

The role of the cerebellum in schizophrenia: from cognition to molecular pathways

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Beside its role in motor coordination, the cerebellum is involved in cognitive function such as attention, working memory, verbal learning, and sensory discrimination. In schizophrenia, a disturbed prefronto-thalamo-cerebellar circuit has been proposed to play a role in the pathophysiology. In addition, a deficit in the glutamatergic N-methyl-D-aspartate (NMDA) receptor has been hypothesized. The risk gene neuregulin 1 may play a major role in this process. We demonstrated a higher expression of the NMDA receptor subunit 2D in the right cerebellar regions of schizophrenia patients, which may be a secondary upregulation due to a dysfunctional receptor. In contrast, the neuregulin 1 risk variant containing at least one C-allele was associated with decreased expression of NMDA receptor subunit 2C, leading to a dysfunction of the NMDA receptor, which in turn may lead to a dysfunction of the gamma amino butyric acid (GABA) system. Accordingly, from post-mortem studies, there is accumulating evidence that GABAergic signaling is decreased in the cerebellum of schizophrenia patients. As patients in these studies are treated with antipsychotics long term, we evaluated the effect of long-term haloperidol and clozapine treatment in an animal model. We showed that clozapine may be superior to haloperidol in restoring a deficit in NMDA receptor subunit 2C expression in the cerebellum. We discuss the molecular findings in the light of the role of the cerebellum in attention and cognitive deficits in schizophrenia.

KEYWORDS: Schizophrenia; Cerebellum; N-methyl D-aspartate receptor; Gamma amino butyric acid; Antipsychotics.

Yeganeh-Doost P, Gruber O, Falkai P, Schmitt A. The role of the cerebellum in schizophrenia: from cognition to molecular pathways. Clinics. 2011;66(S1):71-77.

Received for publication on March 2, 2011; Accepted for publication on March 3, 2011

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INTRODUCTION

Schizophrenia has a worldwide prevalence of about 1% and mainly strikes young adults between the ages of 20 and 35 years. It is a severe psychiatric disorder leading to lifelong disability in more than 50% of sufferers and therefore constitutes one of the 10 most costly illnesses worldwide.¹ The course of the disease is heterogeneous with approximately 50% of patients requiring one or more readmissions during follow-up. Only 20% of patients will be able to gain full employment and only 30% maintain a stable relationship.²

Schizophrenia has been regarded as a syndrome. In recent decades, symptom classifications have been calculated in four or five main domains. These include positive symptoms with exaggeration of normal function, such as hallucinations, delusions, disorganized speech, and disorganized behavior. The negative symptoms comprise a diminution in mental functions, such as blunting, avolition, alogia, and anhedonia, and a deficit in social interaction.^{3,4} Besides affective symptoms (e.g., depressive mood), another domain refers to cognitive symptoms with declarative episodic and working memory as well as attention, which

possess special relevance for schizophrenia.⁵⁻⁸ Especially persistent cognitive deficits are very reliable predictors of a relapse and therefore an unfavorable long-term outcome.^{9,10} Further concepts of phenotypes include the appearance of neurological soft signs such as dysdiadochokinesis or deficits in motor coordination^{11,12} and eye tracking abnormalities with deficits in smooth pursuit eye movements.^{13,14} However, the pathophysiology of the disease is broadly unknown.

Pathophysiology

The dopamine hypothesis of schizophrenia postulating a dopaminergic hyperactivity in the limbic circuitry is based on the evidence of typical neuroleptics with a D2-dopamine antagonism being effective in the treatment of positive symptoms.¹⁵ The glutamate hypothesis of schizophrenia is based on the observation that phencyclidine and ketamine, which block the ion channel of the glutamatergic N-methyl-D-aspartate (NMDA) receptor and initiate NMDA hypofunction, precipitate psychosis. This psychosis not only models the positive symptoms of schizophrenia, but patients even develop a chronic deteriorative psychosis that resembles the deficit state of schizophrenia.^{16,17}

