Psychological Medicine (2015), **45**, 1263–1275. © Cambridge University Press 2014
doi:10.1017/S0033291714002360

ORIGINAL ARTICLE

Efficacy of bilateral repetitive transcranial magnetic stimulation for negative symptoms of schizophrenia: results of a multicenter double-blind randomized controlled trial

J. J. Dlabac-de Lange[1,2,3]*, L. Bais[3,4], F. D. van Es[1], B. G. J. Visser[1], E. Reinink[4], B. Bakker[4], E. R. van den Heuvel[5], A. Aleman[3] and H. Knegtering[1,2,3,4]

[1] *University of Groningen, University Medical Center Groningen, Department of Psychiatry, Hanzeplein 1, Groningen, The Netherlands*
[2] *University of Groningen, University Medical Center Groningen, Rob Giel Research Centrum, Hanzeplein 1, Groningen, The Netherlands*
[3] *University of Groningen, University Medical Center Groningen, Department of Neuroscience and BCN Neuroimaging Center, Antonius Deusinglaan 2, Groningen, The Netherlands*
[4] *Lentis Research, Center for Mental Health, Hereweg 80, Groningen, The Netherlands*
[5] *University of Groningen, University Medical Center Groningen, Department of Epidemiology, Hanzeplein 1, Groningen, The Netherlands*

Background. Few studies have investigated the efficacy of repetitive transcranial magnetic stimulation (rTMS) treatment for negative symptoms of schizophrenia, reporting inconsistent results. We aimed to investigate whether 10 Hz stimulation of the bilateral dorsolateral prefrontal cortex during 3 weeks enhances treatment effects.

Method. A multicenter double-blind randomized controlled trial was performed in 32 patients with schizophrenia or schizo-affective disorder, and moderate to severe negative symptoms [Positive and Negative Syndrome Scale (PANSS) negative subscale $\geqslant$15]. Patients were randomized to a 3-week course of active or sham rTMS. Primary outcome was severity of negative symptoms as measured with the Scale for the Assessment of Negative Symptoms (SANS) and the PANSS negative symptom score. Secondary outcome measures included cognition, insight, quality of life and mood. Subjects were followed up at 4 weeks and at 3 months. For analysis of the data a mixed-effects linear model was used.

Results. A significant improvement of the SANS in the active group compared with sham up to 3 months follow-up ($p = 0.03$) was found. The PANSS negative symptom scores did not show a significant change ($p = 0.19$). Of the cognitive tests, only one showed a significant improvement after rTMS as compared with sham. Finally, a significant change of insight was found with better scores in the treatment group.

Conclusions. Bilateral 10 Hz prefrontal rTMS reduced negative symptoms, as measured with the SANS. More studies are needed to investigate optimal parameters for rTMS, the cognitive effects and the neural basis.

Received 11 February 2014; Revised 22 July 2014; Accepted 1 September 2014; First published online 30 October 2014

Key words: Cognition, dorsolateral prefrontal cortex, insight, negative symptoms, randomized controlled trials, schizophrenia, transcranial magnetic stimulation.

Introduction

Negative symptoms of schizophrenia include apathy, anhedonia, blunted affect, alogia and avolition. These symptoms are an important predictor of poor functional outcome (Fenton & McGlashan, 1991, 1994; Milev *et al.* 2005) by negatively influencing patients' ability to perform activities of daily living, or maintain stable relationships and employment. Although a majority of schizophrenia patients suffer from negative symptoms, current treatment options yield disappointing results (Leucht *et al.* 1999; Gasquet *et al.* 2005; Murphy *et al.* 2006). Studies have suggested that dysfunctioning of the prefrontal cortex, in particular hypofunctioning of the dorsolateral prefrontal cortex (DLPFC), may be part of the pathophysiology of negative symptoms (Wolkin *et al.* 1992; Shioiri *et al.* 1994; Selemon *et al.* 2003; Glahn *et al.* 2005).

Neuroimaging studies have found negative symptoms to be associated with left DLPFC (Klemm *et al.* 1996) and right DLPFC dysfunction (Wolkin *et al.* 1992; Potkin *et al.* 2002), and also with bilateral DLPFC dysfunction (Sabri *et al.* 1997; Gonul *et al.*

* Address for correspondence: J. J. Dlabac-de Lange, Department of Psychiatry, University of Groningen, University Medical Center Groningen, Postbox 30.001, 9700 RB Groningen, The Netherlands.
(Email: j.j.l.a.s.n.dlabac@umcg.nl)

2003). Also, several studies have found negative symptoms to be associated with a diminished blood flow in the fronto-parietal brain circuits (Lahti *et al.* 2001; Gonul *et al.* 2003). Impairment of fronto-striatal brain circuits has also been implicated in negative symptoms of schizophrenia (Sanfilipo *et al.* 2002). In conclusion, hypoactivity of the DLPFC and dysfunctioning of the fronto-parietal and fronto-striatal brain network may be associated with negative symptoms of schizophrenia.

The neuromodulation technique repetitive transcranial magnetic stimulation (rTMS) may be useful in adjusting impaired functioning within the fronto-parietal and fronto-striatal networks. rTMS is a relatively safe and non-invasive method (Loo *et al.* 2008) that uses alternating magnetic fields to induce an electric current in the underlying brain tissue. By administering high-frequency rTMS to the DLPFC it is possible to increase brain activity locally and in connected brain areas. Animal studies have found that high-frequency rTMS resulted in persistent effects on NMDA (*N*-methyl-D-aspartate) and 5-HT_{1A} (5-hydroxytryptamine receptor 1A) binding sites (Kole *et al.* 1999), up-regulation of β-adrenergic receptors in the frontal cortex, down-regulation of these receptors in the striatum and down-regulation of 5-HT2 receptors in the frontal cortex (Ben-Shachar *et al.* 1999). In healthy humans, several positron emission tomography studies have been performed after rTMS was administered to the DLPFC. One study found rTMS of the DLPFC to increase regional cerebral blood flow in several prefrontal cortical areas apart from the directly stimulated area, including the ventrolateral prefrontal cortex (Eisenegger *et al.* 2008). Another study found that rTMS of the DLPFC moderated dopamine release in the ipsilateral caudate nucleus (Strafella *et al.* 2001). Finally, one study found that rTMS of the left DLPFC modulated aspects of tryptophan/5-HT metabolism in limbic areas (Sibon *et al.* 2007). So, besides increasing brain activity of prefrontal cortical areas, rTMS of the DLPFC may also modulate brain metabolism in the prefrontal cortex, the limbic lobe and in the striatum, which in turn may positively influence negative symptoms of schizophrenia.

