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The role of glial cells in schizophrenic brain

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Abstract. Schizophrenia, as a complex neurological disorder, has many distressing symptoms such as hallucinations and some of the common mood or cognitive disorders commonly associated with mental illness. Once suffering from schizophrenia, people's work and life will be greatly troubled. It is also often associated with other psychiatric disorders, which makes it extremely difficult to treat clinically. However, a diverse of different studies have been able to identify a clear link with neurotransmitter signaling pathways and some brain activity, such as dopamine projection pathways and a significant reduction in gray matter in patients. This research will focus on another dimension, namely the reduction of gray matter volume, to investigate the relationship between oligodendrocyte and astrocyte function and schizophrenia, in an attempt to provide a new vision for the clinical treatment system. In addition, it is expected that this research can also provide a new idea for the development of new drugs for schizophrenia.

Keywords: glial cells, astrocytes, oligodendrocytes, schizophrenia.

1. Introduction

Schizophrenia is an extremely complex psychiatric disorder. There have been many hypotheses as to its cause, such as serotonin dysregulation and glutamate dysregulation and the most widely known dopamine hypersensitivity reaction. The symptom of schizophrenia is mainly dependent on individual, but there are also some traits that are common to see in this mental disease. There are positive symptoms including delusion, hallucinations and illusions, disordered thinking or behavior, phobia, and negative's such as diminished emotional expression (happiness and excitement), agitation, inappropriate reactions, interest in activities or motivation to do anything, unwilling to communicate. For example, disordered speech or thinking is an vary common symptom, which is mainly noticed by disorganized speech. However, the symptom of teenagers is difficult to notice, although it is quite similar to that of adults. And the symptom in teenagers is mainly: lack of motivation, self-isolation (reduced contact with other individuals), long lasting sadness, and so on.

The absence of deficits in the response following arousal of emotional stimuli in the experimental condition is a consistent finding in reports from past studies of schizophrenic patients with deficits in emotion in this century [1]. In addition, individuals with or without the disorder expressed consistent levels of self-reported startle when presented with emotional pictures. However, the responses of healthy controls were maintained after removal of the stimuli from the visual field, but no longer sustained in patients with schizophrenia. After a study using MRI for imaging shadows in the brains of schizophrenic patients, it was found that the gray matter volume in their brains was significantly

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reduced throughout the brain, but the white matter volume remained largely normal. These changes also varied by gender. In common, both males and females had a reduction in the volume of the dorsolateral prefrontal cortex, but the significant difference was that males had a greater reduction in the volume of the dorsomedial prefrontal cortex than females. Also, the mean midbrain volume was smaller in male schizophrenics than in female controls. Only one study found that the reduction in total brain volume was limited to gray matter compared to controls, and there was no relationship between brain volume and specific deficits in patients with schizophrenia. In the case of the parahippocampal gyrus (PHG), although the PHG is not volumetrically abnormal, it appears to have many associations with schizophrenia-specific cognitive functions.

There are a large number of glial cells in the brain and they are 10 to 50 times more numerous than neurons. The most abundant glial cells in the brain are astrocytes, which regulate chemicals in the extracellular space and are involved in the formation of the blood-brain barrier. Another very important type is the oligodendrocyte, which forms myelin sheaths in the central nervous system and is able to communicate with immune cells, causing them to change their behavior. These two types of glial cells do not successfully differentiate in the brain of schizophrenic patients. Imaging and postmortem studies have demonstrated a disruption of the myelin sheath itinerary in the brain of schizophrenic patients which is likely a reflection of a failure of maturation and impaired regeneration of a few glial cells. Oligodendrocyte precursors can form synapses with interneurons and the integrity of these synaptic connections is extremely dependent on cognition If there is interference between these connections it is likely to be the cellular basis of mental illness. Oligodendrocyte precursors can form synapses with interneurons and the integrity of these synaptic connections is extremely dependent on cognition If there is interference between these connections it is likely to be the cellular basis of mental illness.

