MDD And Structural Change in Hippocampus and Mpfc

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Abstract: MDD (major depressive disorder) is a serious, often chronic, and disabling mental disorder, which affects various brain areas. MDD is characterized by at least two weeks of pervasive low mood, low self-esteem, and loss of interest or pleasure in normally enjoyable activities. Stress model including chronic stress and early life stress could be the trigger for MDD and neurotransmitter disorder theory is the mainstream explanation of the disease. MDD would cause disfunction of the brain from different aspects. The MDD mainly affect the brain structure by neurotoxic progress, which includes multiple pathways and neurotransmitter causing the brain structural changes. Hippocampus and mPFC are the most common brain areas could be affected by the MDD, the structural changes could be found by fMRI. The review would focus on introducing mainstream models and how they affect the brain structure. At the end, this review would also involve the regular antidepressants and aspects of future study.

1. Introduction

Major depressive disorder (MDD) is a serious, often chronic, and disabling mental disorder. MDD is also known as depression, is a mental disorder characterized by at least two weeks of pervasive low mood, low self-esteem, and loss of interest or pleasure in normally enjoyable activities. Introduced by a group of US clinicians in the mid-1970s [1], the term was adopted by the American Psychiatric Association for this symptom cluster under mood disorders in the 1980 version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) classification, has become widely used since. The MDD patients primarily suffer from a depressed mood for over two weeks, and a loss of interest or pleasure. MDD patients experienced the symptoms, or a period characterized by symptoms of MDD is called major depressive episode (MDE). Most of the experiments are done on MDE patients. Mainstream theories explaining MDD are focusing on changes in brain areas like hippocampus and mPFC. The hippocampus is part of the limbic system and plays important roles in the consolidation of information from short-term memory to long-term memory, and in spatial memory that enables navigation [2]. Hippocampus is also related to rules of rewards, which is related to MDD symptoms [3]. For mPFC, it is part of the PFC. The basic activity of PFC is considered to be orchestration of thoughts and actions in accordance with internal goals [4]. Many authors have indicated an integral link between a person's will to live, personality, and the functions of the prefrontal cortex [5].

2. Current hypothesis about the mechanism of MDD

There are always multiple ways of cause for psychology. Mainstream causes could be divided into two major parts, internal factor, monoamine model and external factors, stress model. The void of monoamine neurotransmitters is widely considered as the main reason causing MDD. Stress model is also considered as another main reason causing structural change in brain areas.

In both hypothesizes, hypothalamic–pituitary–adrenal axis (HPA axis) plays a vital part. HPA axis includes three major parts: hypothalamus, the pituitary gland and the adrenal glands. These organs and their interactions build up the HPA axis, a major neuroendocrine system [6], which controls reactions to stress and regulates many body processes, mood and emotions, the immune system are the major parts related to the cause of MDD. There is a bi-directional communication and feedback between the

HPA axis and the immune system. The HPA axis modulates the immune response with high levels of cortisol resulting in a suppression of immune and inflammatory reactions. The HPA axis in turn modulates the immune response, with high levels of cortisol resulting in a suppression of immune and inflammatory reactions [7]. The HPA axis could modulate inflammatory responses throughout the whole body [8]. During the immune response, proinflammatory cytokines are released into the circulation system. After pass through the blood brain system, proinflammatory cytokines could interact with the brain and activate HPA axis [9]. Interactions between the proinflammatory cytokines and brain can cause dysfunction of neurotransmitters and cause depression-like symptoms such as fatigue, depressive mood [9].

2.1 Monoamine Neurotransmitters

Monoamine neurotransmitters (including serotonin and dopamine) are a vital group of transmitters that are related to motivations and joy. Decrease of motivation and disability to experience pleasure are the major symptoms of MDD.

For the hypothesis of monoamine, the abnormal activation of monoamine oxidase, which degrades monoamines more than regular, would cause MDD.

The hypothesis was first brought up after hypertension patients used reserpine. Reserpine would cause an acute depletion of tryptophan-a necessary precursor of serotonin. Repeating the experiment on animals, model animals would show a lower percentage of sucrose preference and in forced swimming experiment has lower motionless time. Both results indicate that the model animals are experiencing MDE. The result suggests that the lessen of 5-HT is one of the major reasons of MDD.

According to a research animal with smaller locus coeruleus size, observed obvious MDD symptoms like lower percentage of sucrose preference and in forced swimming experiment has lower motionless time. The activity of tyrosine hydroxylase decline, which leads to decline of the dopamine. So, the lack of pleasure would occur. The above evidence concludes that the decrease of adrenergic neurotransmission in depression [10].

