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Participation of the Limbic System in the Treatment of Parkinson's Disease with Depression

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Abstract: ***Parkinson's disease (PD) is a common chronic neurological disease in the elderly, starting from motor disorders such as static tremor and bradykinesia. However, with the evolution of the disease, the incidence of non-motor symptoms increases year by year, among which it is mainly depression. With the emergence of depressive symptoms, seriously affected the quality of life of PD patients, but also induce aggravating movement disorders and a series of related symptoms, for the pathogenesis of PD patients with depression is not clear, most people think it with the brain of dopamine, serotonergic neurons change, this paper will start on the brain structure, from the ancient limbic system, its definition and structure, and the mechanism between PD patients with depression, through consulting relevant literature, expand the following review.***

Keywords: Limbic system, Parkinson's disease, Depression, Review**.**

1. Introduction

Parkinson's s disease (PD) is a progressive neurodegenerative disease [1], Movement disorders are multiple manifestations, but non-motor disorders are also often accompanied by around. Depression has been reported [2] Is a common occurrence of non-motor disorders in PD patients, with an incidence of approximately 40-50% [3]. In addition to causing the inherent emotional symptoms, depressive symptoms usually have a further impact on the quality of life, motor disorders, cognition and other functions of PD patients [2,4,5,6], Delay and delay the diagnosis and treatment plan and drug efficacy of PD patients [7]. However, there are still many opinions about the pathogenesis of Parkinson's disease with depression, which has not been explored. At present, the pathogenesis of PD patients with depression (Parkinson's disease patients with depression, PDD) is mainly related to the nuclear groups of dopamine and serotonergic neurons in the brain. Related studies show that the brain areas related to the limbic system play a role in regulating cognitive impairment, mood, memory and other aspects [8] Therefore, the author makes the following review of the neural mechanism of the brain limbic system involved in Parkinson's disease with depression, to provide new ideas for better understanding and understanding of the pathophysiological mechanism of PDD, and to better prevent, treat and improve the disease.

2. Definition of the Limbic System

The development of the limbic system has undergone major reform and changes, and its birth is a milestone for the neurology field. It was first used in 1664 by doctor Thomas Willis (Thomas Willis) [9]. At that time, there was no much understanding of the system, and the emergence of Papez and McLean connected the limbic system with human emotional functions [10]. With the progress of medicine, people gradually realize that the limbic system is mainly composed of cingulate gyrus, hippocampus, amygdala, subthalamic nucleus and nucleus accumbens [11], With dense intrinsic connections [12]. It is mainly involved in memory, cognition, emotion, motivation and other crucial brain structural complexes [9]. The vulnerability of mesolimbic structures in Parkinson's disease (PD) to neurodegeneration was found from the basic structure of the brain and the imaging of imaging brain function [9] Therefore, understanding the structure and function of the limbic system has a valuable role in the diagnosis and treatment of the concomitant symptoms of PD, including motor and non-motor diseases.

3. The Limbic System Participates in Brain Functional Nuclei Related to PDD

According to the study [9,11,13] Found that the amygdala, anterior cingulate cortex, subthalamic nucleus, hippocampus and nucleus accumbens regional changes, may lead to depression, combined with PD itself of neural vulnerability, so we go to understand the structure of the brain region organization changes, to find more possibility of the disease.

3.1 Mechanisms of the Amygdala in PDD

The amygdala (amygdala), also known as the amygdala complex, is located in the medial temporal lobe of the brain [13], One of the components of the limbic system is an important brain region for the emotional processing and motivation behavior [14]. Its main components include [15] The basolateral nucleus (basolateral amygdala, BLA) and the central nucleus (central nucleus of the amygdala, CeA). Impaired amygdala may be one of the main pathogenesis of PDD. At present, the diagnosis of PDD is basically assessed by subjective means such as symptoms and the Hamilton Depression Scale. With the development of imaging technology, it technologies become used to explore the objective diagnostic biological markers of PDD [16]. Resting-state functional magnetic resonance imaging (RS-FMRI) is the main feasibility method to explore the pathogenesis of PDD [16], Mainly through low frequency amplitude analysis (amplitude of low frequency fluctuation, ALFF), measure the amplitude of regional low frequency activity, resting state brain blood oxygen level dependent (blood oxygenation level dependent, BOLD) signal has physiological significance in the low frequency field, so as to judge the abnormal activity of brain area [17]. And Huang P et al [18] Human recruited 19 depressive PD, 19 non-depressed

PD and 28 normal control subjects through clinical evaluation of all subjects, including the Unified Parkinson's Disease Assessment Scale, the Hamilton Depression Assessment Scale and the Mini-Mental State Examination. Structural and resting-state functional brain images were also obtained to assess volumetric and functional changes in the amygdala, and the functional connectivity between the right amygdala and frontoparietal regions was found to be reduced in depressed PD compared to non-depressive focal patients. HuX class [19] Twenty depressed PD patients, 40 non-inhibitory PD patients, and 43 healthy controls were recruited for neuropsychological testing and resting-state functional MRI scans. Group differences in the amygdala functional connectivity networks were examined using a t-test. Compared with non-inhibitory PD patients, the left amygdala function and left amygdala to the left superior temporal gyrus with depressed PD also showed increased connectivity with the left amygdala but the left putamen, left inferior frontal gyrus, and right cerebellum, and the right amygdala decreased functional connectivity to the left inferior orbital frontal gyrus, left rectus gyrus, and right putamen. From the above trial data, the increased connectivity between limbic system regions and the decreased connectivity between cortical limbic networks may reflect impaired higher-order cortical regulatory effects on emotion-related limbic areas, which may lead to emotion dysregulation.

Therefore, through imaging evaluation combined with the symptoms of PDD patients, better bridge the mechanism of action between amygdala and PDD, through more trials and data support analysis, to find more stimulation targets, better serve and treat PDD patients.

3.2 Mechanism of the Anterior Cingulate Cortex (Anterior Cingulate Cortex, ACC) in PDD

The ACC is located in the inner side of the cerebral hemisphere and is connected to the corpus callosum. Interconnected with a group of other limbic and related regions, including the amygdala and orbitofrontal cortex, are systems collectively involved in affective and reward-related processing [20]. The ACC contains 25,24,32,33 parts of its subgenus. Each area accessory part, participate in the regulation of different regions, including proof for depression, the neurons in the cingulate cortex, for the expression of negative emotions significantly higher than positive emotions, it suggests that the cingulate cortex may be extremely active in depression, through deep brain stimulation may help treat some people's depression [20-22]. Based on functional studies, the connectivity of depressive function between the ACC and the lateral orbital frontal cortex is higher, which may be related to more transmission of non-rewarding information to the anterior cingulate, which accelerates and leads to depression [20,24]. Relevant neuropathological findings, some in PD with depression, involve the progressive degeneration of the nigrostriatal and mesocorticolimbic dopaminergic systems [25]. Wei L [25], et al. investigated circuit-related abnormalities in PD with depression by assuming resting-state fMRI and seed-based functional connectivity in a dopaminergic midbrain region (that is, substantia nigra (SN) and ventral tegmental area (VTA)). The results demonstrated increased functional connectivity between the VTA and the anterior cingulate cortex (ACC) in patients with depressed PD (DPD) relative to healthy controls (HC) and non-depressed PD (NDPD), suggesting that dysfunctional mesocortical perimbic dopaminergic neurotransmission may be associated with depression in PD. Furthermore, the abnormal connectivity between VTA and ACC was associated with the severity of depression in PD patients [26]. Chagas MHN [27] Based on imaging cranial magnetic resonance analysis, et al recruited 43 PD patients into three groups according to the severity of depressive disease. All participants received magnetic resonance imaging to assess cortical thickness, cortical and subcortical volume, and spectroscopy of bilateral putamen and cingulate cortex. Volume analysis showed that the ACC and the right amygdala and left cerebellar white matter were smaller in the current major depressive disorder (MDD) group as compared to the control group. The results suggest that current and lifetime MDD negatively affect the neurodegenerative process of PD, with reduced volume and / or cortical thickness in the temporal and frontal regions, anterior cingulate cortex, amygdala and cerebellar white matter.

The diagnosis of PDD patients will be more considerable and clear. In addition to the reliable basis based on the scale, the corresponding treatment plan will be more targeted through the symptoms involved in the damage of the limbic system organization.

3.3 Mechanism of the subthalamic Nucleus (Subthalamic Nucleus, STN) in PDD

The STN is a small lens-like, iron-rich nucleus [27], Although bilateral high-frequency stimulation (HFS) of STN has been found to be the preferred surgical therapy for motor disorders in advanced PD, the procedure may cause unexplained debilitating psychiatric effects, including depressive disorders [28]. research finding [28], HFS of STN suppresses midbrain 5-serotonin (5-HT) neurons to cause behavioral changes associated with depression (STN). In the depression experiment (forced swimming test), in the PD rat model, we objectively observed that bilateral HFS of STN was consistently depressed (40-50%) of the firing rate of 5-HT neurons in the dorsal fin nucleus, rather than adjacent non-5-HT neurons. Through pre-and post comparison, the depression-like behavior caused by HFS of STN was reversed by selective 5-HT enhanced antidepressants, thus linking behavioral changes with reduced 5-HT neuronal activity, and linking these reduced 5-HT function with the HFS psychiatric effect of STN observed in PD patients, better serving the clinical management model. The 5-HT system has been widely appreciated in PDD, with evidence beyond the pathological loss of 5-HT axon markers and cell bodies in the dorsal midbrain nucleus and median costal nuclei [29], The latter hypothesis comes from recent findings that highlight the close interaction between the basal ganglia and the 5-HT system, not only in movement but also in terms of limbic function. These findings include evidence that clinical depression is a side effect of deep brain stimulation (DBS) in the subthalamic nucleus (STN) and, moreover, recently demonstrated [28,29], STN DBS in animal models inhibits 5-HT neurotransmission, and this change may support depressive-like side effects. Abnormal α oscillations in the terminal stribed nucleus and subgenus cingulate correlated with symptom severity in depressed patients, and Sun Y et al

[30] Through a retrospective case-control study of 36 PD patients, the difference in θ oscillation in the spectral density and local field potential (LFP) of α field recorded in STN during deep brain stimulation (DBS), and their correlation with the Hamilton Depression Rating Scale (HAMD) in PD patients during the same period. The results showed that the PD group had a higher PSD α oscillation with depression, a lower PSD of the left ventral STN was θ oscillation, and PSD of the left ventral STN α oscillation was positively correlated with the severity of depressive symptoms, while PSD of θ oscillation at this position was negatively correlated with the severity of depressive symptoms. Abnormal α and θ oscillations in the left ventral STN can be used as focal release biomarkers with depressive symptoms to guide STN-DBS treatment.

Therefore, the pathogenesis study in patients with PDD is not only on 5-HT feedback mechanism, through STN and the corresponding stimulation shock pop, detect the corresponding local biological signs, further for the treatment of PDD patients have a certain help, so combined with the corresponding area of the brain response better treatment of the patients with depression, after the development of medicine has certain enlightenment.

3.4 Mechanism of the Hippocampus in PDD

The hippocampus is composed of hippocampus, dentate gyrus (DG), Conumonis (CA) region 1-4, subthalamus and entorhinal cortex, among which the CA region is further divided into four subregions: C A1-CA4 [31]. Recent research has found that the No [32,34], As a special form of neuroplasticity, the hippocampal nerve is not only manifested in cognitive and emotional behavior under physiological conditions, but more importantly, the field of depression is also concerned, which may be related to the related emotional aspects caused by its dysregulation. The advent of this field began to study the effects of drugs on adult neurogenesis, especially psychoactive drugs, which include antidepressants [35], Participate in the regulation of adult neurogenesis and the effects of drugs with evoked neural and antidepressant activity through modulation of the transcription factor NF- κ B signaling pathway. And Gyorfi O et al [36] Based on FreeSurfer software, hippocampal subfield volumes of 35 newly diagnosed PD patients without cognitive impairment and 30 matched healthy control individuals, rapidly acquired gradient echo images prepared by T 1-weighted 3D magnetization, and free surfing v 6.0 for image analysis, showed a selective reduction in CA2-CA3 volume and returned to normal after a 24-week treatment period. Higher depressive symptoms are associated with smaller CA2-CA3 volumes, and these results suggest that in the absence of cognitive impairment, the CA2-CA3 subfield is structurally affected during the earliest stages of PD, and that this structural abnormality, normalized by levodopa, is associated with depressive non-motor symptoms. PD is characterized by the contents of α synucleosin in the patient brain [37], Cognitive impairment and depression associated with hippocampal dysfunction are frequently observed in these disorders. Although various inclusions of α -nuclenucleproteins were found in hippocampal formation [38], But accumulating evidence suggests that small α synuclein aggregates or oligomers may be truly responsible for neurotransmission and neurogenesis defects in the hippocampus and related brain regions that constitute the main mechanisms of hippocampal dysfunction as well as associated neuropsychiatric manifestations in synucleinopathies.

Through the study of the hippocampus, we see more objective, not only in the disease of cognitive disorders, for more early hippocampal volume, may affect aggravating Parkinson's disease with depression, so through the analysis of local structure, understanding, better to understand, judge, so as to better prevention and control of the condition.

The role of the 2.5-volt accumbens (nucleus accumbens, NAc) in PDD

NAc is in the lowest part of the striatum, connected to the limbic system, and its role in emotion, reward and motivation are focused. As the primary projection neurons in the NAc and the dorsal striatum, multiple spine neurons (MSN) may have functions related to stress and depression. Dopamine is the main neurotransmitter in the NAc, and the amygdala-basal ganglia-prefrontal cortex circuit has regulatory functions that together form part of the brain circuit to serve emotional and behavioral emergence, especially in some of the most common and serious mental disorders, such as depression. Zhang Y [39] And others found different pathway between parafascial (PF) thalamic subgroups projected to the caudate nucleus (CPu), subthalamic nucleus (STN) and nucleus accumbens (NAc), including PF projection to NAc circuit inhibition will induce similar inhibition, thus found that the activation of NAc projection PF neurons rescued the depression-like phenotype, therefore, targeting PF thalamic circuit may be a feasible solution for the treatment of PDD.

4. Conclusion

With the development of medical technology, the continuous and deep understanding of PDD is no longer limited to a single biological mechanism to explain and participate in the process of its treatment. We can intrinsically connect from the brain tissue structure itself, To explore the associated possibilities of the disease itself, But based on the understanding of brain function, We are still mostly based on imaging studies, The relevance of intrinsic neural pathway mechanisms needs to be further confirmed and explored, This is supported by a lot of experimental data, We need to dig very hard, Of course, about the understanding of limbic systems about the related aspects of PDD, And the effectiveness of its participation in treatment needs more data to support it, But, on the better hand, We have the hope to break through these difficulties to test our conjecture and assumptions step by step, But the disadvantage is that we still can only rely on the imaging technology to assist the support, So how to find more biological targets, To accelerate our progress in treating PDD, Treat more patients, Prolonged quality of survival, Is a work that we need to do urgently right now, In addition to the symptomatic-treated antidepressant medication, How, through the target-site mechanism, The combination of TCM with syndrome differentiation is also an urgent problem to be solved at present. Therefore, the future of the development of multivariable, multimodal biomarkers, including the cingulate cortex, is bright.

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