Brain imaging genetic study on mental retardation and cognitive impairment in depression

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Abstract: Depression is a disease mainly clinically characterized by persistent low spirits, accompanied by mental retardation, loss of interest, cognitive impairment and related physical discomfort, such as sleep disorders, fatigue, loss of appetite and other symptoms. In this study, we discuss the cognitive deficits of depression from the perspective of brain imaging genetics of mental retardation and cognitive impairment in depression, and illustrate the abnormal macro-brain activity and micro-molecular markers behind the cognitive deficits. In future research, genetic and neuroimaging methods should be expanded, emphasis should be placed on the measurement of environmental factors, and the pathological model of depression should be constructed by integrating genetic, neuroimaging and environmental variables. Furthermore, the subtypes of depression were classified, providing a scientific basis for in-depth understanding of the pathogenesis of depression and individualized diagnosis and treatment.

1. Introduction

Depression is a common and life-threatening chronic disease. The prevalence rate of depression is about 10%, and 15% of patients with depression commit suicide [1]. The World Health Organization predicts that by 2020, depression will become the second leading cause of non-aging death and disability and will rank second in the global disease burden. In order to effectively prevent and treat depression [2], people have been exploring its highly consistent pathophysiological mechanism. In recent years, studies on depression in China and abroad have shown that patients with depression have significant cognitive impairment, especially the reduction in executive, control, attention and memory functions [3], and executive dysfunction in the frontal lobe is one of the main manifestations of depression combined with cognitive dysfunction.

Studies in China and abroad have shown that patients with depression have structural and functional abnormalities in the prefrontal cortex, cingulate gyrus, thalamus, and hippocampus, as well as significant cognitive impairment [4–5]. Decreases in executive control, attention, and memory functions were most significant. Executive dysfunction in the frontal lobe is one of the main manifestations of depression combined with cognitive dysfunction. However, the results of related studies on the brain functional areas of cognitive dysfunction in young people after the first episode of depression have not yet been conclusive.

Given that genes indirectly affect behavior by affecting the structure and function of the nervous system, these neural structures or functions regulated by genes can be called intermediate phenotypes [6]. Compared with disease phenotypes, intermediate phenotypes have a more direct genetic basis and thus have higher sensitivity in genetic association analysis. with the help of neuroimaging technology, more and more studies have explored the genetic influence by using neural structure and function as intermediate phenotypes, and image genetic methods have emerged.

2. Image genetics method

Image genetics is a new research paradigm that combines heredity and neuroimaging, aiming to investigate the effects of genetic variation on brain structure and function through neuroimaging indicators. Commonly used imaging methods include functional magnetic resonance imaging, electroencephalogram positron emission computed tomography, etc. Most of the genetic variables

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are candidate genes related to neural activity.

At the neural level, patients with depression have structural and functional abnormalities in multiple brain regions involved in emotional processing, including the amygdala, anterior cingulate gyrus, medial prefrontal cortex, dorsal lateral prefrontal cortex, and hippocampus, thalamus and other subcortical regions [7]. At the molecular genetic level, neurotransmitters such as serotonin, dopamine, and glucocorticoids are likely to play important roles in the pathological mechanism of depression. Behavioral association analysis found that many genes related to the above neurotransmitter metabolism were associated with depression.

Image genetics provides a new perspective for understanding the pathological mechanism of mental illness. First, genetic and intermediate phenotypic (brain) association studies can provide a reasonable mechanism for explaining how genes affect behavior. Second, when the gene locus we studied has a definite function, the locus can provide a molecular genetic basis for explaining individual differences in brain function. Third, studying neural and genetic variables allows us to better integrate with animal model studies (e.g., single cell records, gene knockout, photoperiod inheritance, etc.). Fourth, by focusing on relatively more objective intermediate phenotypes, studies were made less susceptible to disease classification heterogeneity and self-reporting bias.

3. Effects of dopamine system genes on cerebral blood flow and brain function in depression patients with mental retardation

3.1. Dopamine receptor system and depression

Previous studies have shown that depression may be related to the low extracellular level of dopamine. Studies in mice have found that the absence of D3 receptor leads to a significant increase in extracellular dopamine level [8]. In the forced swimming experiment reported in the literature [9], it was observed that mice with D3 receptor deficiency were more sensitive to the effects of antidepressants, suggesting that dopamine at the extracellular level affected the occurrence, development and treatment of depression. In recent years, experimental studies have found that the non-response time of D3 receptor-deficient mice after stress treatment in the tail suspension test is not significantly different from that in the control group ($P > 0.05$), while the non-response time of wild-type mice is significantly changed under the same experimental conditions, suggesting that D3 receptor-deficient mice may have better compressive strength due to the increased extracellular dopamine level.