In 1999 the first pilot study was performed using rTMS of the prefrontal cortex to improve negative symptoms (Cohen *et al.* 1999). Subsequently, a number of studies have been conducted, mostly targeting the left DLPFC. Recently, three meta-analyses on rTMS treatment for negative symptoms of schizophrenia were published. One meta-analysis of seven studies found a trend for improvement of negative symptoms (Slotema *et al.* 2010). The other, including nine studies, found a small to medium positive effect (Dlabac-de Lange *et al.* 2010). Sub-analyses revealed that a longer treatment duration (⩾3 weeks) at a frequency of 10 Hz enhanced treatment effects (Dlabac-de Lange *et al.* 2010). The third, including 13 studies, found a moderate positive effect (Shi *et al.* 2014). Sub-analyses revealed that stimulating the left DLPFC at a frequency of 10 Hz, and at 110% of the motor threshold during three consecutive weeks were the best rTMS parameters for the treatment of negative symptoms (Shi *et al.* 2014).

In this multicenter double-blind randomized controlled trial, we aimed to assess the effect of 3 weeks of 10 Hz rTMS treatment of the bilateral DLPFC for negative symptoms of schizophrenia. Our primary hypothesis was that bilateral high-frequency rTMS would reduce negative symptom severity more than the sham condition. Our secondary hypothesis was that bilateral high-frequency rTMS would improve cognition, insight, quality of life and mood more than sham stimulation. We administered rTMS to the left DLPFC in the morning and rTMS to the right DLPFC in the afternoon. It has been suggested that a larger number of pulses are more effective (Gershon *et al.* 2003). In our study we applied a total amount of 60 000 pulses, which is at least twice the amount of any earlier published rTMS study for negative symptoms (Cohen *et al.* 1999; Klein *et al.* 1999; Hajak *et al.* 2004; Holi *et al.* 2004; Jandl *et al.* 2005; Sachdev *et al.* 2005; Jin *et al.* 2006; Novak *et al.* 2006; Goyal *et al.* 2007; Mogg *et al.* 2007; Prikryl *et al.* 2007, 2013; Fitzgerald *et al.* 2008; Schneider *et al.* 2008; Cordes *et al.* 2010; Barr *et al.* 2012). Negative symptoms were measured using the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1982) and negative symptoms subscale of the Positive and Negative Syndrome Scale (PANSS; Kay *et al.* 1987). Since rTMS might also have an antidepressant effect (Loo & Mitchell, 2005), we controlled for depressive symptoms as measured by the Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979).

Method

Participants

During the period of February 2009 to February 2013, 47 participants were recruited from in- and out-patient facilities of the Department of Psychiatry of the University Medical Center Groningen (UMCG) and three regional mental health care institutions (Lentis, GGz Drenthe and GGz Friesland). Recruitment of the trial ended after inclusion of the required 32 patients for analysis. From the recruited patients, seven did not meet the inclusion criteria and six declined to participate. Two patients withdrew from the study after

https://doi.org/10.1017/S0033291714002360 Published online by Cambridge University Press

baseline testing but before randomization, the first due to exacerbation of psychotic symptoms and the second because she thought the rTMS treatment twice daily would be too strenuous. All patients were 18 years or older, and met the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria for schizophrenia or schizo-affective disorder, which was confirmed by a trained interviewer, using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN 2.1; Giel & Nienhuis, 1996). Patients were included if they had moderate negative symptoms, i.e. a score of 15 or more on the negative subscale of the PANSS. All patients were stable on medication for 6 weeks prior to participating in the study and for the duration of the study. Exclusion criteria were rTMS and magnetic resonance imaging (MRI) contraindications, neurological disorders (e.g. epilepsy), head injury with loss of consciousness in the past, substance dependency within the previous 6 months, previous treatment with rTMS, severe behavioral disorders, inability to provide informed consent and pregnancy. Participants gave oral and written consent after the procedure had been fully explained. The study was executed in accordance with the Declaration of Helsinki and approved by a licensed local medical ethical committee (METC-UMCG).

There were two treatment locations, one at the UMCG and one at the long-term psychiatric care facility of Lentis in Zuidlaren. In the UMCG, both in- and out-patients ($n = 23$) from the four participating institutions were treated. Out-patients were admitted to an in-patient care unit for the duration of the trial, when daily travel to the UMCG was too demanding. In Zuidlaren, only patients living in the long-term care facilities ($n = 9$) were treated and remained there for the duration of the rTMS treatment.

Study design

The study was a multicenter double-blind randomized controlled trial with two co-operating centers (UMCG and Lentis). Patients were randomized to receive either active ($n = 16$) or sham rTMS ($n = 16$) treatment. Allocation concealment was achieved by using sequentially numbered sealed envelopes, containing tokens that were randomly allocated by an independent colleague. The envelopes were opened just before the first treatment session by the researcher. Only the researcher and the trained nurses who administered the rTMS were aware of the treatment condition. The rater and the patients were blinded to treatment. The rTMS treatment was delivered twice daily. In the morning the left DLPFC was stimulated and in the afternoon the right DLPFC, with a minimum of 5 h between the two sessions. This interval of 5 h between sessions was applied to reduce the risk of an epileptic seizure, as 2000 pulses were administered per hemisphere per treatment session. The rTMS treatment was carried out for 3 weeks, Monday to Friday, for a total of 30 treatment sessions. Clinical ratings were performed at baseline, after the rTMS treatment, at 4 weeks follow-up and at 3 months follow-up. Treating psychiatrists were requested to maintain the treatment constant for the duration of the trial and to report any unforeseen changes in treatment.