Astrocytes play a key regulatory role in early neurodevelopmental processes and any impairment in their morphological and functional maturation may lead to abnormalities associated with the pathogenesis of schizophrenia. Schizophrenic patients show a heterogeneous increase in the level of glial cell material in the brain, with astrocyte hyperplasia in 70% of patients. Excess astrocytes may trigger alterations in components of the extracellular matrix system, which may cause inflammation and participate in the function of the neurotransmitter system (glutamate). Glutamate activates interneurons, and the glutamate transporter in the brain of schizophrenic patients presents a lower expression. The previously mentioned symptoms are all negative and consist mainly of reduced or absent emotion-related functions for which effective treatments are currently in place to alleviate the symptoms. There are four main treatment modalities, of which medication is the most effective. Psychological treatment is usually combined with pharmacological treatment. However, hospitalization and ETC are the last two options because they can produce significant results but there are safety risks. Currently, the main treatment for schizophrenia relies on psychotropic drugs (e.g. haloperidol, fluphenazine and chlorpromazine), but these drugs are usually associated with side effects and only reduce the positive symptoms of the disorder. Figuring out the molecular mechanisms by which these psychotropic drugs work in the brain will be a key breakthrough point in improving this situation. In this regard oligodendrocytes are an important structure to find new therapeutic targets to make disease research more comprehensible and potentially develop novel treatments.

The research will discuss the differentiation of oligodendrocytes and astrocytes and the generation of their functions and the neurotransmitter pathway signals that may be involved in these processes. Then, the research will also talk about separately the relationship between the two types of glial cells and the main variant genes of this disease. There is also a review of the current main approaches to treating schizophrenia and an attempt to compare the brain complement activity before and after treatment to discover their more precise activity and role in the brain, afterwards identify new therapeutic targets that could provide new perspectives for future research.

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2. Brain activity of schizophrenic patient

Currently, imaging techniques such as CT and MRI have been wildly used to infer the structural and functional changes in the brain by scanning and imaging the brain at different periods of time. As shown in Figure 1, this image can refer to the volume and shape of regions of the brain, so that enabling modules and analysis to be carried out in order to observe the brain activity of a schizophrenic brain. It shows that the effects of schizophrenia on the brain are very widely distributed, both structurally and functionally [1]. These alterations of the structure of brain is mainly overlapped with where were the pathway of dopaminergic projection, which may be responsible for the hallucinations experienced by patients. Scanning the brain from two different aspects reveals that the functional and structural alterations do not coincide at the same point in the brain. For example, in the occipital lobe, only functional changes are observed and no structural changes occur, in addition to one area of the brain, the cerebellum, which does not appear to be affected by any functional or structural changes. This also corresponds to the fact that schizophrenic patients do not have motor dysfunction. However, this is sufficient to show that the dopamine projection pathway as the main therapeutic target is not sufficient, because there are many brain areas other than the areas through which dopamine projection (such as parietal lobe and the occipital lobe) occurs that are altered in the schizophrenic brain.

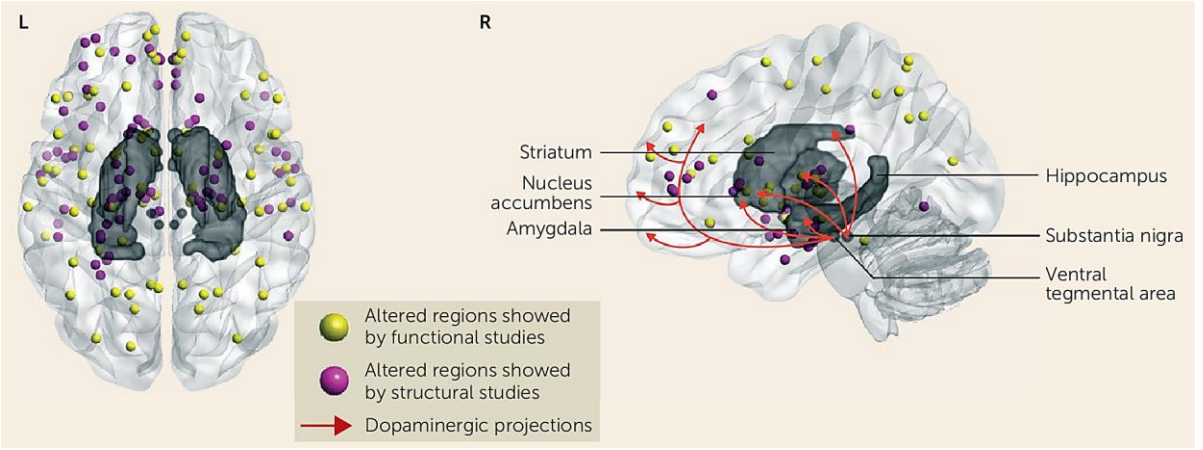

Figure 1. An image of the brain of a schizophrenic patient through MRI from both a horizontal view and a sagittal view [1].