To date, the prevailing hypothesis of schizophrenia is that multifactorial interactions between risk genes and environmental factors impact both early and late brain developmental changes. Several lines of evidence support this neurodevelopmental hypothesis.¹⁸ In recent years, several

risk genes such as dysbindin, DAOA (D-amino acid oxidase activator), COMT (catechol-O-methyltransferase), and RSG4 and neuregulin 1 (NRG-1) have been identified, each contributing a small amount to the risk of developing the disease. Most of these genes such as NRG-1 are hypothesized to affect the glutamatergic NMDA receptor.¹⁹ Mutations in NRG-1 have been identified on chromosome 8p21 in schizophrenia.^{19,20} In post-mortem studies, several isoforms have been shown to be differentially expressed in schizophrenia, possibly contributing to the pathophysiology of the disease.^{21,22}

Disturbances in neuronal networks

Since the beginning of the last century, schizophrenia has been regarded as a brain disorder. Neurotransmitter hypotheses postulated disturbances in the dopaminergic and glutamatergic system.^{23,24} Structural, functional, and spectroscopic magnetic resonance imaging (MRI) as well as diffusion tensor imaging studies revealed alterations in fronto-temporal-thalamic-cerebellar networks including the heteromodal association cortex and hippocampus with resulting disturbances in macro- and microconnectivity.^{25,26} At the cellular and molecular level, deficits in the number and function of oligodendrocytes and myelin components as well as synaptic proteins are prominent.²⁷⁻³⁰ They may be related to neurodevelopmental disturbances and, in subgroups of patients, an additional non-typical neurodegenerative component. It has been hypothesized that the disorder originates from brain neurodevelopmental neuropathology with symptoms and neuropsychological deficits arising from alterations in precisely defined brain regions or functional neuronal circuits.³¹

The thalamus acts as a central relay station, transferring peripheral sensory inputs to the cortex and receiving projections from the cerebellum. It plays a critical role in filtering sensory information, in regulating cognitive input to the cortex, and in mediating corticocortical connections between areas particularly implicated in schizophrenia, such as the frontal and temporal regions. In schizophrenia patients, positron emission tomography (PET) studies show a dysfunction of the cortico-cerebellar-thalamic-cortical neuronal circuit (Figure 1) contributing to "cognitive dysmetria", i.e., impaired cognition and other symptoms of the disease.^{32,33} the inability to receive and process information rapidly, to retrieve the relevant associated constructs, and to produce a well-modulated and fine-tuned response. Thus, schizophrenia patients have subtle abnormalities of posture, gait, emotional response and expression, and cognitive performance.

Cerebellum and cognition: evidence from schizophrenia

The cerebellar cortex is divided into three different cellular layers containing five different types of glutamatergic and gamma amino butyric acid (GABA)ergic neurons (Figure 2). Inputs to the cerebellum are from excitatory climbing fibers from the inferior olive and from glutamatergic mossy fibers connecting the brainstem and cerebral cortex with the cerebellum via the pons³⁴ (Figure 2). It has been shown that, by connection via the thalamus, the cerebellum innervates not only motor areas of the cortex, but also prefrontal and parietal heteromodal association cortices involved in cognition.³⁵ First insights revealed that the cerebellum is known to be involved in predicting motor

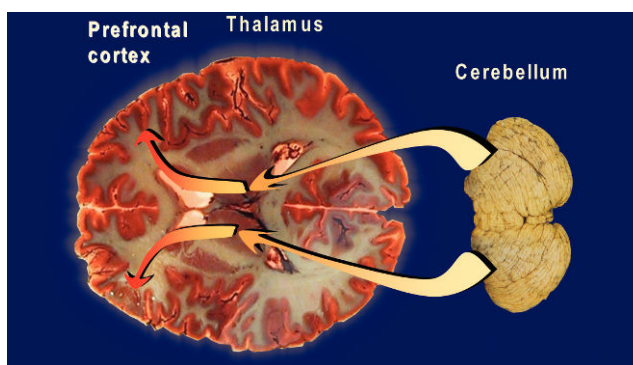


Figure 1 – The connections of the cerebellum. It is projecting to the thalamus and prefrontal cortex. Disturbances of this circuit have been proposed to play a role in the pathophysiology of schizophrenia.

control of movement outcomes.³⁶ After cerebellar damage, neurocognitive symptoms and a cognitive affective syndrome including blunted affect and inappropriate behavior have been shown.³⁷ In addition, lesions of the lateral cerebellum impair cognitive functions including speech, and induce mutism and amnesic aphasia. The right cerebellum, in connection with the dorsolateral prefrontal cortex, is involved in executive and working memory functions, e.g., subvocal rehearsal mechanisms of verbal working memory.³⁸⁻⁴²

