary motor cortex, low-frequency stimulation (1 Hz) usually causes neuronal inhibition, whereas high-frequency stimulation (10–20 Hz) induces neuronal excitability [62,63]. The main target of rTMS in the treatment of mental disorders is the dorsolateral prefrontal cortex (DLPFC). Studies have shown that stimulation of the DLPFC by rTMS is a safe and effective alternative treatment for intractable depression [64,65]. The basic principle of MDD targeting the DLPFC is based on functional neuroimaging studies that show reduced activity in the left prefrontal lobe. The DLPFC is also an important node in the dorsal executive system, which is involved in cognitive control in emotion regulation. Cognitive control functions include selective attention, inhibitory control, and cognitive re-evaluation. The role of the DLPFC in regulating these functions has been supported by previous research [65,66]. Although rTMS has made many achievements in the treatment of cognitive function in MDD, the efficacy in many patients is different because of the heterogeneity of MDD. Many aspects of current research are unraveling the mechanism of rTMS itself; however, rTMS is still very promising for the treatment of MDD.

**Psychotherapy for MDD**

The recurrence rate of MDD is very high; with each repeated attack, the depression situation worsens, and the risk of the next recurrence increases [67,68,69]. One study found that the risk of recurrence after one episode of major depression was 50% and 80% after two attacks and may be as high as 90% after three episodes. These relapses have caused great burdens on individuals, families, and society [25,70]. Therefore, preventing the recurrence of depression is an important clinical treatment index for the long-term supervision of patients with MDD.

Psychotherapy plays an important role in cognitive, interpersonal, dynamic, marriage, and family therapy, it may produce some skills, and patients can continue to practice after treatment ends to adjust their emotional states and reduce the internal and external triggers of relapse or recurrence [68]. Cognitive therapy is one of the most commonly used methods for the treatment of mental disorders [71]. According to cognitive therapy, patients' unreasonable beliefs and distorted attitudes toward themselves and the future are the main causes of their depressive symptoms and cognitive dysfunction. The purpose of cognitive therapy is to challenge and correct patients' unreasonable beliefs and attitudes, re-examine their thoughts and ideas and change related behaviors in real life such as self-negation and self-avoidance to relieve depression. The depressive symptoms of some patients with MDD are related to cognitive distortion, psychosocial stress, inner conflict, interpersonal difficulties, or other psychological factors, and psychotherapy is especially effective for these patients [68,72,73].

Behavioral therapy is based on the learning theory or conditioned reflex theory and employs techniques to correct and eliminate abnormal conditioned reflex

behavior displayed by patients. Repeated training to change and correct bad behavior attempts to establish new conditioned reflex behavior. The goal of treatment is to change people's behavior–that is, to eliminate bad behavior that we consider to be symptoms–and to shape good and healthy behavior. The therapeutic effect is to reduce and alleviate the depressive symptoms caused by social stress, improve the medication compliance of patients receiving antidepressant treatment, and correct various adverse psychosocial consequences secondary to depression, such as marital disharmony; feelings of inferiority and withdrawal, and in some cases, to prevent suicide; and to maximize the recovery of social and professional functions [7475].

Compared to other treatments, more attention should be paid to psychotherapy for MDD [76,77]. Patients undergoing psychotherapy generally have good compliance, almost no adverse reactions, and a low recurrence rate, but the degree of intervention by doctors is greater and the cost is higher [78]. Therefore, in underdeveloped countries, it is more difficult to see a doctor for behavioral therapy, so there are fewer patients who receive reasonable and appropriate psychotherapy at present

**Exercise Therapy for MDD**

Since no single treatment is effective for patients, there has been great interest in the development and evaluation of alternative therapies for MDD, and physical exercise is one of the treatments that has received considerable attention [79,80]. Studies have shown that the beneficial effects of exercise on depression depend on the regulation of neurotransmitters, neurogenesis, neurotrophic factors, and cerebral blood flow [81]. It has been reported that exercise can induce an increase in the level of BDNF and helps improve the ability of mice to resist anxiety and depression [82]. D-β-hydroxybutyrate can pass through the blood-brain barrier, and the possible mechanism underlying the effect of exercise is that the accumulation of endogenous D-β-hydroxybutyrate in the hippocampus inhibits class I histone deacetylase, specifically increases the expression of BDNF, and affects synaptic transmission [82]. In a mouse model of depression caused by sleep deprivation, exercise increased the level of BDNF, thus playing a neuro-protective and neurotrophic role. Experiments have shown that BDNF can be increased by exercise, which regulates synaptic plasticity by acting on axon and dendritic remodeling, synaptogenesis, and synaptic function [82,83]. BDNF activity is speculated to be closely related to learning and memory function. In addition, studies have shown that exercise preconditioning can prevent depressive behavior and changes in neurotransmitters such as increased levels of noradrenaline, serotonin, and their metabolites in the brains of a sleep-deprived mouse depression model [83,84,85]. In addition, in an animal model of depression induced by maternal separation, the levels of 5- hydroxytryptamine and tryptophan hydroxylase in the dorsal raphe decreased, whereas exercise alleviated depression-like behavior by increasing the expression of these factors [86,87].

Although the etiology of MDD is unclear, many factors have been found to affect the development of the disease, such as changes in neurotransmitters, decreased synaptic plasticity, and reduced hippocampal size. The hippocampus plays an indispensable role in learning and memory, has a high degree of neural plasticity, and is one of only two areas of the brain that show adult neurogenesis (the other being the olfactory bulb) [88,89,90]. Exercise has been shown to increase the volume and blood flow of the hippocampus, stimulate neurogenesis, regulate synaptic plasticity, and increase the expression of growth factors, such as BDNF, which optimize brain function [81]. There is no direct comparison between pharmacological treatments and exercise therapy for cognitive dysfunction therefore, there is no way to quantify the effect of exercise to improve cognitive dysfunction [91,92].

Physical exercise can be used as an auxiliary and individualized treatment for MDD [93,94] or as a strategy to prevent MDD [95]. Physical exercise has a positive effect on synaptic plasticity and neurogenesis via various biological mechanisms [96,97]. Patients with MDD participate less in physical activity, show lower cardiopulmonary adaptability, and have an increased risk of metabolic diseases and premature death [98]. From another point of view, it should be noted that a large number of acute exercises are stressful events, and the intensity of acute exercise determines the magnitude of stress [99], therefore, patients with MDD should be aware of exercise intensity and try to exercise aerobically [99,101].

**Conclusion**

Although tremendous progress has been made in predicting, diagnosing, and ameliorating the symptoms of MDD, it remains a serious disease that imposes a heavy burden on both individuals and society [102]. In the treatment of MDD, the widely accepted outcome is symptomatic remission; that is, patients return to pre-ictal functional levels with no or only mild depressive symptoms. Combination therapy is currently advocated for MDD treatment [103]. Studies have found that, after antidepressants are administered in the acute phase of MDD, psychotherapy seems to be an effective strategy, and the effect is ideal in preventing relapse [68104]. There are still many unresolved problems associated with the combined treatment of MDD. For example, there are different treatment methods recommended for use in the acute exacerbation and remission periods of MDD; there is controversy as to which should be used as the main treatment, which should be adjuvant treatment, and when adjuvant treatment should be carried out [105]. However, these problems are significant. Therefore, an in-depth understanding of MDD is very important, and there is a long way to go before MDD can be successfully treated.

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**Conflict of interests**

The authors declare that they have no conflicts of interest.

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