Mainstream treatment for MDD may not be effective for some patients, the depression is called treatment resistant depression (TRD). In TRD patients, the raise of concentration of monoamine in the synapses would not work effectively. According to the results of MRI, both MDD and TRD has same outcome, the volume of hippocampus and mPFC decreases. The results indicate that both of disease share a same neuro mechanism. Clinical and preclinical data leads to a model [11], which illustrate chronic/severe life stress could trigger MDD, also the volume decreasing in both brain areas.

2.2 Stress Model

The stress model explains the role of chronic stress and neurotoxic processes on reduce of brain volumetric and MDD illness progression. Chronic life stress could trigger the initial development of hippocampus and mPFC volume reductions. On the other hand, stress also initiates a set of neurotoxic processes (hypothalamic pituitary adrenal (HPA) axis dysregulation, inflammation, neurotransmitter disturbances) that interact and may drive the development of a more chronic type of MDD marked by further reductions in hippocampal and mPFC volume reductions [12]. Also, several monoamine neurotransmitters are important in regulating the HPA axis, especially serotonin. This could enhance the relationship between two current hypotheses.

Stress would also initiate other neurotoxic processes. The development of both pathologies could lead to chronic type of MDD, which was marked by further reductions in hippocampus and mPFC volumes.

3. Structural Change and Causes

According to a meta-analysis examining clinical predictors of hippocampal volume in patients with MDD [13], compared with healthy controls, MDD patients show reduced hippocampus and mPFC volumes. This section would focus on different causes for volume reduction in MDD.

3.1 Structural Change in Hippocampus and mPFC

The Hippocampus is related to the recall of memories and rules of rewards [3]. The meta-analyses show that compared with health controls, MDD patients have a smaller hippocampus [14]. In stress model [11] and other evidence shows that stress can cause neurotoxic process though HPA axis [15]. Thus, hippocampus volume reduced occurs. An fMRI study indicates [16] MDD patients have less brain activities. In general, decrease volume of hippocampus and reduced functional activity would cause negative emotion and inability to feel pleasure and negative emotion.

Based on previous reports, changes in mPFC have been considered as the most common region which have abnormal anatomic abnormity in MDD. Owing to fMRI study, mPFC activities decrease as MDD develops. The mPFC plays an important role in emotional, motivational, and attentional functions [17]. The volume of mPFC decreases compared with health control group and would increase after drug treatment [18].

3.2 Stress and Volume Reduction of Hippocampus and mPFC in MDD

Two types of stress-related models have been proposed to explain how stress affect depression. Stress sensitization and stress autonomy models. Both models are focused on MDE since the volume reduction are related with illness duration [19]. The structural reductions are always significantly tied to MDD illness progression markers, especially greater number of MDE, longer illness duration, and treatment resistance. Clinical survey found that, compared with first time MDE patients, MDE patients with prior history have lower chance experience severe stressful life events [20]. In research that support the stress sensitization model, when non-severe life stress occurs in the three months period before the episode, for those patients who has a MDE history, would cause the MDE onset increased in the longitudinal studies. A human study found that a greater number of stressful life events in the three-months prior to an initial MDE was linked to further hippocampal volume reductions in males with a first MDE. The recent study indicates that individuals with a history of multiple MDEs exhibited smaller hippocampal and mPFC volumes, for those patients, less perceived life stress are reported, compared to those with fewer episodes [31]. This concludes that high levels of stress (daily or chronic stress) play an important role in initiating hippocampal decreasing with the first MDE, but for individuals who had previous MDE onset, the relationship may be weaker. Future prospective work is needed to focus on whether hippocampal and mPFC volume decline related to MDD illness progression are linked to stress dependent or independent mechanisms.

3.3 HPA Axis Dysregulation in Stress-Mediated Hippocampal and mPFC Deficits

According to a research, animals with prolonged stress could be found with HPA axis hyperreactivity and depressed behaviors along with hippocampus and mPFC abnormalities [21]. High level of glucocorticoids also shows a trend to cause the neuronal atrophy and dendritic retraction within the mPFC [22]. In a meta-analysis of clinical studies indicate that MDD patients show higher basal cortisol levels [23]. High level of glucocorticoid receptor has been connected to decline of neurogenesis [24]. The analysis highlighted substantial variability in HPA axis functioning in MDD [23]. Among health control and MDD samples, higher baseline of cortisol levels has been linked to smaller hippocampus and mPFC volumes [25]. For stress could initiate HPA axis, the study further the importance of stress of facilitating initial structural damage, rather than the presence of MDD. In addition to these positive findings, the imaging studies in MDD failed to find the relationship between cortisol and structural abnormalities [26-28]. The imaging studies did not take prior life stress into consideration. Moreover, these studies failed to examine the relationships between structural changes and cortisol levels vary during the MDD illness progress. Brain structural deficits may appear after stress exposure, further studies should focus on linking distinct cortisol trajectories with different life stress profiles and illness progress. This would clarify potential HPA axis-related mechanisms which leads to structural deficits of hippocampus and mPFC in MDD.