In addition, PET and functional magnetic resonance (fMRI) studies have demonstrated the involvement of the cerebellum in different cognitive tasks: sensory discrimination,⁴³ attention⁴⁴⁻⁴⁶ or, more recently, the attentional part of working memory demands,^{38,47} semantic association,⁴⁸ verbal learning and memory,⁴⁹ visuospatial functions,⁵⁰ and complex problem solving.⁵¹ The cerebellum has also been linked to higher order cognitive control processes referred to as executive functions.^{52,53} All these domains are disturbed in schizophrenia patients.⁵⁴ In a series of fMRI and behavioral studies, we investigated the functional integrity of distinct brain systems underlying maintenance-related subprocesses of working memory (articulatory rehearsal, non-articulatory maintenance of phonological information, maintenance of visuospatial information) in patients with schizophrenia and other major psychoses.⁵⁵⁻⁵⁹ By means of circuit-specific experimental paradigms, we were able to provide first evidence for a possible subtype of schizophrenia with a selective dysfunction of the articulatory subsystem of verbal working memory, which functionally involves the cerebellum.^{60,61} Moreover, we were able to show that familial (and probably also genetic) loading impacts on the functional integrity of this articulatory rehearsal mechanism in schizophrenia,⁶² suggesting that selective dysfunction of this mechanism may characterize a schizophrenia subtype with a more homogeneous underlying pathophysiology and genetic etiology.^{60,63}

Brain imaging studies of the cerebellum in schizophrenia

In recent decades, the cerebellum has been implicated in the pathophysiology of schizophrenia, with the cortico-thalamo-cerebellar circuit³³ receiving particular attention. Schizophrenia patients reveal deficits supporting impairment of cerebellar functions: neurological soft signs,

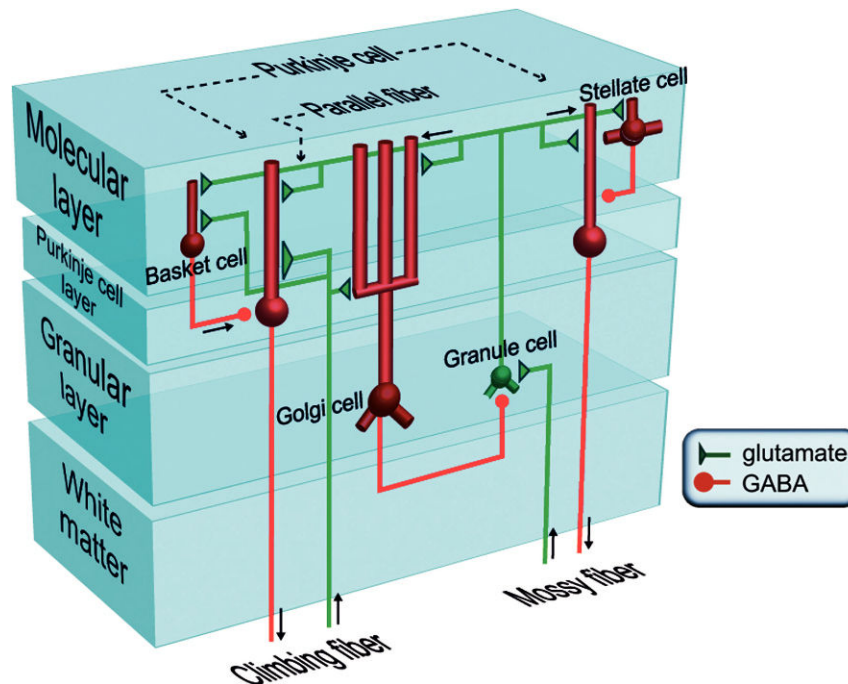


Figure 2 – The cerebellum contains three layers and five distinct types of neurons. Glutamatergic neurons are shown in green and GABAergic neurons in red. In schizophrenia, a deficit in the glutamatergic NMDA receptor may lead to a GABAergic deficit and, as a consequence, to disturbed glutamatergic projections.