The density of D1 receptor is significantly increased in the limbic system of rats receiving long-term stress treatment, but it is decreased in rats receiving long-term antidepressant treatment [10], indicating that one of the targets of antidepressants is the D1 receptor, and proving that the D1 receptor is involved in the occurrence and development of depression.

On the signaling pathway, the subunit that significantly correlates with mood disorder is GNβ3, and its 825C/T polymorphism has been considered as a therapeutic target of drugs [11]. Other researchers found low PKA and protein kinase C (PKC) activities when using peripheral blood extracts from patients with depression and autopsy of brain sections, and found abnormally low PKA and PKC activities in patients with severe depression and suicide. These results suggest the dysfunction of classical signaling pathways in depression.

3.2. Interaction between genes and environment

By combining the measurement of environmental factors, image genetic method can deepen our understanding of the pathological mechanism of depression on many levels, that is, to explore which genes influence the onset of depression by regulating the structure or function of which neural circuits under what environmental conditions.

About 80% of patients with depression experience early stressful life events [12]. Genetic polymorphisms associated with functional metabolism such as serotonin, dopamine, HPA axis, BDNF, and NPY affect the structure and function of multiple brain regions related to emotional processing, and most of the genes interact with stress environmental factors. Serotonin pathway-

related genes (5-HTTLPR, HTR1A, MAOA, TPH2, etc.) may affect the function of the amygdala, anterior cingulate gyrus, dorsal anterior cingulate gyrus, and dorsal lateral prefrontal cortex by regulating the level of serotonin metabolism, further affecting the emotional experience, emotional regulation, and executive control functions in negative events. Dopamine-related genes (COMT, DRD2, DRD4, etc.) may affect the structure and function of ventral striatum, nucleus accumbens, frontal cortex and other brain regions by regulating dopamine metabolism, thus affecting the pleasure experience and motivation level. Due to the complex interactions between genes, the actual situation is much more complicated than the above speculation.

4. Genes related to cognitive impairment in depression

4.1. Brain -derived neurotrophic factor gene

BDNF (Brain-derived Neurological Factor Gene) is one of the important nerve growth factors, which plays an important role in neuronal growth, differentiation and maintaining synaptic plasticity in adulthood. BDNF gene is located on chromosome 11p13. Literature [13] used the Merriam-Webster memory scale to test the episodic memory of 641 Japanese schizophrenia patients and families, and found that the A/A genotype of BDNF gene rs6265(G196A) had episodic memory impairment, and even in the healthy control group, the A/A genotype had the worst episodic memory. Recent studies have shown that individuals with the A allele at rs6265 have lower BDNF levels than individuals with the G allele. Animal study has shown that the decline of BDNF level in the brain tissue of mice is related to depression [14]. The above results suggested that the A allele at rs6265 might affect the occurrence of depression through the level of BDNF. On this basis, it is speculated that the A allele at rs6265 site may lead to cognitive impairment in patients with depression by affecting the level of BDNF. Further verification is needed to prove whether damages such as reasoning ability and speech memory are related to rs6265 polymorphism in the future.

4.2. Methylenetetrahydrofolate reductase gene

MTHFR (Methylenetetrahydrofolate Reductase) is an essential enzyme for folate metabolism, which plays an important role in cell division, growth and protein synthesis. MTHFR gene is located at chromosome 1p36.3. The research on MTHFR gene and cognitive impairment in depression mainly focused on SNPrs1801133(C677T). In terms of rs1801133 polymorphism and cognitive function, a study in China evaluated 426 healthy elderly people with the Montreal Cognitive Assessment Scale, and no polymorphism was found related to cognitive function. Both the MTHFR RS180131I (A1298C) C allele carrier and the MTHFR rs2274976(G1793A)G/A genotype individual were found to have impairment of abstract ability.

Among the elderly patients with depression, some studies have also shown a negative result: a study involving 147 elderly patients with depression in China found no association between the rs1801133 polymorphism and cognitive impairment due to depression through the Mini Mental State Scale [15]. In patients with depression, the low level of folic acid is related to the increase of serum homocysteine and the decrease of monoamine neurotransmitter level [16], and the low level of monoamine neurotransmitter is an important reason for inducing depression and cognitive impairment. At present, there is no consistent conclusion about the racial and age differences in the relationship between MTHFR polymorphism and cognitive impairment, and further studies need larger samples and more accurate age division.

