Negative symptoms of schizophrenia

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Chapter 1

Introduction
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Schizophrenia is a chronic clinical syndrome with a lifetime prevalence of 0.3-0.66%\(^1\). Schizophrenia is characterized by several psychopathologic domains, including positive symptoms, negative symptoms, affective and cognitive symptoms. The positive symptoms include psychotic symptoms such as hallucinations, delusions and disorganization of thought and behavior. Positive symptoms can often be diminished with antipsychotics and usually only occur periodically. Negative symptoms of schizophrenia include the flattening of affect, alogia, avolition, apathy and asociality. In contrary to positive symptoms of schizophrenia, negative symptoms often persist and about 25% of all patient with schizophrenia suffer from severe and persistent negative symptoms.\(^2\) Treatment options for negative symptoms of schizophrenia are limited and often yield disappointing results.\(^3-5\) The cognitive symptoms include deficits in working memory, executive functioning, processing speed and difficulty in paying attention. Cognitive symptoms are also enduring features of schizophrenia and may co-occur with negative symptoms. Positive symptoms, negative symptoms and cognitive symptoms are usually invalidating and interfere with every-day functioning of patients. Patients with schizophrenia have a decreased life expectancy of 12-15 years, mainly due to its association with smoking, the metabolic syndrome, obesity, little exercise and to a lesser extend an increased rate of suicide.\(^1\)

Schizophrenia is a heterogeneous syndrome, and the prognosis of schizophrenia varies. About one third of the patients have a good prognosis, one third an intermediate prognosis and one third a poor prognosis as expressed in symptomatology and social outcome.\(^6\) Negative and cognitive symptoms of schizophrenia are associated with a poorer prognosis and may be a major cause of the functional impairment associated with schizophrenia.\(^7\) Indeed, negative symptoms of schizophrenia have been associated with impaired work/school functioning,\(^8,9\) poor social functioning\(^8,10\) and higher family burdens.\(^11\) Earlier research on schizophrenia focused on the positive symptoms of schizophrenia. However, the relationship of positive symptoms and functioning appears to be weak.\(^9\) It seems that positive symptoms do not constantly hamper a patients ability to work, study or engage in social activities. On the one hand this may be due to the available antipsychotics to treat positive symptoms, on the other hand patients may learn to cope with or adequately compensate for these symptoms. Whereas positive symptoms do not constantly hamper daily functioning, negative symptoms are associated with impairments in daily performance. Patients with predominant negative symptoms are often unemployed, the majority do not have long-term intimate relationships or children, and they often experience problems in living independently and keeping their lives organized. Therefore it is important to investigate the cause and possible therapeutic interventions to diminish negative symptoms in order to improve social outcomes for people suffering from schizophrenia and related disorders. This thesis will focus on the negative symptoms of schizophrenia. It will discuss possible treatment options for negative symptoms and the underlying possible neural substrates of these symptoms.
Multidimensionality of negative symptoms

A distinction can be made between primary and secondary negative symptoms. Primary negative symptoms may compromise a core feature thought to be intrinsic to schizophrenia and often occur earlier in life than positive symptoms. Secondary negative symptoms refer to negative symptoms seemingly caused by other factors such as positive symptoms, side effects of medication or social isolation. For example, social withdrawal may be secondary to paranoid delusions, stigmatization may contribute to social isolation and a side effect of antipsychotic medication can be blunted affect or reduction of initiative. In clinical practice, it is difficult to make a clear distinction between primary and secondary negative symptoms. In addition, primary and secondary negative symptoms may co-exist.

Recently there has been a shift to an approach of negative symptoms based on symptom dimensions. Originally negative symptoms were considered to constitute one dimension, but several studies have found two, three and even five dimensions of negative symptoms. Most studies have found two factors in negative symptoms. The first factor seems related to social-emotional withdrawal/avolition and the second factor to expressive deficits such as diminished verbal and non-verbal expression. Interestingly, there is evidence that the social-emotional withdrawal/avolition factor, but not the expressive deficits factor, is related to deficits in anticipatory pleasure. Acknowledging the multidimensionality of negative symptoms, and focusing on expressive deficits and social-emotional withdrawal/avolition as two separate domains can help to further improve diagnosis and treatment options and to better understand their underlying pathophysiology.