dyscoordination, abnormal posture, impaired eyeblink conditioning, procedural learning deficits, and poor cognitive performance.⁶⁴ Neurological soft signs were correlated with reduced gray matter volumes in the cerebellum and related networks.^{65,66} Structural MRI studies revealed decreased volumes of the total cerebellum, left cerebellar hemisphere, and right vermis,^{67,68} as well as correlation of the volume reduction with psychopathological subscores.^{69,70} Evidence from PET as well as fMRI studies investigating resting state or working memory and periodic sequence learning tasks has shown decreased activation of cerebellar subregions.^{54,67,71}

¹H-spectroscopic MRI studies have revealed decreased N-acetylaspartate (NAA) and creatine in the anterior vermis and cortex, pointing to altered neuronal integrity of neurons, dendrites, and axons.^{72,73} Reduction in NAA indicates a loss of functional and structural integrity of neurons, dendrites, and axons. Such neuronal dysfunction may involve a glutamatergic deficit in the cerebellar subregions of schizophrenic patients.

The cerebellar glutamate system and schizophrenia

An NMDA receptor hypofunction has been proposed to play a role in schizophrenia,²⁴ resulting in a final hypoglutamatergic state of corticostriatal projections.^{24,74} The NMDA receptor is composed of different subunits responsible for various functional properties.^{75,76} The obligate NR1 subunit combines two or three NR2 subunits (NR2A, NR2B, NR2C, and NR2D) to form the functional receptor. Studies using brain tissue obtained post mortem have examined the expression of glutamate receptor subunits, and support the hypothesis of a glutamate dysfunction in schizophrenia.⁷⁷

In cerebellar Purkinje and Golgi neurons, all NMDA receptor subunits are expressed^{78,79} and may be altered in

schizophrenia. In the left cerebellum, a study by Akbarian et al.⁸¹ found no differences in NMDA receptor expression. To determine whether NMDA receptor alteration is present in the right and left cerebellar vermis and hemispheres in schizophrenia, we measured NMDA receptor binding and gene expression of the NMDA receptor subunits in a post-mortem study of elderly patients with schizophrenia and non-affected subjects. The results revealed a significantly higher expression of the NR2D subunit in the right-side anterior hemisphere and vermis compared with our group of normal elderly control subjects. In contrast, we found no difference in NR2D expression in the left cerebellar subregions as well as levels of NR1, NR2A, NR2B, and NR2C expression.⁸⁰ These results point in the same direction as increased expression of NR2D subunit in the left prefrontal cortex.⁸¹ In contrast to receptors containing a combination of NR1 with NR2A or NR2B subunits, NMDA receptors assembled from NR1 and NR2D subunits show a prolonged decay rate of glutamate-induced ion currents and a lowered threshold for a voltage-dependent magnesium blockade.^{76,77} This causes “hyperexcitable” counteracting reduced postsynaptic activity. Therefore, increased expression of the NR2D subunit in schizophrenic patients may be interpreted as a secondary regulation to glutamatergic hypoactivity in the right cerebellum.

As the expression of the NR2C subunit has been reported to be regulated by NRG-1 maturing synapses of the cerebellar granule cells,⁸² and thus the NRG-1 risk genotype may alter the expression or function of the NMDA receptor in the cerebellar subregions, we genotyped the samples for the NRG1 polymorphism rs35753505 (SNP8NRG221533). This variant forms part of the previously reported risk haplotype for schizophrenia, and has been described as a tagging single nucleotide polymorphism (SNP) of the core

at-risk haplotype.^{19,83} Positive association findings with this risk gene and schizophrenia and schizophrenic-related phenotypes have been reported in several studies.⁸⁴⁻⁹⁴ In both groups in our post-mortem study, the NRG1 SNP8NRG221533 schizophrenia-risk genotypes containing at least one C-allele (CC and CT) decreased gene expression of the NR2C subunit in the molecular layer of the right vermis and hemisphere compared with the TT genotype. Again, on the left side, we found no genotype-specific differences.⁸⁰ This finding was confined to the molecular layer of the right cerebellum. Decreased expression may lead to an NMDA receptor hypofunction, as NR2C, as a major NMDA receptor subunit of the cerebellum, exhibits less marked voltage-sensitive magnesium blockade and a prolonged decay rate of glutamate-induced ion currents.⁷⁶ A deficiency in this subunit may cause decreased receptor activation during glutamatergic stimulation and, as a consequence, diminished synaptic sprouting. Accordingly, in another post-mortem study, the glutamatergic synaptic protein complexin 2 was reduced at the mRNA and protein levels in the granule cell layer of the cerebellar cortex of schizophrenia patients compared with healthy control subjects,⁹⁵ supporting the hypothesis of a glutamatergic dysfunction in schizophrenia.

Our results confirm that the cerebellum is lateralized and, as shown in an fMRI study, the right cerebellum and the left prefrontal cortex are both activated during a silent fluency task in right-handed healthy subjects.⁹⁶

Alterations in the cerebellar GABAergic system and at the cellular level

Cognitive functioning depends on the plasticity mediated, in part, by NMDA receptors. A hypofunction of the NMDA receptor bearing on inhibitory GABAergic interneurons gives rise to reduced GABAergic inhibitory tone. In the long term, these target neurons could be injured by increased neurotransmission at ionotropic glutamatergic AMPA ($(\pm)$ - α -amino-3-hydroxy-5-methylisoxazole-4-propionoc acid), kainite, and cholinergic receptors with subsequent cell damage and a final hypoglutamatergic state.^{24,74,97} Thus, an NMDA receptor hypofunction and a GABAergic deficit of interneurons may both result in disturbed pathways at the molecular and cellular levels. Indeed, there is evidence of impaired interneuron function. For example, the GABA synthesizing enzyme glutamic acid decarboxylase 67 (GAD67) and reelin, both expressed in GABAergic interneurons, have been reported to be downregulated at the mRNA and protein levels in the cerebellum of schizophrenia patients.^{98,99} Besides GAD67, GAD65 and the GABA transporter 1 have been shown to be downregulated along with increased GABA_A receptor subunits, pointing to a deficit in GABAergic neurotransmission.¹⁰⁰ This may be related to a deficit in the NMDA receptor, as its antagonist phencyclidine causes similar alterations in cerebellar Golgi cells.¹⁰¹ However, altered cell numbers of Golgi cells remain to be investigated. In contrast, the cell density of GABAergic Purkinje neurons has been reported to be decreased in schizophrenia patients and heterozygous reeler mice with a deficit in reelin expression.¹⁰²

Influence of antipsychotic treatment

As all patients involved in post-mortem studies had been treated with antipsychotics for decades, medication effects may have influenced the results. Accordingly, we con-

ducted an additional animal study closely investigating the effects of a typical (haloperidol) and an atypical (clozapine) antipsychotic medication on NMDA receptor binding and gene expression of subunits of the NMDA receptor in different cerebellar rat brain regions after drug administration for up to 6 months. Here, we demonstrated that expression of NR2C was increased in clozapine-treated animals compared with haloperidol treatment. Therefore, clozapine may be superior to haloperidol in restoring a deficit in NR2C expression in the right cerebellum.⁸⁰ In an animal study of antipsychotic treatment, both haloperidol and clozapine increased the GABAergic marker GAD67 in the cerebellum.¹⁰⁰

We hypothesize that atypical antipsychotics may restore brain function by influencing the glutamatergic system and consecutive changes in neuroplasticity and brain activation. For example, antipsychotics are known to influence gray matter volumes in the cortex and, after 8 weeks of treatment, a volume increase has been found in the bilateral cerebellum as well.¹⁰³ A recent fMRI study during saccades to visual targets revealed less activation of the cerebellum and related networks in antipsychotic-naïve first-episode schizophrenia patients and the restoring effects of subchronic treatment with the atypical antipsychotic risperidone.¹⁰⁴ During presentation of pictures of facial emotions of happy faces, risperidone activated the right cerebellum compared with treatment with typical neuroleptics, suggesting superior effects of atypical antipsychotics.¹⁰⁵ As a glutamatergic deficit in the cerebellum may contribute to cognitive symptoms in the disease, medication with glutamate agonists may be beneficial in chronic schizophrenia.

ACKNOWLEDGMENT

This study was supported by the European Commission under the Sixth Framework Programme (BrainNet Europe II, LSHM-CT-2004-503039). The paper reflects only the authors' views and the Community is not liable for any use that may be made of it.

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