4.3. Other genes

CANCNA 1c (calciumvoltage-gatedchannelsubunitalpha1C) is widely expressed in the brain and involves the normal work of many neural circuits. A study used word fluency test to evaluate 40 patients with depression and 40 healthy controls. It was found that the treatment speed of depression patients was significantly decreased, and the one with A allele at rs1006737 locus of CACNA1C gene was the worst. The damage might be related to the activation of left inferior frontal gyrus in depression patients [17].

EPO (erythropoietin) is a glycoprotein mainly synthesized by kidney, which can stimulate and protect the growth of brain, heart, liver and other organs. The study found that EPO injection or titration could improve the visual learning ability of patients with depression [18].

5. Imaging genetics of depression

5.1. Imaging genetics of TPH gene and related brain regions

Tryptophan hydroxylase converts tryptophan to 5- hydroxytryptamine, and its gene is located on the short arm of human chromosome 11 (11p15.3-p14). At present, two subtypes, namely, TPH1 and TPH2, have been found in the study. TPH2 is a protein with high homology with TPH1. TPH1 is mainly distributed in the periphery, and partially expressed in brain regions. TPH2 is only expressed in 5-HT-ergic neurons of the central nervous system, which is the main type of TPH in the brain. Some scholars in China conducted a meta-analysis study on the relationship between the TPH2 gene and affective disorder, and found that the rs4570625 G allele was a risk factor for depression [19].

5.2. Imaging genetics of 5-HT1A gene and related brain regions

5-HT1A receptor is mainly distributed in dorsal raphe nucleus, hippocampus, frontal cortex and other regions. The density of 5-HT1A receptor in the raphe nucleus is higher than that in the non-depressed population, which may lead to the reduction of the functional activity of the 5-HT system and the content of 5-HT, leading to the occurrence of depressive symptoms. The 5-HT1A gene promoter with 5-HT1A rs6295 polymorphism accompanied by higher expression of 5-HT1A receptor increases the prevalence of depression, and it is as high as four times in suicide patients.

Carriers of the 5-HT1A (rs6295)C allele have been found to have small hippocampus volumes. In the study on the relationship between the amygdala and genes, a total of 27 depression patients were selected in the literature [20] to observe the amygdala response in the face of joy, sadness, and anger, and the results showed that the activity of the amygdala in people with G allele was significantly increased. In the normal population, however, G-allele carriers showed reduced amygdala activity in the face of fear. This may suggest that the alleles of the same species work in the opposite direction in normal and depressed patients.

5.3. Imaging genetics of MAOA gene and related brain regions

Monoamine oxidase A is present in astrocytes and neurons and is an enzyme that promotes the catabolism of serotonin, dopamine, and norepinephrine. MAOA, located on the X chromosome and in the short arm of X 11.23–11.4, has a polymorphism of -30bp variable number tandem repeat (u-VNTR) in its promoter region and is able to selectively affect protein transcription and thus enzyme activity.

The prevalence of depression in female patients is higher than that in male patients, so studying the candidate gene on X chromosome is of unique significance. Literature [21] has studied whether different alleles of MAOA have effects on brain function, and healthy female population with 3R/3R genotype showed increased hippocampal activity in the face of fear face. Literature [22] Researchers have found that compared with patients carrying a low-activity L allele (MAOA-L), in the face of negative emotions, patients with depression carrying a high-activity H allele showed increased activation of brain regions in the middle frontal gyrus and left inferior frontal gyrus. The above studies have shown that the polymorphism of MAOA gene can affect the functional activities of brain regions and neural circuits for emotional regulation, and thus affect the regulation of negative emotions by individuals, thus increasing the susceptibility to emotional disorders and suicide.

6. Conclusions

Gene imaging can use brain structure and function imaging technology to explore the relationship between gene polymorphism, brain structure and function, and behavior, revealing the

potential neurobiological basis behind complex behaviors from the "gene-brain-behavior" model. There are many studies on the correlation between dopamine receptors and depression, but many problems remain to be further studied and clarified. The correlation between depression and dopamine system is complex, and there are many unknown areas to be explored. At present, the most studied ones are still focused on the classical dopamine pathway and the targeted therapy for depression. However, with the deepening of the study, the relationship between the two will gradually uncover the mystery. In the future studies, specific or combined treatment regimens (such as medication, psychotherapy, and brain stimulation) can be formulated for abnormal biological markers, a large number of clinical samples can be collected for machine learning training and testing, and the optimal therapy suitable for specific populations can be explored to achieve individualized diagnosis and treatment from subjective to objective.

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