All participants were asked to fill in a questionnaire about side effects and which treatment (sham or active treatment) they thought they had received to check for blinding success. After 3 months, when the trial period had ended, patients were de-blinded to their treatment condition, and offered to receive real treatment if they had been allocated to the sham condition.

rTMS protocol

rTMS was administered by using a Medtronic MagPro X100 stimulator (Medtronic, USA) with a 75 mm figure-of-eight coil. Motor threshold was determined in patients who were allocated to the active treatment condition. We did not determine the motor threshold in the sham group, since it may have de-blinded the participants to their treatment condition. The resting motor threshold is defined as the minimum intensity to induce a noticeable movement of the dominant hand in five out of 10 pulses administered on the contralateral primary motor cortex (Schutter & van Honk, 2006). Patients were stimulated with 20 trains of 10 s at a frequency of 10 Hz, with an inter-train interval of 50 s. The long duration of stimulation (10 s) may increase seizure risk. In order to decrease the risk of an epileptic seizure, stimulation intensity was set at 90% of the motor threshold and the inter-train interval was set at 50 s. Thus, per session, 2000 pulses were delivered with a total of 60 000 pulses per treatment course. The F3 and F4 locations from the EEG 10–20 system were used to target the bilateral DLPFC (Beam *et al.* 2009). For sham stimulation, we tilted the coil 90° off the scalp with two wings of the coil touching the scalp.

rTMS treatments were only administered by trained nurses, under medical supervision of a psychiatrist. A physician was always on call and available within 5 min in case of any adverse events. Moreover, a rectiole with diazepam was ready in the treatment room.

Clinical measures

Negative symptoms were assessed using the semi-structured interviews SANS and PANSS. The MADRS was administered to rate depressive symptoms. To measure insight, the Birchwood Insight Scale was used (Birchwood *et al.* 1994). This eight-item self-report scale measures three dimensions of insight: awareness

https://doi.org/10.1017/S0033291714002360 Published online by Cambridge University Press

of illness, relabeling of symptoms as pathological, and need for treatment. Quality of life was measured with the World Health Organization (WHO) Quality of Life-BREF (WHOQOL-BREF) (Anonymous, 1998). This 26-item self-report questionnaire developed by the WHO generates scores for the physical, psychological, social and environmental domains. Two additional questions cover the subject's overall perception of quality of life and the subject's overall health perception.

Neuropsychological tests

A number of neuropsychological tests were conducted to assess cognitive functioning at baseline, post-treatment and at 4 weeks follow-up. Besides processing speed and memory as a general index of brain function, tests were selected with a focus on executive functioning (i.e. relying on frontal cortex function). These tests included the Digit Symbol Substitution Test (Wechsler, 1997), which is a Wechsler Adult Intelligence Scale, 3rd edn. (WAIS-III) subtest, the Trail Making Test Parts A and B (Anonymous, 1944), a computerized version of the Wisconsin Card Sorting Test (WCST; Grant & Berg, 1948), the Dutch version of the Rey Auditory Verbal Learning Test (Rey, 1958; van den Burg *et al.* 1985) and the Verbal Fluency Test. The computerized version of the WCST could not be administered to the first six participants due to delayed delivery by the supplier. The semantic Verbal Fluency Test was conducted among a subgroup of 20 patients; initially only the letter Verbal Fluency Test was administered. For the semantic verbal fluency, the categories animals and professions were applied. For the letter fluency task three parallel versions were used with similar levels of difficulty. Pre-morbid intelligence was estimated with the National Adult Reading Test-Nederlandse Leestest voor Volwassenen (NART-NLV; Schmand *et al.* 1991) and level of education was defined according to the scoring system of Verhage (1983). Raw scores were converted to standardized scores using normative data provided in the test manual.

Functional MRI (fMRI) procedure

An fMRI scan was made before and after 3 weeks of rTMS treatment; the results of the fMRI analyses will be discussed in other papers.

Power calculation

We performed a power calculation prior to inclusion to determine sample size. A previous study using the most similar study design and rTMS parameters (Prikryl *et al.* 2007) found significant treatment effects measured with the SANS and PANSS negative symptom subscale, with an effect size of 1.21. By including 16 subjects in each condition, a power of >0.91 would be achieved.

Data analysis

Differences in demographic characteristics and baseline data between the two treatment groups were tested with independent t tests. We applied the χ^2 test to the nominal variables and the Mann–Whitney U test to test for differences in antipsychotic medication dose.

For the SANS, the negative symptom subscale of the PANSS, the MADRS, the Birchwood Insight Scale, the WHOQOL-BREF and the neuropsychological tests, a population-averaged linear mixed model was fitted to the data after baseline. The three repeated measures (post-treatment, 4 weeks follow-up, 3 months follow-up) of each patient were treated as observations from a three-dimensional normal distribution, using time as a categorical variable and assuming an unstructured covariance matrix. To correct for differences at baseline we included the baseline scores as a covariate in the analyses of all outcome measures. In order to correct for the effect of rTMS on depressive symptoms, each subject's three post-treatment scores on the MADRS were added as a covariate in the analysis of the SANS and for the negative subscale of the PANSS. For each analysis, we investigated whether the effect of treatment was consistent during the follow-up periods, which we tested with a group × time interaction in the post-treatment scores. If the effect of treatment did not differ between the time periods, we assumed that the effect of treatment remained constant on all time points after treatment. A p value of 0.05 was chosen as the criterion for statistical significance. All analyses were conducted with IBM SPSS Statistics 20.0 (USA).

In addition, we conducted an exploratory analysis on quality of life as measured by the WHOQOL-BREF excluding patients from our analysis with very poor insight, because we assumed patients with high disease insight were able to realize changes in their restrictions in daily living more clearly than patients with low insight (Karow & Pajonk, 2006; Aghababian *et al.* 2011).

Trial registration

The trial is registered in the Nederlands Trial Register under the name of 'Effect of high frequency rTMS on negative symptoms and cognitive functioning in schizophrenia' (no. NTR1261; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1261). The full trial protocol is available from the corresponding author (J.J.D.L.).

https://doi.org/10.1017/S0033291714002360 Published online by Cambridge University Press