3.4 HPA Axis and Volume Reduction of Hippocampus and mPFC in MDD

Research treating animals with prolonged stress could lead to depressive behaviors [21]. The research also indicates that prolonged stress could cause HPA axis hyperreactivity, which leads to overreaction of neurotoxic process. The major neurotoxic pathway is that chronic stress triggering HPA axis dysfunction and enhanced production of cell-mediated immune cytokines, which activate indoleamine 2,3-dioxygenase (IDO) [29]. In the neurotoxic process, the IDO plays a role of an enzyme that catabolizes precursor of serotonin, causing 5-HT depletion. IDO would also product neurotoxic metabolites, the neurotoxic production would upregulate oxidative stress. As a result, the pathway may trigger hippocampal and mPFC cellular damage and volume reductions [30]. For MDD patients, stress could trigger the pathways and produce further brain structural decline. Additionally, as inflammation is enhanced, the production of IDO would drive depressive behavior.

Furthermore, the HPA axis itself, could excrete glucocorticoids when modulating stress reactions. Exposed to high concentrations of glucocorticoids would cause deficiency of hippocampus. This helps to protect the organism from a lethal overactivation of the immune system and minimizes tissue damage from inflammation [7].

3.5 Monoamine and Volume Reduction in MDD

Neurotransmitter disturbances are considered prominent pathways to illness progression in MDD. Few studies have examined associations between the volume reductions and monoamine system dysfunction. But for common antidepressants could increase the volume of two certain brain area, this could be another point for the study. Most studies are focused on serotonin receptors and transporters, which is the main target for medicine treatment of MDD. At the same time, meta-analyses failed to find significant alterations in serotonin transporter binding or availability in the hippocampus and mPFC in MDD [32]. For further research, more studies should focus on clarify which serotonergic disturbances are consequences of stress that do not necessarily lead to MDD

4. Mainstream Treatment

The most popular treatments are focused on serotonin deficiency doctrine. There are two major ways for antidepressant drugs. The first type is to raise the concentration of monoamine in the synaptic. The concentration of serotonin in the synaptic in determined by SERTs and the MAOs. SERT stands for recombinant serotonin transporter, MAO stands for monoamine oxidase. They both play a vital part in the serotonin deficiency doctrine. The SERT and MAO work together to reduce the concentration of serotonin in synapses.

Therefore, first one of the options is to inhibit the SERTs, like Amitriptyline, the SERT inhibitors focus on different transporters. After inhibiting the SERTs, the transporters could not transport the serotonin back into the cell, in order to raise the concentration of the serotonin. And another one is the MAOIs [28], like Moclobemide, which inhibit the degradation of the 5-HT.

For most TRD cases, the cause of TRD would normally be chronic life stress. TRD patients may have more significant change in hippocampus and mPFC [11]. Treatments for TRD would be focusing on initiating regular discharge of brain cells. Like transcranial magnetic stimulation (TMS), TMS uses short, magnetic pulses to stimulate nerve cells in the parts of the brain believed to be involved in regulating mood and emotions.

5. Conclusion

The review states the basic information of MDD and relevant brain areas. Stress model and lack of monoamine are the most mainstream explanation of MDD. In stress model, the HPA axis and neurotoxic processes determine the progress of MDD, and the production of neurotoxic processes would directly lead to depressive behaviors also causing the reduction in volume of hippocampus and mPFC. For monoamine deficiency hypothesis, scientist focusing on both the neurotransmitter itself, enzymes and transporters are also the target of current studies. Though finding relationship between

downregulation of monoamine transporter and depressive behaviors in animal, literatures have also demonstrated clear pathways to monoamine dysregulation within specific brain regions that are linked to depressive behaviors, human imaging findings in MDD have been more complicated. Evidence indicates that decreased monoamine receptor mRNA levels within hippocampus with MDD compared with health control group. But few studies focus on associations between hippocampus and mPFC volume reductions and monoamine system dysfunction. Current treatment for MDD would cause volumetrically increase of hippocampus and mPFC. Treatments could also downregulate the response of the HPA axis. The result could be a starting point of studying relationship between monoamine system dysfunction and volume reduction of hippocampus and mPFC.

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