Negative symptoms of schizophrenia

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Chapter 8

Summary and general discussion
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The prognosis of schizophrenia, as measured in symptom severity or social outcome, is highly variable, from poor to good. Major factors that appear to affect the prognosis unfavorably are negative symptoms and cognitive deficits. It is therefore important to investigate the pathogenesis and treatment options of negative symptoms. The aims of this thesis were:

1) To investigate the efficacy of treatment with repetitive transcranial magnetic stimulation (rTMS) for negative symptoms of schizophrenia, including the effects on brain activation.
2) To investigate the underlying neural substrates of negative symptoms of schizophrenia.

In the first section of the thesis, chapters 2-5, the treatment of negative symptoms with rTMS is discussed. Chapter 2 and 3 show that prefrontal rTMS treatment of negative symptoms of schizophrenia may be a promising emerging treatment option that deserves further investigation. Chapter 2 presents the results of a meta-analysis on prefrontal rTMS treatment of negative symptoms of schizophrenia, which found a positive treatment effect: negative symptoms may diminish after treatment with rTMS. Chapter 3 discusses the results of a double blind randomized controlled trial of bilateral prefrontal high frequency prefrontal rTMS treatment for negative symptoms of schizophrenia. A significant improvement in negative symptoms, as measured with the Scale for the Assessment of Negative Symptoms (SANS), was found in the active group compared with sham up to 3 months follow-up. In chapter 4 the possible underlying neural mechanisms of prefrontal rTMS treatment were investigated. The results of this combined rTMS and fMRI neuroimaging study suggest that treatment with rTMS over the dorsolateral prefrontal cortex (DLPFC) increased task-related activation in the frontal areas of patients with schizophrenia. Chapter 5 discusses the results of a combined rTMS treatment and H-Magnetic Resonance Spectroscopy (¹H-MRS) study, investigating whether rTMS treatment may change concentrations of neurometabolites. In this exploratory study, rTMS treatment influenced glutamate and glutamine (Glx, neurotransmitter and precursor) concentration in the left DLPFC of patients with schizophrenia, but not N-Acetyl Aspartate (NAA) concentration.

In the second section of the thesis, chapters 6 and 7, investigates the possible underlying neural substrates of negative symptoms of schizophrenia were investigated. Findings discussed in chapter 6 suggest that higher levels of expressive deficits in patients with schizophrenia may be associated with diminished activation of the fronto-thalamic circuit and the ventromedial prefrontal cortex during ambiguous social appraisal. Findings discussed in chapter 7 suggest that “social amotivation” (social-emotional withdrawal) as a measure of apathy may be related to abnormal activation in thalamus and parietal regions as measured by a planning task performed during fMRI scanning.
rTMS treatment of negative symptoms of schizophrenia

In our studies, described in chapters 2 and 3, treatment with high frequency prefrontal rTMS alleviated negative symptoms of schizophrenia in the rTMS group as compared to sham treatment. Chapter 4 shows that this positive treatment effect in our study was accompanied by an increased task-related activation of the frontal brain areas in the rTMS group.

The meta-analysis in chapter 2 found that, on average, negative symptoms diminish in patients treated with rTMS. The overall mean weighted effect size for rTMS versus sham was in the small-to-medium range \(d=0.43\), and the effect size of our randomized controlled trial (chapter 3) was small directly after treatment \(d=0.3\) but was in the small-to-medium range at 4 weeks follow-up \(d=0.41\). According to the nomenclature of Cohen, \(d=0.2\) is considered a small effect size, \(d=0.5\) a moderate effect size and \(d=0.8\) a large effect size.89 For a clinically meaningful effect, one would expect a moderate to large effect size. Thus, although there was a positive treatment effect, the treatment did not reach the threshold of being clinically meaningful. It should be noted that there are no other treatments with larger effect sizes regarding improvement of negative symptoms. This stresses the need of further development of novel approaches.