Table 1. *Demographic and baseline clinical characteristics*

	Real TMS ($n = 16$)	Sham TMS ($n = 16$)	p
Mean age, years (S.D.)	41.8 (11.6)	32.3 (9.7)	0.018
Sex, *n*			0.654
Male	14	12	
Female	2	4	
Mean education score, Verhage (S.D.)	4.8 (1.8)	5.4 (1.1)	0.261
Nationality, *n*			0.386
Dutch	14	15	
Iranian	1	–	
Congolese		1	
Surinamese	1	–	
Mean age of onset, years (S.D.)	26.1 (7.4)	22.4 (6.1)	0.135
Diagnosis by SCAN, *n*			
Schizophrenia	15	16	
Schizo-affective disorder	1	–	
Mean illness duration, months (S.D.)	188 (121)	119 (107)	0.099
D_2 receptor occupancy[a], *n*			0.555
1st quartile	–	–	
2nd quartile	3	4	
3rd quartile	7	3	
4rd quartile	6	9	
Type of medication, *n*			
Clozapine	6	6	
Olanzapine	4	3	
Risperidone	3	3	
Paliperidone	1	–	
Aripiprazole	2	4	
Haloperidol	1	1	
Other classical	1	1	
Antipsychotic polypharmacy	3	5	
In-patients, *n*	8	13	
Out-patients, *n*	8	3	
Mean motor threshold[b], % (S.D.)	59.4 (3.4)	–	
Mean SANS (S.D.)	56.6 (15.7)	44.6 (17.3)	0.049
Mean PANSS negative (S.D.)	20.6 (3.7)	19.7 (5.4)	0.570
Mean PANSS positive (S.D.)	13.0 (4.1)	12.6 (4.3)	0.770
Mean PANSS general psychopathology (S.D.)	34.8 (8.0)	29.2 (5.2)	0.027
Mean MADRS (S.D.)	20.7 (9.3)	14.6 (8.7)	0.064
Mean WHOQOL-BREF (S.D.)	299 (41)	317 (41)	0.220

Data are given as mean (S.D.) or as number of patients.

TMS, Transcranial magnetic stimulation; S.D., standard deviation; SCAN, Schedules for Clinical Assessment in Neuropsychiatry; SANS, Schedule for the Assessment of Negative Symptoms; PANSS, Positive and Negative Syndrome Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; WHOQOL-BREF, World Health Organization Quality of Life-BREF.

[a] Dopamine D_2 receptor occupancy as a percentage was estimated for each participant according to the prescribed dose of antipsychotic medication (Lako *et al.* 2013). Next, the 0–100% range was divided in quartiles (1st quartile, 0–25%; 2nd quartile, 26–50%; 3rd quartile, 51–75%; 4th quartile, 76–100% quartile). In accordance to their D_2 receptor occupancy percentage, participants were allocated to the corresponding quartile. Antipsychotic effect occurs at occupancies between 65 and 80%, while receptor occupancies above 80% may elicit extrapyramidal side effects (Kapur *et al.* 1995).

[b] Some data are missing.

Results

Demographic and clinical characteristics

Table 1 shows the demographic and baseline clinical characteristics of the 32 participants. Mean age was significantly higher in the active group (mean = 41.8, S.D. = 11.6 years) than in the sham group (mean = 32.3, S.D. = 9.7 years) ($p = 0.02$). Also, a significant difference in baseline SANS scores ($p = 0.049$) between the active (mean = 56.6, S.D. = 15.7) and the sham (mean = 44.6,

https://doi.org/10.1017/S0033291714002360 Published online by Cambridge University Press

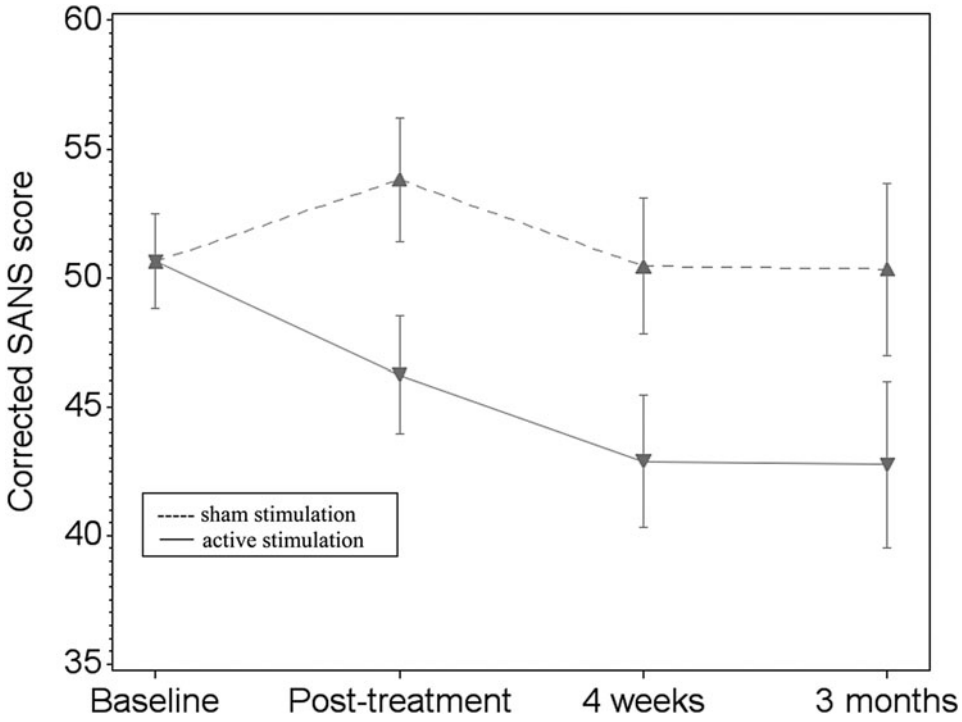

Fig. 1. Total Scale for the Assessment of Negative Symptoms (SANS) scores at baseline, post-treatment, 4 weeks and 3 months per treatment arm, corrected for baseline SANS (50.63) and Montgomery–Åsberg Depression Rating Scale (MADRS) (17.6). Data are means, with standard errors represented by vertical bars.

S.D. = 17.3) group was found. Finally, there was a significant difference in baseline PANSS general psychopathology ($p = 0.03$) between the active (mean = 34.8, S.D. = 8) and the sham (mean = 29.2, S.D. = 5.2) group. There were no significant differences in the remaining characteristics.

rTMS safety, tolerability and blinding

All participants tolerated the rTMS treatment well and completed the entire trial. No serious adverse events occurred. Common reported side effects were twitching of the facial muscles during rTMS stimulation and transient mild headache after rTMS stimulation.

The blinding process was successful, since in both groups 10 patients thought they had received the active rTMS treatment, five patients thought they had received sham stimulation and one patient did not know which treatment he or she was allocated to.

Primary outcome measure: negative symptoms

Fig. 1 shows the estimated means of the SANS scores over time, corrected for baseline SANS and MADRS. Fig. 2 shows the percentage change between the baseline and the mean of the post-treatment measurements for the active and sham groups. Table 2 displays the scores on the clinical outcome measures at all four time points and the results of the statistical analysis.