3. The role of oligodendrocytes

Typical functions of oligodendrocyte myelination are to enable action potentials to be generated during sheath-like axons [2]. Furthermore, they are also involved in functions such as axonal metabolism, support and information processing. Oligodendrocytes are value-added cells capable of migration before they mature. Their large amount of value-added gives them the ability to express more myelin-associated proteins upon maturation. Myelin-associated proteins which be expressed by the oligodendrocytes including proteolipid protein (PLP), myelin basic protein (MBP), myelin OL glycoprotein (MOG), and myelin-associated glycoprotein (MAG). MBP and the PLP are crucially important because they can help with the stability of myelin sheath by enhancing its adhesiveness. Oligodendrocyte lesions may be the cause of phantom hearing in psychiatric patients. Abnormalities in the central myelin sheath can lead to signs of auditory neuropathy.

In order to analyze auditory information processing in adult brains with impaired oligodendrocyte function, three different degrees of myelin dysplasia in mice were compared using an acute porosimeter. Two different strains of mice with mutations in Mbp (MBP is a protein that is required in the process of myelin growth and compaction) were compared. One type is CNS with almost complete deletion of myelin (Mbpshi/shi), and this type of mouse has a truncated Mbp gene. The second type of mouse has only less than 50% of the level of MBP expression (Mbpneo/neo). The last model has

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myelin but shows a defect in metabolic support of oligodendrocytes in axons. This mouse lacks metabolic support for the axon of the Slc16A1 gene (Mct1/-) heterozygous null mutant showing the process of the monocarboxylate transporter protein MCT1 been expressed [3], as shown in Figure 2. The auditory nerves in the brains of all Wt mice were free of problems. Projections and myelin were also free of abnormalities, except for specific nerves. In Mbpshi/shi mice, the response thresholds in controls were consistent with their presentation. All central auditory stations showed a noticible display of ABR waves, and the delay gradually increased. However, cochlear function was not abnormally expressed in Mbpshi/shi mice nor in peripheral conduction, due to the formation of myelin by chevron cells in the external region of the auditory nerve, which does not require the involvement of MBP. However, both the loudness from waves II and III tended to decrease (showing by lowered amplitude), while waves IV and V showed the opposite result of a slight increase in amplitude. This downstream compensation of reduced brainstem ABR amplitude suggests a mechanism of compensation of hearing loss for changes in peripheral nerve gain. Another similar aspect is in the hearing threshold. It is suggested that central myelin dysplasia can lead to only minor lesions of the auditory nerve.