Neural correlates of negative symptoms

For a better understanding of negative symptoms, the investigation of the underlying neurobiology is important. Several neuroimaging studies have found reduced activation of the prefrontal cortex (PFC), and more specifically in the dorsolateral prefrontal cortex (DLPFC), in patients with negative symptoms of schizophrenia. Also, decreased levels of perfusion of the thalamus and abnormalities in the anterior cingulate cortex (ACC) and the striatum have been found. Additionally, fMRI studies have shown a negative correlation between ventral-striatal activation during reward anticipation and apathy, and evidence for a relationship between dysfunctional striato-cortical connectivity and negative symptom severity. The PFC, ACC, the striatum and thalamus are brain regions involved in reward and motivation and abnormalities in information processing on the fronto-striatal networks may play a part in negative symptoms of schizophrenia. Also, decreased blood flow in the fronto-parietal network in patients with negative symptoms has been found. Interestingly, the fronto-parietal network is implicated in attentional control and goal directed behavior.
The abnormal brain activity found may be reflected by changes in several neurotransmitters and thus in the neuronal metabolism in these brain regions. In the prefrontal cortex, dopaminergic transmission is primarily mediated by D1 receptors, and there is evidence of D1 dysfunction in patients with negative symptoms.36,37 Furthermore, a relationship between reduced N-Acetyl Aspartate (NAA) concentration in the frontal cortex and severity of negative symptoms has been found.38-40 In addition, there is evidence for a correlation of severity of negative symptoms and glutamate levels in the ACC.41

Thus, changes in several transmitters may be implied in the pathophysiology of negative symptoms. Dysregulation of the prefrontal-striatal-thalamic and fronto-parietal neurocircuits may be involved in the pathogenesis and maintenance of negative symptoms, but the underlying mechanism is not fully understood and further research is needed to better understand the underlying neural substrates.

**rTMS treatment of negative symptoms**

As mentioned earlier, treatment options for negative symptoms of schizophrenia are limited and often yield disappointing results.3-5 A recent large meta-analysis on treatments of negative symptoms of schizophrenia including 168 randomized-placebo controlled trials found a significant reduction of negative symptoms after treatment with second-generation antipsychotics, antidepressants, the combination of these pharmacological agents, glutamatergic medications and psychological interventions.42 However, the effect of treatment was limited, as none of the treatments reached the threshold for clinically significant improvement.42

Repetitive Transcranial Magnetic Stimulation (rTMS) is an emerging treatment option in psychiatry which has been approved by the Food and Drugs Administration for the treatment of major depressive disorder. It is a relatively safe and non-invasive method to change neuronal activity via electromagnetic induction.43 By using alternating magnetic fields at a certain frequency it can induce an electric current in the brain tissue underlying the stimulation site. High-frequency rTMS increases local cortical excitability and low-frequency rTMS decreases excitability. Besides changing brain activity in the directly stimulated area, rTMS has also shown to change brain activity in connected brain areas.44

Using rTMS treatment to increase brain activity in the prefrontal cortex in patients with negative symptoms may adjust abnormalities in the fronto-striatal or fronto-parietal networks, thereby diminishing negative symptoms of schizophrenia. Up to date five meta-analysis on rTMS treatment of negative symptoms have been published.42,45-48 One meta-analysis involving five studies48 did not find a significant improvement of negative symptoms after rTMS. A meta-analysis on brain stimulation (both rTMS and Transcranial Direct-Current Stimulation) including eight studies42 also did not find a significant improvement of negative symptoms after brain stimulation. The other three meta-analyses only
included studies using rTMS. One, including seven studies, found a trend for improvement of negative symptoms, the other two containing a larger number of studies (nine and thirteen) found a positive treatment effect. In conclusion, there is a growing body of evidence for the efficacy of rTMS treatment for negative symptoms of schizophrenia, but little is known about the optimum rTMS treatment parameters and underlying neuronal working mechanisms.

The aims of this thesis are:
1) To investigate the efficacy of treatment with rTMS for negative symptoms of schizophrenia, including the effects on brain activation.
2) To investigate the underlying neural substrates of negative symptoms of schizophrenia.

Outline of the thesis
This thesis focuses on the treatment of negative symptoms of schizophrenia with repetitive transcranial magnetic stimulation (rTMS) and on the underlying neural substrates of negative symptoms. The first section of the thesis, chapter 2-6, focus on rTMS treatment of negative symptoms of schizophrenia, including effects on brain activation of the treatment. The second section of the thesis, chapter 6 and 7, examines the underlying neural substrates of negative symptoms.

In the second chapter, a review of the literature and the results of a meta-analysis on the treatment of negative symptoms of schizophrenia with rTMS is presented and discussed. The third chapter presents the results of a double blind randomized control trial of rTMS treatment for negative symptoms of schizophrenia. The forth chapter presents and discusses the results of a combined rTMS treatment and fMRI neuroimaging study. The fifth chapter presents the results of a combined rTMS treatment and H-Magnetic Resonance Spectroscopy (MRS) study.

The second section, chapter 6 and 7, discusses the possible underlying neural substrates of negative symptoms of schizophrenia based on the results of two fMRI neuroimaging studies conducted in patients with schizophrenia and healthy controls. These studies also analyze the neural substrates of the two domains of negative symptoms. The eight and final chapter of this thesis include the summary and discussion.