A significant improvement of negative symptoms as evaluated with the SANS in the active group compared with the sham group up to 3 months follow-up ($p = 0.03$, $F = 5.33$) was found. In the post-treatment period, there was no significant group × time interaction and therefore the effect was considered consistent across the complete post-treatment period ($p = 0.71$). The post-treatment SANS scores were 7.6 points lower in the active group as compared with the sham group, a reduction of 15%. Without correcting for depressive symptoms, the effect remained significant ($p = 0.049$, $F = 4.19$).

There was no significant improvement on the PANSS negative symptom score ($p = 0.19$, $F = 1.84$). This lack of effect was consistent across the complete post-treatment period ($p = 0.93$).

Secondary outcome measures: cognition, mood, quality of life and insight

Table 3 shows the scores on all the neuropsychological tests and the results of the statistical analysis. Most tests showed no differences. A significant improvement of semantic verbal fluency was found in the active group ($n = 10$) compared with the sham group ($n = 9$) up to 4 weeks follow-up ($p = 0.006$, $F = 9.31$).

https://doi.org/10.1017/S0033291714002360 Published online by Cambridge University Press

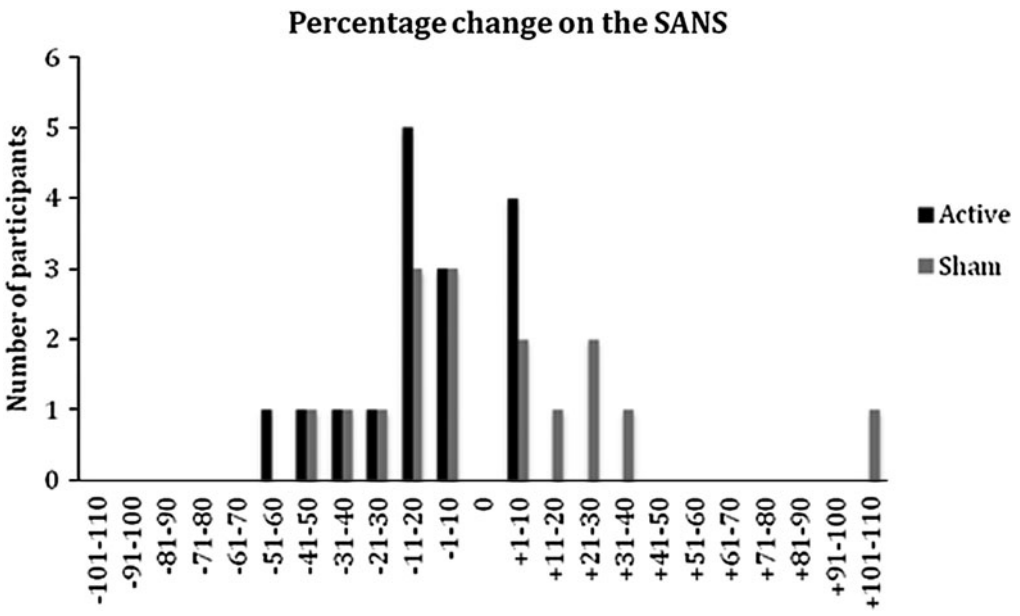

Fig. 2. Scale for the Assessment of Negative Symptoms (SANS) percentage change between the baseline and mean of the post-treatment measurements for the active and sham groups.

Table 2. *Clinical outcome at baseline, end of the treatment, and at 4 weeks and 3 months follow-up*

		Pre-treatment scores	Post-treatment scores				
	Groups	Baseline	End of treatment	4 Weeks follow-up	3 Months follow-up	*F*	*p*
SANS	Active ($n = 16$)	56.6 (15.7)	51.1 (19.6)	46.9 (17.6)	48.1 (18.8)	5.33	0.03
	Sham ($n = 16$)	44.6 (17.3)	45.3 (18.7)	43.9 (17.8)	40.9 (19.7)		
PANSS negative	Active ($n = 16$)	20.6 (3.7)	19.3 (5.2)	18.2 (5.1)	18.1 (4.6)	1.84	0.19
	Sham ($n = 16$)	19.7 (5.4)	19.2 (6.0)	18.6 (6.0)	18.2 (6.0)		
PANSS positive	Active ($n = 16$)	13.0 (4.1)	12.6 (4.1)	11.3 (4.1)	11.9 (4.1)	0.001	0.98
	Sham ($n = 16$)	12.6 (4.3)	11.5 (3.8)	11.8 (4.3)	12.3 (4.8)		
PANSS general	Active ($n = 16$)	34.8 (8.0)	32.6 (7.8)	31.3 (6.7)	29.4 (8.0)	0.02	0.89
	Sham ($n = 16$)	29.2 (5.2)	28.1 (3.9)	28.3 (4.6)	28.8 (5.1)		
MADRS	Active ($n = 16$)	20.7 (9.3)	16.3 (7.9)	16.8 (7.7)	16.7 (9.7)	0.07	0.79
	Sham ($n = 16$)	14.6 (8.7)	11.8 (6.8)	13.4 (8.1)	10.4 (6.0)		
Birchwood Insight Scale	Active ($n = 16$)	8.84 (3.1)	9.22 (2.7)	8.9 (2.8)	9.1 (2.2)	7.31	0.01
	Sham ($n = 16$)	7.63 (3.9)	7.0 (3.7)	6.7 (4.0)	7.2 (3.1)		

Data are given as mean (standard deviation).

SANS, Scale for the Assessment of Negative Symptoms; PANSS, Positive and Negative Syndrome Scale; MADRS, Montgomery–Åsberg Depression Rating Scale.

As there was no significant group × time interaction in the post-treatment period, the effect was considered consistent across the complete post-treatment period ($p = 0.15$). Post-treatment, the active group improved 20.9% more on the semantic Verbal Fluency Test as compared with the sham group. However, no significant improvements were found for phonemic verbal fluency, or on the other neurocognitive tests.

There was no significant difference between the active and the sham group on depressive symptoms as measured with the MADRS up to 3 months follow-up ($p = 0.79$).