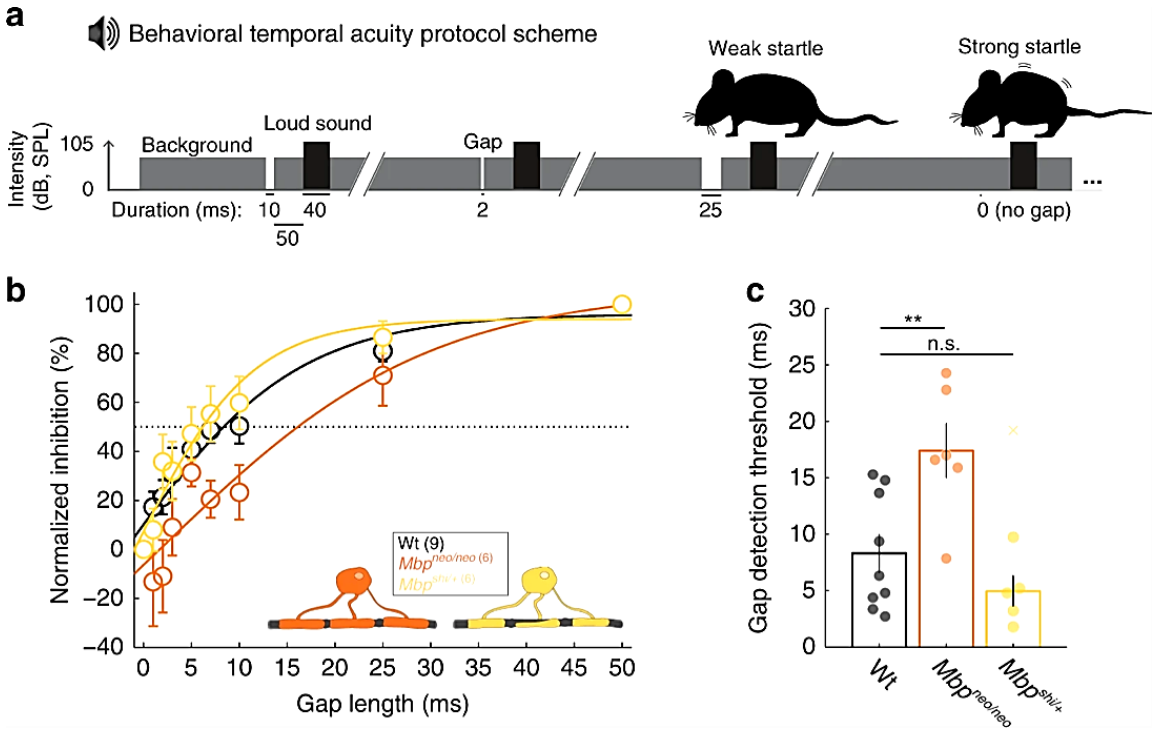

Figure 2. Measurement of the activation of a series of brain structure by using a five-wave auditory brainstem response [3].

4. Unfavorable myelin formation

The ability of the nervous system to conduct sound correctly without error and to maintain this accuracy while focusing to a non-stopped stream of sound is fundamental and critical for auditory coding as well. By placing tungsten electrodes in primary auditory cortex IV recordings in mice, the function of myelin during the analysis of time-related information was examined in relation to oligodendrocytes. In Mbpshi/shi mice, altered distribution of Kv channels in axonal excitatory domains (dispersed along the internode and overexpressed in Mbpshi/shi) can be used to explain the deficits in temporal reliability can. The slowed nerve conduction velocity in the brain of mutant mice is proportional to the level of myelin formation. A large amount of potassium ions flux into the optic axons leads to energy loss (due to ATP depletion associated with repolarization), consequently make the less reliability of temporal processing. This phenomenon supports mutated axons having irregular

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control of ions fluxing. The following important point of auditory information storage is temporal acuity. The ability to perceive and identify short silent intervals while receiving the disturbance of white noise in human speech processing is also significant. Such small gaps are not perceived by cortical neurons in Mbpshi/shi mice. A temporal acuity deficit reflecting impaired levels of myelin formation was observed in Mbpneo/neo mice. mct1/-mice also showed a gap detection deficit. This may be because poor metabolic function of glial cells on specific sites of the axon may affect the loss of temporal lobe acuity.

Some observed phenomenom of differences performance of baseline in mice had been certain. Myelin dysplasia (Mbphi/shi and Mbpneo/neo) and metabolic defects (Mct1/-) from incomplete axonal glial cells were found to cause tiredness to cortical auditory loud compared to Wt littermates. In the absence of impaired myelin formation, this will cause a disruption of glial lactate output. This would thereby cause an energy deficit in axons and a failure of conduction in the auditory pathway during repetitive neuronal firing. In the Mbpshi/shi mouse mutant, there are other factors like redistributed ion channels that may also contribute to this condition.

5. Astrocyte-related functions in schizophrenia

The glutamatergic neurotransmission is primarily controlled by the astrocytes. The glutamatergic hypothesis of SZ suggests that SZ-related symptoms underlie NMDAR hypofunction in the prefrontal cortex and other distinct brain areas, as well as a range of types of specialized cells [4]. Hypofunction is caused by an imbalance in neurotransmitter action, which may result from abnormalities in NMADA receptors and GABAergic neurons. The percentage of astrocytes in the cerebral cortex that undergo upregulation of gene expression is highest compared to the entire rest of the brain, as has been tentatively demonstrated by evidence from genetic testing.

Abnormal astrocyte function undergoing synaptogenesis and synaptic elimination would be a key to studying schizophrenia [5]. On the basis of diminished volume of prefrontal gray matter is proved highly attached to schizophrenia, reduced synaptic density, and hypoconnectivity in different brains [6]. This leads to the conclusion that excessive synaptic elimination is extremely likely to be a potential cause of schizophrenia, or too little synaptic formation. Therefore, a potential reason for the increased probability of developing schizophrenia is that altered astrocyte activity leads to excessive elimination of synapses during human brain development.

New evidence suggests that during synaptogenesis and synaptic elimination, where in many pathways in the brain can found that astrocytes release a number of synaptogenic factors that play a regulatory role [3]. In experiments using mice as a model, one of the identified synaptic factors is FABP7, which plays an extremely important role in the formation of new synapses in the medial prefrontal cortex (mPFC) [5]. Animals that do not have the ability to communicate verbally have significantly lower FABP7 complexity, density, and spinal maturation, and show a strong correlation with behavioral deficits associated with SZ and related disorders. Astrocytes can facilitate synapse elimination in a Ca2-dependent manner, although the cellular mechanisms have not been precisely identified.