Indeed, the lack of clinically meaningful treatment options is an important issue in the treatment of negative symptoms.42 Several factors may contribute to this. Negative symptoms of schizophrenia are often present in early stages of schizophrenia and they tend to persevere.8 Studies on negative symptoms of schizophrenia, including our studies, are often conducted among patients who have long illness duration and are often using high dosages of antipsychotics. Because negative symptoms have a negative influence on functional outcome, it may be important to intervene and treat negative symptoms early. Research should therefore focus on patients with negative symptoms in recent onset schizophrenia, as recovery in the early phase of schizophrenia may have the largest impact on future functioning. Another factor which may contribute to the lack of clinically meaningful treatment effect is a reduced brain plasticity in patients with schizophrenia.163 There is evidence that cortical excitability, connectivity and plasticity are impaired in patients with schizophrenia in all stages of the disease.163 Although the effect of antipsychotic medication is unclear, it is possible that they, in part, contribute to this reduced brain plasticity.13 To improve the efficacy of rTMS treatment it may be necessary to target neural plasticity, i.e. by using more powerful stimulation protocols and by investigating optimal rTMS parameters. Also, treatment effects may be enhanced by combining different treatment options for negative symptoms of schizophrenia, for example combining rTMS treatment with psychosocial interventions. Currently, a randomized controlled trial conducted in the North of The Netherlands by our research group, is also investigating the effect of a combined rTMS treatment and Behavioral Activation Therapy for apathy (https://apathiestediie.wordpress.com/).
Another issue to address is the two factors (or maybe more) in negative symptoms, namely expressive deficits and social-emotional withdrawal/avolition.\textsuperscript{216} Originally negative symptoms were considered to constitute one dimension, and studies have investigated negative symptoms as such. In recent studies two factors were found: social-emotional withdrawal/avolition factor which appears to be related to deficits in anticipatory pleasure, and the expressive deficits factor which is related to deficits in the ability to express oneself.\textsuperscript{18-20} The two separate symptom domains of negative symptoms may reflect different mechanisms in the brain and may respond to different treatment strategies (see also chapter 6 and 7).

Finally, research efforts targeting negative symptoms are still limited. This may be due to the properties of patients experiencing negative symptoms such as lack of motivation, in addition to other symptoms in many patients with schizophrenia, like lack of illness awareness, psychotic symptoms or experiencing problems in abstract reasoning. Finding patients with negative symptoms that sufficiently understand the aim of the study, are motivated to participate and are able to give informed consent, is a challenge. As a consequence, the number of studies and of patients included in clinical trials is small. Also, it is likely that within the group of patients with negative symptoms there is a selection bias, as most patients suffering from severe negative symptoms may be too demotivated or impaired to participate.

Notably, the efficacy of rTMS treatment for depression has been validated in placebo-controlled trials conducted among more than 3000 patients, and there is sufficient evidence to evaluate the efficacy of treatment using high frequency rTMS over the left DLPFC with level A (definite efficacy).\textsuperscript{261} Thus, it is possible that the effect of rTMS on negative symptoms may be in part attributed to the antidepressant effect of rTMS. In our clinical trial we therefore controlled for the antidepressant effect of rTMS but the studies included in our meta-analyses often did not. Our findings are in line with three other trials suggesting that the improvement of negative symptoms could not be attributed to the antidepressant effect of rTMS.\textsuperscript{72,73,76}

It is important to note that the optimal rTMS treatment parameters for treatment of negative symptoms are unknown. In our clinical trial, we applied 3 weeks of 10 Hz rTMS bilaterally, targeting both the left and right DLPFC at 90% of the motor threshold (MT). However, a recent meta-analysis found the best parameters for the rTMS treatment included applying a frequency of 10 Hz, at least 3 weeks of treatment instead of two as used in the earlier rTMS trials, treatment site of the left DLPFC and a 110% MT.\textsuperscript{46} It is possible that the treatment effect we found in our trial may be primarily attributed to treatment of the left DLPFC and not the bilateral DLPFC. This may explain the lack of effect found in two earlier trials applying bilateral rTMS.\textsuperscript{80,124} A major difference between these two trials and our trial was the total number of pulses that were applied. We used a total of 60,000
pulses, namely 30,000 pulses per hemisphere. The other two trials used 30,000 pulses and 15,000 per hemisphere. Only one other study investigating unilateral rTMS treatment applied 30,000 pulses to the left DLPFC, and this study found a significant improvement of negative symptoms\textsuperscript{126} all other studies applied less pulses. As mentioned earlier, there is evidence that brain plasticity in patients with schizophrenia may be reduced, and increasing the number of pulses delivered may enhance treatment response\textsuperscript{163}. Furthermore, we applied an intensity at 90\% of motor threshold (MT) because applying a higher MT\% may increase the risk of an epileptic seizure, and also may cause more discomfort during stimulation. However, applying rTMS at an intensity of 110\% MT is suggested to have the best efficacy on negative symptoms\textsuperscript{46} Notably, in all earlier rTMS trials for negative symptoms of schizophrenia using an intensity of 110\% MT no serious side effect or seizures occurred\textsuperscript{72,73,76,80,82,83,125,126,188} Nonetheless, as we applied more pulses than other rTMS trials for negative symptoms, which could also contribute to increased risk of inducing a seizure, we decided beforehand to adhere to a safe percentage of motor threshold. Fortunately, no seizures occurred in our trial. Thus, probably better rTMS treatment protocols are possible, in accordance with new insights in efficacy as well as safety issues.