Furthermore, treatment did not affect quality of life as measured with the WHOQOL-BREF in the whole sample. However, exploratory analysis excluding four patients with very poor insight, as defined by a

https://doi.org/10.1017/S0033291714002360 Published online by Cambridge University Press

Table 3. *Cognitive outcomes at baseline, end of the treatment, and at 4 weeks follow-up*

		Pre-treatment scores	Post-treatment scores		Mixed linear modeling	
	Groups	Baseline	End of treatment	4 Weeks follow-up	*F*	*p*
Verbal Learning Test, recall	Active ($n = 16$)	40.9 (12.7)	47.5 (15.9)	43.4 (14.2)	0.58	0.45
	Sham ($n = 16$)	39.9 (9.3)	46.6 (12.7)	39.4 (11.0)		
Verbal Learning Test, delayed recall	Active ($n = 16$)	42.8 (10.0)	46.0 (10.8)	42.1 (11.3)	0.63	0.44
	Sham ($n = 15$)	41.2 (7.3)	48.7 (10.6)	40.7 (9.7)		
Digit Symbol Substitution Test	Active ($n = 16$)	52.6 (22.5)	60.4 (23.0)	63.6 (23.9)	1.04	0.32
	Sham ($n = 16$)	66.6 (17.0)	70.6 (17.5)	75.5 (19.4)		
Trail Making Test A	Active ($n = 16$)	43.9 (17.1)	47.9 (18.4)	48.9 (19.9)	0.59	0.45
	Sham ($n = 16$)	45.1 (11.1)	50.8 (10.5)	51.4 (13.5)		
Trail Making Test B	Active ($n = 14$)	45.6 (15.5)	49.5 (20.7)	52.1 (17.0)	0.21	0.65
	Sham ($n = 16$)	42.6 (10.9)	48.0 (9.5)	50.1 (9.3)		
Semantic Verbal Fluency	Active ($n = 10$)	61.8 (12.6)	71.0 (17.7)	76.8 (15.0)	9.31	0.01
	Sham ($n = 9$)	71.3 (15.8)	69.7 (20.6)	67.8 (12.1)		
Phonemic Verbal Fluency	Active ($n = 16$)	40.4 (10.9)	44.6 (8.2)	46.2 (9.1)	0.025	0.88
	Sham ($n = 16$)	48.8 (12.2)	49.5 (11.3)	53.1 (9.6)		
Wisconsin Card Sorting Test, correct rate, %	Active ($n = 12$)	65.5 (24.1)	71.1 (23.1)	77.1 (21.9)	0.16	0.70
	Sham ($n = 13$)	68.1 (20.0)	69.8 (22.6)	77.2 (19.2)		
Wisconsin Card Sorting Test, total error rate, %	Active ($n = 12$)	34.6 (24.1)	29.1 (23.0)	22.9 (21.9)	0.25	0.63
	Sham ($n = 13$)	31.9 (20.0)	30.2 (22.6)	22.8 (19.2)		
Wisconsin Card Sorting Test, perseverative rate, %	Active ($n = 12$)	15.8 (9.8)	17.6 (18.1)	11.6 (11.5)	0.13	0.72
	Sham ($n = 13$)	20.2 (14.8)	20.5 (19.6)	12.5 (11.9)		
Wisconsin Card Sorting Test, perseverative error rate, %	Active ($n = 12$)	13.8 (8.1)	15.4 (14.0)	10.5 (9.4)	0.70	0.41
	Sham ($n = 13$)	18.2 (12.6)	17.9 (16.1)	11.1 (9.4)		
Wisconsin Card Sorting Test, non-perseverative error rate, %	Active ($n = 12$)	20.6 (21.0)	13.6 (13.4)	12.4 (15.2)	0.85	0.37
	Sham ($n = 13$)	13.9 (8.9)	12.2 (8.6)	11.5 (10.7)		

Data are given as mean (standard deviation).

baseline score on the Birchwood Insight Scale of 2.5 or less, revealed a significant improvement ($p = 0.03$, $F = 5.01$) up to 3 months follow-up on overall perception of health in the active group ($n = 14$) as compared with the sham group ($n = 14$). There was no significant group × time interaction in the post-treatment period; thus the effect was consistent across the complete post-treatment period ($p = 0.39$). The post-treatment overall perception of health scores were 13.5 points higher in the active group than in the sham group, an increase of 25.2%.

A significant difference on the Birchwood Insight Scale ($p = 0.01$, $F = 7.31$) was found, and this effect was consistent across the complete post-treatment period ($p = 0.98$). This effect was caused on the one hand by an improvement of insight in the active group after rTMS and on the other hand by a decrease in insight in the sham group. Sub-analysis revealed a significant difference on the four-item subscale measuring the awareness of the need for treatment. In the active group the awareness of the need for treatment increased and in the sham group the awareness decreased ($p = 0.01$). No significant differences were found on the subscales awareness of illness ($p = 0.24$) and relabeling of symptoms as pathological ($p = 0.13$).

Discussion

Confirming our primary hypotheses, we found a significant improvement of negative symptoms as measured with the SANS after 3 weeks of 10 Hz bilateral rTMS of the DLPFC up to 3 months follow-up compared with sham rTMS. A post-treatment reduction of 15% on the SANS was found in the active group as compared with sham. Considering the long follow-up period of 3 months and the clinical characteristics of the included patients [many patients had a long duration of illness and were prescribed high dosages of (multiple) antipsychotics], this effect is of considerable relevance, as it is proof-of-principle evidence of the potential of rTMS to improve negative symptoms. The

https://doi.org/10.1017/S0033291714002360 Published online by Cambridge University Press

blinding was successful and no data of the SANS, PANSS and MADRS were lost at follow-up.

Secondary outcome measures included cognition, mood, quality of life and insight. Cognitive performance in both the sham and the active groups improved to a similar extent during follow-up, which might be due to a learning effect. Importantly, the treatment did not result in adverse effects on cognitive functioning, an issue that often arises in the context of other brain stimulation techniques (Lisanby *et al.* 2000; Berman *et al.* 2008). Furthermore, rTMS may even have some beneficial effects on cognitive functioning, since we found a significant improvement on the semantic Verbal Fluency Test in the active group compared with sham. Near-infrared spectroscopy (NIRS) studies in schizophrenia patients have shown the Verbal Fluency Test to be a very sensitive task to measure prefrontal functioning (Ehlis *et al.* 2007; Ikezawa *et al.* 2009). Possibly, this task is also more sensitive to detect improved prefrontal functioning than the other cognitive measures. Finally, we found a significant difference on the Birchwood Insight Scale. This was due to an improvement of insight in the active group and a decrease in insight after sham rTMS and therefore more difficult to interpret. Especially the awareness of the need for treatment increased in the active group but decreased in the sham group. Perhaps this can partially be attributed to fluctuations in insight characteristics for patients with schizophrenia on the one hand and the rTMS treatment effect on the other hand. Notably, frontal areas have been implicated in lack of insight (Shad *et al.* 2006), adding to the plausibility of change through increased activation of dorsolateral prefrontal areas. No significant improvement on quality of life and mood was found.

Meta-analyses have confirmed the efficacy of rTMS treatment over the DLPFC for major depressive disorder (Berlim *et al.* 2013). It could be argued that a putative improvement of negative symptoms in schizophrenia may be due to an improvement of depressive symptoms. Therefore, we controlled for a possible antidepressant effect of rTMS by correcting for change in depressive symptoms. The results showed improvement of the SANS scores to be irrespective of the observed changes in depressive symptoms.

From a clinical perspective, it is interesting to know more about the durability of the effect of rTMS on negative symptoms. The present trial is the first to study the effectiveness with such a long follow-up period. Only one previous randomized controlled trial had a follow-up period of 6 weeks (Novak *et al.* 2006), but found no effect of a 2-week rTMS treatment at 20 Hz. Two other studies included a follow-up period of 4 weeks (Klein *et al.* 1999; Schneider *et al.* 2008), one applying low-frequency rTMS found no effect (Klein *et al.* 1999), and another study by Schneider *et al.* (2008), with quite similar treatment parameters as in our study, found a significant treatment effect that lasted up to 4 weeks follow-up. All other randomized controlled trials did not include follow-up measures of more than 2 weeks.

Studies on rTMS treatment of depression have suggested a higher efficacy with a greater number of rTMS pulses (Gershon *et al.* 2003; George & Post, 2011). Our study administered at least twice the amount of pulses than in earlier published rTMS studies for negative symptoms, namely a total of 60 000 pulses (30 000 per hemisphere). Two studies applied a total amount of 30 000 pulses, 15 000 per hemisphere, but found no significant effect (Fitzgerald *et al.* 2008; Barr *et al.* 2012). Two other studies applied a total amount of 22 500 pulses to the left DLPFC and both found a significant improvement after rTMS (Prikryl *et al.* 2007, 2013). All other studies administered fewer pulses. Of these studies, three randomized controlled trials found a significant improvement of negative symptoms (Hajak *et al.* 2004; Goyal *et al.* 2007; Schneider *et al.* 2008) and six randomized controlled trials found no significant effect (Klein *et al.* 1999; Holi *et al.* 2004; Novak *et al.* 2006; Mogg *et al.* 2007; Schneider *et al.* 2008; Jin *et al.* 2012). In conclusion, applying a greater amount of pulses may indeed enhance treatment effects.

rTMS was applied bilaterally in this study. In two earlier studies, bilateral rTMS was applied, but these studies did not find any significant improvement of negative symptoms (Fitzgerald *et al.* 2008; Barr *et al.* 2012), although one study did find a trend of improvement on the autistic preoccupation scale of the PANSS (Fitzgerald *et al.* 2008). In these studies the right and left DLPFC were treated during a single session, whereas in our study, the left DLPFC was treated in the morning and the right DLPFC in the afternoon. Interestingly, one study performed among healthy volunteers found inhibition of the left DLPFC impaired striatal dopamine neurotransmission but inhibition of the right DLPFC did not result in impaired striatal dopamine neurotransmission (Ko *et al.* 2008). In addition, the evidence for left DLPFC hypoactivity in schizophrenia is more extensive than for right DLPFC hypoactivity. Indeed, a recent meta-analysis found the treatment site of the left DLPFC to be the best rTMS parameter for negative symptoms (Shi *et al.* 2014). Thus, perhaps the treatment effect in our study can be primarily attributed to the rTMS treatment of the left DLPFC.

Although rTMS treatment appeared to positively affect the negative symptoms in terms of the SANS scores, this effect was not confirmed by the scores on the PANSS negative subscale. This may be due to

https://doi.org/10.1017/S0033291714002360 Published online by Cambridge University Press

low statistical power, considering the relatively small sample size. In addition, it has been suggested that the SANS is a more sensitive measurement of negative symptoms than the negative subscale of the PANSS (Strous *et al.* 2003; Lane *et al.* 2005). The SANS covers multiple domains and multiple items per domain and is thus considered to be a more extensive and reliable measure of negative symptoms than the PANSS negative subscale (Kirkpatrick *et al.* 2006). Also, a recent meta-analysis found the effect size generated from studies using the SANS was consistently larger (0.80) when compared with the effect size generated from studies using the PANSS (0.41) (Shi *et al.* 2014). Indeed, only a moderate correlation between the SANS and the negative subscale of the PANSS has been observed (Rabany *et al.* 2011). This can be explained by the fact that the seven items of the PANSS negative subscale do not seem to cover negative symptoms completely (Liemburg *et al.* 2013).

Recently, a new tool for assessing negative symptoms designed for use in clinical trials has been developed, namely the Brief Negative Symptom Scale (BNSS), which has a strong inter-rater, test–retest and internal consistency (Kirkpatrick *et al.* 2011). Also, recent findings suggest that the Calgary Depression Scale for Schizophrenia is most useful in discriminating depressive symptoms from negative symptoms (Lako *et al.* 2012). Future studies may benefit by also using the BNSS to measure negative symptoms and by using the CDSS instead of the MADRS for measuring depressive symptoms.

A potential limitation of the present study includes the differences between the active and sham groups at baseline. Despite randomization, the groups differed on age, baseline PANSS general psychopathology and baseline SANS scores. As we had a small sample size, the risk of bias and imbalance is greater. Stratification during randomization would have decreased this risk. To correct for the imbalance, we included the baseline scores in all our analyses as a covariate, hereby increasing the precision of our treatment effect estimate. However, regression to the mean cannot entirely be ruled out. Still, our participants have been sick for a long time, and negative symptoms are relatively stable over time. Combined with the fact that our results are in line with previous positive findings (Dlabac-de Lange *et al.* 2010; Shi *et al.* 2014), the improvement seen in the active rTMS group cannot completely be attributed to regression to the mean.

Another potential limitation includes the small sample size and the heterogeneity of the group. Ideally, research is conducted among a larger and more homogeneous sample. We focused on recruiting patients with negative symptoms. Considering that one of the main features of negative symptoms is lack of motivation, it was difficult to recruit these patients for our trial. By including both out-patients and patients living in long-term care facilities we were able to complete our inclusion. Future research should preferably include a larger number of patients, perhaps by performing larger multicenter trials.

An important issue to address is the method of sham stimulation. In our study, we applied sham TMS by tilting the coil 90°. This method has been demonstrated to induce some voltage in the brain, albeit 73% less than active TMS (Lisanby *et al.* 2001). However, the same study found the 90° sham condition to be devoid of biological effects and this form of sham stimulation did not elicit motor-evoked potentials (Lisanby *et al.* 2001). Also, with this method of sham stimulation there is some scalp stimulation. Recently, new sham coils have been developed, which use built-in electrodes to replicate scalp sensation (Mennemeier *et al.* 2009). This method of sham stimulation is preferred as it does not create a significant magnetic field (Mennemeier *et al.* 2009), and both patient and rTMS administrator can more easily be kept blind to the treatment condition.

Conclusion

In conclusion, we found a significant reduction of negative symptoms after a 3-week trial of bilateral prefrontal 10 Hz rTMS. Overall, the active group improved on several domains compared with the sham group. The rTMS treatment was well tolerated and no serious adverse events occurred. This study was conducted among a relatively small group of patients of whom many were chronically and severely ill, often using high dosages of (multiple) psychopharmaceutical drugs. Applying rTMS treatment to patients with a short duration of schizophrenia or patients using antipsychotic monotherapy in a low dose may enhance treatment effects. Future studies should include a larger number of patients, preferably in a multicenter setting. Combining rTMS treatment with neuroimaging will provide more information about neural effects. Finally, more studies are needed to find the optimum in rTMS parameter settings.

Acknowledgements

The study was supported by means of an unconditional research grant from AstraZeneca and an unconditional research grant from Stichting Roos. This work was supported in part by a European Science Foundation EURYI grant (NWO no. 044035001) to A.A.

We would like to thank all the participants of this study. We would also like to thank the trained nurses of the UMCG and of the Lentis department in Zuidlaren administering the active or sham treatment and the raters administering the tests.

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Declaration of Interest

None.

References

Aghababian V, Auquier P, Baumstarck-Barrau K, Lancon C (2011). Relationship between insight and self-reported quality of life among schizophrenic patients. *L'Encephale* **37**, 162–171.

Andreasen NC (1982). Negative symptoms in schizophrenia. Definition and reliability. *Archives of General Psychiatry* **39**, 784–788.

Anonymous (1944). *Army Individual Test Battery: Manual of Directions and Scoring*. War Department, Adjutant General's Office: Washington, DC.

Anonymous (1998). Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group. *Psychological Medicine* **28**, 551–558.

Barr MS, Farzan F, Tran LC, Fitzgerald PB, Daskalakis ZJ (2012). A randomized controlled trial of sequentially bilateral prefrontal cortex repetitive transcranial magnetic stimulation in the treatment of negative symptoms in schizophrenia. *Brain Stimulation* **5**, 337–346.

Beam W, Borckardt JJ, Reeves ST, George MS (2009). An efficient and accurate new method for locating the F3 position for prefrontal TMS applications. *Brain Stimulation* **2**, 50–54.

Ben-Shachar D, Gazawi H, Riboyad-Levin J, Klein E (1999). Chronic repetitive transcranial magnetic stimulation alters β-adrenergic and 5-HT2 receptor characteristics in rat brain. *Brain Research* **816**, 78–83.

Berlim MT, van den Eynde F, Tovar-Perdomo S, Daskalakis ZJ (2013). Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. *Psychological Medicine* **44**, 225–239.

Berman RM, Prudic J, Brakemeier EL, Olfson M, Sackeim HA (2008). Subjective evaluation of the therapeutic and cognitive effects of electroconvulsive therapy. *Brain Stimulation* **1**, 16–26.

Birchwood M, Smith J, Drury V, Healy J, Macmillan F, Slade M (1994). A self-report Insight Scale for psychosis: reliability, validity and sensitivity to change. *Acta Psychiatrica Scandinavica* **89**, 62–67.

Cohen E, Bernardo M, Masana J, Arrufat FJ, Navarro V, Valls-Solé J, Boget T, Barrantes N, Catarineu S, Font M, Lomeña FJ (1999). Repetitive transcranial magnetic stimulation in the treatment of chronic negative schizophrenia: a pilot study. *Journal of Neurology, Neurosurgery, and Psychiatry* **67**, 129–130.

Cordes J, Thunker J, Agelink MW, Arends M, Mobascher A, Wobrock T, Schneider-Axmann T, Brinkmeyer J, Mittrach M, Regenbrecht G, Wolwer W, Winterer G, Gaebel W (2010). Effects of 10 Hz repetitive transcranial magnetic stimulation (rTMS) on clinical global impression in chronic schizophrenia. *Psychiatry Research* **177**, 32–36.

Dlabac-de Lange JJ, Knegtering R, Aleman A (2010). Repetitive transcranial magnetic stimulation for negative symptoms of schizophrenia: review and meta-analysis. *Journal of Clinical Psychiatry* **71**, 411–418.

Ehlis AC, Herrmann MJ, Plichta MM, Fallgatter AJ (2007). Cortical activation during two verbal fluency tasks in schizophrenic patients and healthy controls as assessed by multi-channel near-infrared spectroscopy. *Psychiatry Research* **156**, 1–13.

Eisenegger C, Treyer V, Fehr E, Knoch D (2008). Time-course of "off-line" prefrontal rTMS effects – a PET study. *NeuroImage* **42**, 379–384.

Fenton WS, McGlashan TH (1991). Natural history of schizophrenia subtypes. II. Positive and negative symptoms and long-term course. *Archives of General Psychiatry* **48**, 978–986.

Fenton WS, McGlashan TH (1994). Antecedents, symptom progression, and long-term outcome of the deficit syndrome in schizophrenia. *American Journal of Psychiatry* **151**, 351–356.

Fitzgerald PB, Herring S, Hoy K, McQueen S, Segrave R, Kulkarni J, Daskalakis ZJ (2008). A study of the effectiveness of bilateral transcranial magnetic stimulation in the treatment of the negative symptoms of schizophrenia. *Brain Stimulation* **1**, 27–32.

Gasquet I, Haro JM, Novick D, Edgell ET, Kennedy L, Lepine JP, SOHO Study Group (2005). Pharmacological treatment and other predictors of treatment outcomes in previously untreated patients with schizophrenia: results from the European Schizophrenia Outpatient Health Outcomes (SOHO) study. *International Clinical Psychopharmacology* **20**, 199–205.

George MS, