

## Research Progress On Volume Changes of Nucleus Accumbens and Mental Disorders

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### Abstract

*Nucleus accumbens (NAc) is one of the larger nuclei in the basal forebrain. It has complex connections with other structures in the brain and has various functions. In recent years, a large number of studies have found that a variety of mental diseases may lead to abnormalities in the volume of nucleus accumbens and related nerve loops. With the development of imaging, it will be helpful to observe the volume changes of nucleus accumbens. This article reviews the research progress on the changes of nucleus accumbens volume and several common clinical mental disorders.*

**Keywords:** Nucleus Accumbens; Mental Disorder; Neural Loop

### Introduction

Since the 1960s, researchers have conducted a large number of studies on how addictive substances act on the brain's reward system, and found that in rats, cats, monkeys and other animals, almost all parts of the brain (except the neocortex) are related to reward, and the center of the reward system may be located in the midbrain limbic dopaminergic system that controls emotional response. The nucleus accumbens (NAc) and ventral tegmental area (VTA) are of interest to researchers. It has been found that nucleus accumbens has the functions of behavioral regulation, analgesia, participation in the generation of schizophrenia, drug addiction, learning and memory and the regulation of motor activities [1]. The mesencephalic limbic dopamine system associated with nucleus accumbens is considered to be the neuroanatomical basis of brain reward system and reinforcement learning. The cell bodies of midbrain dopaminergic neurons are mainly concentrated in the substantia nigra and ventral tegmental area, which affect the neural function through the nigrostriatal pathway and the marginal pathway of the mesencephalic cortex. The mesocortical limbic pathway related to reward mechanism can be divided into mesencephalic cortical pathway and mesencephalic marginal pathway, which is composed of ventral tegmental area and its projection target nucleus accumbens, prefrontal cortex, amygdala, hippocampus and so on. It is the main structure of dopamine reward loop and participates in the reward effects related to neuropsychiatric disorders and drug addiction. Nucleus accumbens is the integrated center of limbic system and extrapyramidal system. The polypsinous neurons of nucleus accumbens not only form synaptic connections with the afferent fibers of ventral tegmental area, but also receive

axonal terminals from hippocampus and prefrontal cortex. Therefore, the neurons in the nucleus and shell can integrate the projection information from dopaminergic and glutamatergic nerve fibers in the cortex and marginal areas, so as to coordinate the uploaded perceptual information (such as motivation and goal orientation) and the descending action response. It plays an important role in a variety of functional activities, such as behavior, motivation, stress, reward and drug addiction [2]. With the clinical application of ultra-high field magnetic resonance, 3.0T magnetic resonance equipment has obvious advantages in signal-to-noise ratio, resolution and scanning time, which provides a better hardware platform for the clear display of brain fine structures[3]. Generally speaking, in recent years, several experiments have found that the volume of nucleus accumbens and the corresponding nerve loop are related to the pathophysiological processes of a variety of mental diseases, including schizophrenia, bipolar disorder, substance use disorder, obsessive-compulsive disorder and so on.

### Schizophrenia

Schizophrenia is a group of severe mental disorders with significant abnormal mental activities in many aspects, such as cognition, thinking, emotion, behavior and so on, which seriously damage the professional and social function of the patients. At present, the pathogenesis of schizophrenia is not very clear. Nucleus accumbens is integrated into the dopamine system, and its dysfunction is considered to be the neurochemical basis of schizophrenia.

Previous studies have shown elevated levels of neutrophils and cytokines in the blood of some patients with schizophrenia, suggest-

ing that immune activation may be a part of the disease. In 2014, Stu G. Fillman et al conducted an experiment on the relationship between leukocyte levels and social dysfunction, reduced volume of insular lobe, amygdala and nucleus accumbens in patients with schizophrenia [3, 4]. 55 patients with schizophrenia were scanned by 3.0TMRI. Conclusion (after considering age and sex), the absolute value of neutrophils is significantly negatively correlated with the volume of left nucleus accumbens ( $B=-0.269$ ,  $R=0.269$ ,  $F(54,1)=4.200$ ,  $P<0.05$ ). However, this study can only show that chronic inflammation in patients with schizophrenia may be related to the volume of nucleus accumbens.

In 2015, Catherine Bois et al conducted a cross-sectional comparison of the volumes of hippocampus, amygdala and nucleus accumbens between patients with first-episode schizophrenia and individuals at high family risk. 1.0TMRI scans showed that the subjects mainly had a significant effect on the right nucleus accumbens ( $P=0.017$ ) [5]. The volume of the right nucleus accumbens in the first-episode patient group was significantly smaller than that in the high-risk group ( $P=0.017$ ) and the healthy control group ( $P=0.023$ ). However, the experimental results cannot confirm that the decrease of the volume of nucleus accumbens is one of the high risk factors for the onset of schizophrenia.

In 2017, Mireia Forns-Nadal et al found that subjects who took antipsychotic drugs for the first time (including risperidone, olanzapine, aripiprazole and quetiapine) increased the volume of bilateral nucleus accumbens after controlling age, sex and marijuana use compared with healthy controls, which is different from the above findings [6]. This new finding is helpful for the individualized treatment of schizophrenia. However, there is no correlation between atypical antipsychotic drug exposure and nucleus accumbens volume, and whether there are other factors need to be further studied.

In addition, in terms of treatment, studies on the destruction of nucleus accumbens have been carried out at home and abroad. From 2005 to 2008, the Department of Neurosurgery of Hunan brain Hospital conducted a clinical study on the destruction of nucleus accumbens in the treatment of refractory schizophrenia. Kuang Weiping et al successively treated 126 patients (95 males and 31 females) [7, 8]. Patients with schizophrenia with an average age of 18-52 years old were operated accordingly. The bilateral nucleus accumbens were damaged at 75°C and 60s respectively by radio frequency meter, resulting in 6mm × 6mm × 8mm size lesions. After operation, according to the patient's symptoms, supplemented with corresponding drugs and psychotherapy, the effective rate could reach more than 90%. However, after 81 cases of nucleus accumbens destruction (40 cases of bilateral nucleus accumbens damage and 1 case of unilateral nucleus accumbens lesion), it was found that 52 cases had unbearable systemic fever and other phenomena after Liu Qihua et al performed 81 times of nucleus accumbens destruction (40 cases of bilateral nucleus accumbens damage and 1 case of unilateral damage) [9]. It can still be shown that certain intervention measures to the nucleus accumbens is a new direction for the treatment of schizophrenia.

In terms of related mechanisms, most studies believe that schizophrenia is related to abnormalities of dopaminergic system and glutamatergic system. However, the molecular changes caused

by increased dopaminergic activity associated with schizophrenia are unclear. After repeated use of cocaine or amphetamine (amphetamine), elevated  $\Delta$ FosB levels were found to be associated with chronic subcortical high dopaminergic activity. Therefore, R. CANTRUP et al studied the role of  $\Delta$ FosB signal in the neurodevelopmental animal model of chronic subcortical high dopaminergic activity in schizophrenia [10].  $\Delta$ FosB is a transcription factor against proteolytic degradation, which accumulates after chronic dopaminergic activation. Studies in transgenic mice overexpressed by  $\Delta$ FosB have confirmed that the protein levels of several downstream genes activated by  $\Delta$ FosB in nucleus accumbens neurons, including cyclin dependent kinase-5 (cdk-5), cdk-5 activator p35 and GluR2 subunit of AMPA receptor, are increased in nucleus accumbens. Chronic subcortical dopaminergic hyperactivity is a characteristic manifestation associated with positive symptoms of schizophrenia, which is related to the increase of  $\Delta$ FosB level and transcriptional activity, which leads to the increase of cdk-5 signal in nucleus accumbens of hypothetical neurodevelopmental schizophrenic rat model. These changes seem to cause significant changes in the signals and functions of important neurons, so they may contribute to the study of relevant animal models and the detection of disease progression in patients with schizophrenia.

In order to study the glutamatergic system, Lesley A. McCollum et al analyzed vesicular glutamate transporters vGLUT1 and vGLUT2, which are essential for glutamate uptake and storage into synaptic vesicles [11]. They have complementary localization patterns in cortical and subcortical structures respectively, so the study of these two markers can comprehensively analyze the glutamate input of nucleus accumbens. Compared with the control group, the level of vGLUT2 protein in the nucleus accumbens of the patient group was higher. The increase in vGLUT2 indicates that the nucleus accumbens receives more glutamate input, most likely from the subcortical region. This study reveals the role of nucleus accumbens in patients with schizophrenia and highlights potential abnormalities in the interaction between dopaminergic and glutamatergic systems in this region.

### Bipolar Disorder

Bipolar disorder (BD) is a common mental disorder with both manic or mild manic episodes and depressive episodes (typical characteristics). According to recent studies, the age of onset of BD is declining, indicating that more young children may have BD. Due to the lack of related studies, in 2008, Barbara Geller et al conducted an experiment on the effects of age, sex and independent life events (ILE) on the volume of amygdala and nucleus accumbens in children with bipolar disorder type I (BD-I) [12]. Patients in the observation group met the diagnostic criteria of DSM-IV, including manic type and mixed paroxysmal type (both first episode). A total of 47 subjects aged 7-16 years (21 BD-I patients, 26 normal developmental children) were scanned by 1.5TMRI, and the other variables were controlled. The results showed that the more ILE (including course failure, parents' marital problems, siblings attending boarding school, etc.) in BD-I patients, the smaller the size of the left nucleus accumbens. However, after correction, there is no significant relationship between the two, which may be related to the small sample size.

In 2018, Isabelle E. Bauer et al conducted a trial on patients with bipolar disorder type II and found that after 200 mg/d of lamotrig-

ine (the initial dose was 25mg / day for 2 weeks, then increased to 50mg / day for 2 weeks, week 5 to 100mg / day, week 6 to 200mg/d), after 12 weeks of treatment, the volume of amygdala, cerebellum and nucleus accumbens decreased after 3.0T MRI scan [13]. And only “responders” (patients whose HAMD scores dropped by 50% after treatment) experienced these changes. Similar to previous studies, due to the small number of samples, more targeted studies are needed to confirm the specific mechanism of lamotrigine in the treatment of BD- II patients and its effect on the volume of nucleus accumbens. In addition, lithium treatment can affect the morphology of nucleus accumbens in BD patients, although the specific mechanism is not clear, but Daniela Vecchio et al found that after a period of lithium treatment, the morphology of nucleus accumbens in BD patients was similar to that in healthy controls, and the longer the treatment time, the stronger the regulation of nucleus accumbens morphology [14].

In terms of related mechanisms, dopamine and cyclic adenylyl transferase regulate a phosphoprotein with a molecular weight of 32kDa (DARPP-32) that integrates dopaminergic signal transduction into several other neurotransmitters. Calcineurin (CaN) is located downstream of the dopaminergic pathway and inactivates DARPP-32 by dephosphorylation. Mizuki Hino et al analyzed the expression of DARPP-32 protein in postmortem brain tissues such as nucleus accumbens in patients with schizophrenia and bipolar disorder [15]. The results showed that the content of DARPP-32 in prefrontal cortex of patients with schizophrenia decreased significantly, while the content of CaN increased. However, there was no significant difference in the levels of DARPP-32 and CaN in the nucleus accumbens of patients with schizophrenia and bipolar disorder. However, additional animal studies are needed to study the effects of these proteins on the expression of these proteins in the nucleus accumbens. In addition, due to the small area of nucleus accumbens, less available, uniform sampling is also more difficult, more need a large sample size of related experiments to explore the changes of the above proteins in the nucleus accumbens to ensure the accuracy of the results.

## Substance use disorder Alcohol

Alcohol is recognized as one of the addictive substances in the world, especially for teenagers, it will cause more far-reaching harm. Existing studies have shown that in the behavior caused by the reward mechanism, the functional activity of nucleus accumbens in adolescents is higher than that in children and adults, so more attention should be paid to it [16].

With the approval of the local government, Rachel E. Thayer et al conducted an experiment in 2012 (subjects were 168 teenagers, aged 14-18) [17]. After 3.0T MRI scans, the statistical results showed that the increase in the volume of nucleus accumbens was related to the increase in the frequency of alcohol use in the past three months, but not to alcohol consumption. According to the above results, under ideal conditions, we should improve the effectiveness of the research on alcohol consumption.

Considering that alcohol dependence has a certain familial aggregation, it has been found in the literature that there is a significant positive correlation between the family history density of and the volume / intracranial volume of the left nucleus accumbens

( $\Delta R^2 = 0.04$ ,  $P=0.02$ ), and this effect is only significant in women ( $\Delta R^2 = 0.11$ ,  $P=0.006$ ) [18]. Similar to the above experiments, the subjects are limited to adolescents (12-16 years old). We can further study the relationship between the volume of nucleus accumbens and alcohol use in adults and the elderly [19].

For treatment, the study found that nucleus accumbens is one of the ideal targets for deep electrical stimulation in the treatment of (DBS), and let patients avoid being affected by external pressure during treatment, the effect will be more significant [19].

Alcohol use disorder (AUD) is characterized by chronic recurrence after stopping drinking for a period of time. The most important method for successful treatment of AUD is to prevent high craving and recurrence rate. Chronic ethanol intake can reduce the activity of  $\beta$ -endorphin neurons in the medial hypothalamus of rats, which may be the cause of irritability and depression associated with alcohol withdrawal, and may lead to the continuous use of ethanol. Discontinuation of long-term ethanol use leads to a decrease in extracellular dopamine levels in the nucleus accumbens, which is considered to be one of the key potential causes of negative effects and physiological withdrawal symptoms associated with alcohol withdrawal [20].

In addition, functional connectivity magnetic resonance imaging (rs-fcMRI) in the resting state has been used to identify different brain networks and the development of their functional connections. Studies on the synchronization of resting state in healthy individuals show that nucleus accumbens shows positive functional connection or integration with other areas related to reward and influence, such as orbitofrontal cortex, striatum and amygdala. However, areas related to cognitive function in nucleus accumbens (such as dorsolateral prefrontal lobe and inferior parietal cortex) show negative functional connection or separation. Recent studies in long-term abstinent have shown that the nucleus accumbens reduces the functional connection to the marginal zone (including the caudate nucleus, dorsomedial nucleus and anterior medial nucleus of the thalamus) and enhances the connection to the executive functional brain area. such as the dorsolateral prefrontal cortex and inferior parietal lobule [21]. These mechanisms may be some compensatory mechanisms of continuous abstinence and are related to the performance of neuropsychology.

## Heroin

Heroin belongs to opioids. At present, the global situation of opioid abuse is very serious. Because it can act on the mesencephalic limbic system and increase the level of dopamine, it produces a strong sense of euphoria. Some studies have shown that there is an important relationship between the pathophysiological process of heroin addiction and the reward mechanism, especially the nucleus accumbens.

In 2014, Christian L.Seifert et al conducted an experiment on the relationship between heroin abuse and nucleus accumbens volume [22]. 30 subjects in the observation group (over 18 years old) met the diagnostic criteria of DSM-IV ‘s opioid dependence, and were not allowed to use drugs other than prescription heroin (diacetylmorphine) for maintenance therapy during the study period. 3.0T MRI scans were performed after 72 hours of abstinence and 2 hours of smoking cessation. Compared with the control group, it



was found that there was a significant difference in the volume of the left nucleus accumbens ( $P < 0.049$ ), that is, the volume of the left nucleus accumbens decreased in the heroin dependent group. In addition, the study also measured the Baker Depression scale (BDI). The results showed that there was a significant negative correlation between nucleus accumbens volume and BDI in heroin patients. Thus it can be seen that in addition to the impact of heroin itself, we should also consider the co-disease of patients.

In terms of treatment, similar to the treatment of schizophrenia, for opioid dependence, there have been studies on nucleus accumbens destruction and DBS in China, but Wang Xuelian et al found that DBS is a new method better than nucleus accumbens destruction and has a good effect on relapse [23].

In terms of mechanism, it has been found that astrocytes are considered to be supporting cells to maintain the metabolic homeostasis of neurons, which can directly regulate neuronal activity, and some cells are involved in the process of 90% synaptic contact in some brain regions. Down-regulation of glutamate transporter in parasynaptic astrocytes of nucleus accumbens can induce heroin craving [24]. Their ability to interact with tens of thousands of synapses at the same time makes astrocytes have the function of coordinating neural circuits and play a role in the basic pathology of neuropsychiatric diseases.