Astrocytes can mediate several classified mechanisms of synapse elimination. First, they can act through phagocytosis. This includes phagocytosis stimulating the activation of receptors in astrocytes, as well as mer receptor tyrosine kinase (MERTK) and multiple epidermal growth factor-like structural domain protein 10 (MEGF10). In addition, in the second mechanism, astrocytes build synapses through the self-produced cytokines interleukin 33 (IL-33) and transforming growth factor-β (TGF-β) [5]. The third one corresponds to a series of waterfall responses induced by astrocytes. In the first step it activates the endomyosin-1,4,5-trisphosphate (IP3) pathway thereby releasing calcium ions from organelles such as the endoplasmic reticulum [5].

6. Treatments

There are many measures nowadays seem to be effective to some extend to treat the symptoms of schizophrenia, even though no ultimate cure appeared to any. As a matter of fact that resistance to drug

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are easily to be developed alike other diseases. Since schizophrenia are an extremely complex neurological disease which come across few path ways and various regions in the brain, patient is usually been suggested to undergo multiple combinations of treatments simultaneously, including pharmaceutical, electroconvulsive therapy, deep brain stimulation and psychological.

Pharmaceutical are very acceptable treating measure among all treatments, but it still remains obvious limitations. Although there have been many advances and hypotheses in the study of schizophrenia, the etiology has never been clear enough, which has led to medications that only have the effect of reducing symptoms. Current medications are mainly antagonists of various hormones or neurotransmitter receptors, such as dopamine and glutamate. As a result, the body tends to habituate to the drug, and the therapeutic effect often stops after a certain point. Studies have also shown that gray matter in the dorsolateral prefrontal cortex and temporal lobe is reduced after taking antipsychotics, and the volume of the hippocampus may also be reduced, suggesting that antipsychotics may have potential side effects that impair cognition as well as memory [6]. The differences in the white matter of the treated brain were not as pronounced as the differences in the gray matter, but they showed the same tendency to exhibit certain areas.

Unlike the previous focusing points, target to increase the volume of glial cells onto a normal level may be a novel treating method [7]. Because myelin has been shown to affect auditory pathways, the number of myelin-forming oligodendrocytes is critical. More importantly, they are more distributed in all the brain, instead of majorly in the prefrontal cortex. A decrease in the number of oligodendrocytes in the brain of schizophrenic patients may lead to auditory problems, and this may be reflected in some of the positive symptoms that are already present, such as hallucinations. However, if the number of oligodendrocytes can be maintained, the symptoms of hallucinations in schizophrenic patients may be well improved.

Dopamine is by far the neurotransmitter that has been given the most attention when it comes to developing drugs [8]. It is also the pathway that presents the most significant abnormalities in the brains of schizophrenic patients, but its effect on the number of glial cells is not significant. However, glutamate excitotoxicity can easily affect glial cells and lead to lesions in the white matter of the brain, so if drugs could be developed to protect glial cells from this toxicity and thus reduce white matter damage, then schizophrenia would be effectively improved [9]. In contrast, the cardiac glial cell packet is imperative both in the transmission and regulation of glutamatergic neurotransmitters, it also plays a significant role in getting along with connection and elimination of synapses. Many patients with schizophrenia show a lack of synaptic number, which is closely related to the number of astrocytes [10]. If the number and activity of cardiac glial cells can be maintained at normal human levels, this will reduce the likelihood of developing schizophrenia or other disorders.

7. Conclusion

This research analyzes the role of glial cells in schizophrenic brain. A series of experiments with mouse models demonstrated the close association between glial cells and various symptoms of schizophrenia, in which the neurotransmitter regulation and synaptic deletion of the glutamatergic pathway in star glial cells and the myelin formation in oligodendrocytes are all critical. Because of a considerable amount of decrease of glial volume in the brain of schizophrenic patients, there is also a deficit amount glial cells in the brain of schizophrenic patients. According to previous studies, both oligodendrocytes and astrocytes are essential building blocks of neural structures in the brain, and their lack of function is therefore an important potential cause of schizophrenia. Oligodendrocytes play a vital role in the formation of myelin sheaths and in the reception and processing of auditory information by the individual. If there is a major breakthrough in the treatment of schizophrenic patients at the level of maintaining glial cells, the symptoms of hallucinations may be greatly alleviated, even in other psychiatric disorders that may cause hallucinations.

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