An important issue to address is the application of sham treatment and the manner of blinding of rTMS studies. In our trial and in several earlier studies, sham rTMS was delivered by tilting the coil 45 or 90\º. An advantage of this method is that it may mimic some scalp sensation, however it may also induce a small amount of voltage in the brain\textsuperscript{108} In addition, the person administering the rTMS treatment is aware of the treatment condition and a Rosenthal effect may occur. A Rosenthal effect is the phenomenon whereby higher expectations lead to an increase in performance and lower expectations lead to a decrease in performance. However, as discussed in chapter 3, in our trial blinding was successful - in both treatment conditions the percentage of patients who thought they had received the “real” treatment was the same. Currently, sham coils are available that mimic the scalp sensation. In further studies, new sham conditions, such as a sham coils with built-in electrodes, should be applied.

A promising new emerging TMS technique is theta burst TMS (TBS). In TBS pulses are applied in bursts of three at high frequency (i.e. 50 Hz) with an interburst interval of 200 ms. These patterns of stimulation are based on naturally occurring firing patterns in the brain, and studies conducted among both animals and humans found theta rhythms were associated with long term potentiation\textsuperscript{262-265} One study conducted among humans found increased theta power during encoding of new information\textsuperscript{265} The authors suggest a relationship with hippocampal theta, via hippocampo-cortical feedback loops\textsuperscript{265} Two forms of TBS have been investigated: intermittent and continuous. Intermittent TBS (iTBS) applies stimulation during 2 seconds with an inter-train interval of 8 seconds. This pattern has been found to have an excitatory effect, as after iTBS motor evoked potentials (MEPs)
were facilitated.\textsuperscript{266} Continuous TBS (cTBS) on the other hand has an inhibitory effect by suppressing MEPs. Several advantages of TBS is that it requires less stimulation time and can be applied at a lower motor threshold (usually 80\% MT).\textsuperscript{266} A large study investigating iTBS as compared to 10 Hz TMS for major depression suggests iTBS to be as effective, however duration of treatment of iTBS per session was much shorter.\textsuperscript{267} A study involving 96 patients with prominent negative symptoms compared 10 Hz and 20 Hz TMS and TBS to sham TMS, and found a significant decrease of negative symptoms for all three conditions (10 Hz, 20 Hz rTMS and TBS) as compared to sham TMS, but decrease in negative symptoms in the TBS group was significantly larger as compared to the 10 and 20 Hz groups.\textsuperscript{187} Regarding safety of TBS, TBS may have a higher risk of inducing epileptic seizures as compared to rTMS as it applies high frequency bursts. On the other hand, stimulation duration is shorter and less pulses are needed at a lower intensity. In conclusion, TBS is a promising new technique which may prove to be effective to treat negative symptoms of schizophrenia while requiring less administration time. The number of TBS studies are limited and more studies are needed to investigate its efficacy and safety.

Chapter 4 discusses the results of our neuroimaging study. In this study, conducted in a subgroup of patients participating in the clinical trial, we found an increase in task-related brain activation in the right DLPFC and the right medial frontal gyrus (MeFG) in the active group as compared to sham treatment. In addition, there was a significant difference between active and sham groups in brain activation in the left posterior cingulate, caused by the combined effect of a large decrease in brain activation in the active group and to a lesser extent an increase in brain activation in the sham group. These changes in brain activation were accompanied by a significant decrease of negative symptoms in the rTMS group as compared to sham treatment. Two earlier published studies by Guse et al and Prikryl et al also investigated the effect of rTMS on neural activation in schizophrenia patients.\textsuperscript{161,162} These studies did not find a significant difference in brain activation between the active and sham group. However, the study by Guse et al,\textsuperscript{161} which was part of a larger clinical trial that did not find an significant improvement of negative symptoms after rTMS,\textsuperscript{188} applied much less pulses than our study, namely a total of 15,000 pulses to the left DLPFC as opposed to 60,000 (30,000 per hemisphere) in our study. This was also the case in the study by Prikryl et al,\textsuperscript{162} which applied a total of 22,500 stimuli to the left DLPFC. It is possible there is a dose effect relationship, and significant changes in brain activation may become apparent above a certain threshold.

Our study suggests that rTMS treatment may be able to change brain activation not only in the directly stimulated area, but also in connected brain areas, i.e. the posterior cingulate cortex (chapter 4). This is of considerable relevance, as negative symptoms seem to be associated with dysregulation of the prefrontal-striatal-thalamic and fronto-parietal
neurocircuits. Thus, besides increasing activation in the prefrontal cortex, rTMS is thought to be important to affect relevant circuitry of the prefrontal cortex.

In addition to task-related changes in brain activation, we also investigated changes in brain metabolism of glutamate/glutamine (Glx) and N-Acetyl Aspartate (NAA) in the left prefrontal cortex with H-Magnetic Resonance Spectroscopy (¹H-MRS) in a subgroup of patients for which data were available, as discussed in chapter 5. In this exploratory study we applied a linear regression model to investigate the association between treatment condition and changes in concentration of Glx and NAA. We found a significant association between changes in Glx in the left DLPFC and treatment condition in patients with negative symptoms of schizophrenia receiving rTMS or sham treatment. There was an increase of Glx concentration in the rTMS treatment group and a decrease of Glx concentration in the group receiving sham treatment. The increase of Glx in the prefrontal cortex provides further evidence for the underlying rationale of prefrontal rTMS treatment for negative symptoms, namely that it can increase prefrontal metabolism. An earlier ¹H-MRS study conducted among patients with a depression, also found rTMS treatment increased glutamate/glutamine. The results of our ¹H-MRS study are also in line with our fMRI findings, which found a task-related increase in the prefrontal cortex in the rTMS group as compared to placebo. However, the study was exploratory, and more studies are needed to investigate changes in brain metabolism after rTMS in patients with schizophrenia, including PET studies to detect possible changes in dopamine.

In conclusion, we aimed to investigate treatment with rTMS for negative symptoms of schizophrenia, including possible underlying neural mechanisms. Both the meta-analysis and the clinical trial provide evidence for the efficacy of 10 Hz rTMS of the DLPFC to improve negative symptoms, but the effect size is still too limited to be clinically meaningful. At the same time, it should be emphasized that few treatments yield statistically significant improvement, which rTMS did achieve. Therefore, it would be premature to dismiss rTMS as a potential treatment modality, even though it needs further development to achieve clinical usefulness. Our fMRI study found a task-related increase in the prefrontal cortex, and our ¹H-MRS study found an association between changes in Glx and treatment condition, supporting the underlying rationale of rTMS treatment of negative symptoms. Taken together, our studies contribute to the growing body of evidence for the efficacy of rTMS treatment for negative symptoms. However, the effect size of treatments with rTMS is not as yet clinically satisfactory. Randomized placebo controlled trials are needed to establish the most effective combination of rTMS parameters (including TBS), and interventions may be more effective in earlier phase of the psychotic illness or in combination with psycho-social interventions. In addition, neuroimaging studies are needed to further investigate the underlying neural working mechanism of rTMS treatment.
The underlying neural substrates of negative symptoms of schizophrenia

The second part of the thesis focuses on the underlying neural substrates of negative symptoms. Chapter 6 and 7 both present the results of an fMRI study conducted among patients with schizophrenia and healthy individuals. In contrast to most earlier neuroimaging studies on negative symptoms, we acknowledged two factors of negative symptoms identified with the Positive and Negative Syndrome Scale (PANSS) questionnaire: social-emotional withdrawal and expressive deficits. Chapter 6 investigated the social-emotional withdrawal and expressive deficits factor and chapter 7 focuses on the social-emotional withdrawal factor as a measure of apathy. Chapter 6 presents the results of an fMRI study on emotion perception, which measured emotional ambiguity in a social context by presenting an array of faces with varying degree of consistency in emotional expressions, e.g. some faces look angry, others look happy (the Wall of Faces task). This study found that severity of expressive deficits was negatively correlated with activation of the ventromedial prefrontal cortex when comparing ambiguous emotional decisions to ambiguous gender decisions. Furthermore, higher level of expressive deficits was associated with decreased brain activation in the thalamus, precentral gyrus, precuneus, the superior temporal gyrus and the middle frontal gyrus during emotional ambiguity. However, no significant association was found between the PANSS factor social-emotional withdrawal with brain activation. A limitation of this study could be the artificial nature of the stimulus display (thirty-two faces on one screen). Future studies should use more dynamic and realistic images of real-life social situations. Correlations of brain activation during such tasks with social functioning questionnaires should also be established, even though this will require larger samples.

Chapter 7 presents and discusses the results of an fMRI study during a planning task. Patients with schizophrenia and healthy controls performed the Tower of London task during scanning. The Tower of London task is a test used for the assessment of executive functioning, and more specifically planning. Executive functioning and goal-directed behavior are mediated by a fronto-striatal-parietal brain circuit. Higher levels of social-emotional withdrawal were associated with decreased brain activation in the inferior parietal lobule, the precuneus and the thalamus. Thus, both neuroimaging studies support the hypothesis that dysregulation of the frontal-thalamic and fronto-parietal neurocircuits may be involved in the pathogenesis and maintenance of negative symptoms.

It is indeed likely that the two dimensions of negative symptoms are reflected in distinctive neural correlations. Whereas we primarily observed associations of the expressive deficits dimension with neural activation during the emotional ambiguity task, a recent study primarily observed associations of activation during reward anticipation with social-emotional withdrawal/avolition. In that study Kirschner et al (2015) employed a Monetary Incentive Delay Task. It is possible that patients with high levels of social-emotional withdrawal/avolition withdraw from or avoid activities due to a lack of reward
anticipation. The authors report social-emotional withdrawal/avolition, but not expressive deficits, to be related to ventral striatal hypoactivation during reward anticipation. Similar to the studies in this thesis (Chapter 6 and 7), Kirschner et al performed additional correlations with depressive symptoms, but also with cognitive ability, medication and positive symptoms. None of these confounding variables showed a significant negative correlation with ventral striatal activation. Thus, as was the case in our studies (Chapter 6 and 7), the findings were independent of depressive symptoms. In conclusion, reward anticipation and planning may be more closely related to social-emotional withdrawal/avolition whereas emotional perception may be more related to expressive deficits. This is an important finding, stressing the necessity of focusing on the two (or may be more) factors of negative symptoms, as they appear to have a different underlying neural working mechanism.

Considering the above, it is likely that successful treatment of negative symptoms may need differential treatment approaches. Future studies should acknowledge the two (or more) factors of negative symptoms and further investigate their different underlying neural substrates, and may consider to develop differential treatment approaches in line with these substrates. This also applies for rTMS treatment for negative symptoms of schizophrenia, which may prove to be more effective for one of the two factors. Research and clinical practice may benefit from newer instruments to assess negative symptoms, which take into account the recent advances made in the description of negative symptoms. Better measurement may inform subsequent diagnosis and treatment. Although up to date no clinically meaningful treatment options are available, a recent meta-analysis found several treatment options (including medication and psychological interventions) to have a significant treatment effect. Perhaps combining these different treatment options may enhance treatment effects. For instance, by combining psychological interventions with brain stimulation or treatment with glutamatergic medications. Regarding brain stimulation techniques, treatment of negative symptoms of schizophrenia with TBS deserves further investigation. TBS requires less administration time, which is more patient-friendly and implies lower cost. Taking into account that changes induced by the brain stimulation techniques rTMS and TBS may be temporary, in those patients responding to treatment a tapering course of maintenance treatment may be required. Up to date, few studies have been performed on maintenance treatment with rTMS or TBS and none have been performed on maintenance treatment in patients with schizophrenia. Thus, there is a need for systematic study and standardization of rTMS/TBS maintenance treatment in patient with schizophrenia. In conclusion, considerable additional research on negative symptoms of schizophrenia is needed to better understand these symptoms. Such knowledge will subsequently inform treatment strategies and ultimately improve quality of life in patients with serious mental illness.
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