### Obsessive-compulsive disorder

Obsessive-compulsive disorder, also known as obsessive-compulsive neurosis, obsessive-compulsive disorder is a kind of neurotic disorder characterized by repeated and persistent obsessive-compulsive concept or obsessive-compulsive behavior. Previous studies have confirmed the role of reward mechanism in obsessive-compulsive disorder, and nucleus accumbens is a key structure in reward mechanism, so exploring the relationship between nucleus accumbens volume and disease severity will be helpful for targeted treatment in the future.

In 2013, Janardhanan C Narayanaswamy et al conducted a clinical correlation study on the volume of nucleus accumbens in adult patients with obsessive-compulsive disorder (OCD) [25]. The subjects were 44 patients with obsessive-compulsive disorder (DSM-IV diagnostic criteria) and 36 healthy controls. After 1.5T MRI scanning, it was found that the evaluation age of patients was significantly negatively correlated with the volume of nucleus accumbens ( $r=-0.40$ ,  $P < 0.001$ ) and left ( $r=-0.24$ ,  $P=0.03$ ). There was a significant negative correlation between the volume of right nucleus accumbens and the score of Y-BOCS obsessive-compulsive scale ( $r=-0.48$ ,  $P=0.001$ ). This provides support for specific regions of DBS. However, there was no significant correlation between the volume of the left nucleus accumbens and any clinical variables. In addition, there was no correlation between depression severity score and the volume of nucleus accumbens on the right ( $r=0.28$ ,  $P=0.07$ ) or left ( $r=0.19$ ,  $P=0.23$ ), which was different from the results of previous experiments on the relationship between heroin abuse and nucleus accumbens volume. There was no significant correlation between the course of obsessive-compulsive disorder and the volume of nucleus accumbens on the right ( $r=0.54$ ,  $P=0.12$ ) or left ( $r=0.11$ ,  $P=0.45$ ). There was no significant correlation between the course of obsessive-compulsive disorder

and the volume of nucleus accumbens.

In addition, a trial on gene sequence differences in patients with obsessive-compulsive disorder also found that patients with obsessive-compulsive disorder have a certain effect on the volume of nucleus accumbens, especially in the elderly population [26]. Existing imaging tests also support nucleus accumbens as a target for DBS in the brain of patients with obsessive-compulsive disorder [27]. In general, afferents from the prefrontal cortex, hippocampus and amygdala are excitatory. The dopaminergic projections from the ventral tegmental area to the nucleus accumbens regulate the balance of these excitatory inputs. Several important inputs of nucleus accumbens converge at the junction of internal capsule (IC) and anterior commissure (AC), so it can be speculated that the caudal part of nucleus accumbens connected by IC-AC may be one of the effective targets for deep brain stimulation to improve obsessive-compulsive disorder-related behavioral symptoms [28]. In 2011, a related experiment found that DBS has the characteristics of reversibility, manipulation and low trauma for patients with obsessive-compulsive disorder, especially for elderly patients [29]. On this basis, Wang Xin combined with DBS, of the anterior limb of the internal capsule found that it could not only relieve the obsessive-compulsive symptoms, but also improve the anxiety of the patients [30].

### Conclusion

In the past 20 years, a large number of studies on nucleus accumbens and mental disorders have been carried out, including schizophrenia, bipolar disorder, substance use disorder, obsessive-compulsive disorder and so on. It is found that the volume changes and structural function of nucleus accumbens play an important role in the severity, occurrence, development, prognosis and treatment of a variety of mental diseases. However, it should be noted that patients with the above diseases are likely to be accompanied by varying degrees of anxiety and depression. It has been reported that the severity of anxiety disorder and its corresponding cognitive behavioral therapy and SSRIs drugs will have a certain impact on the volume of nucleus accumbens, so the related co-disease problem is also one of the factors affecting the accuracy of test results [31, 32]. Although many theories are still in the speculative stage, with the application of new technologies such as modern neurobiology, photogenetics and imaging, the research on nucleus accumbens will make further progress.

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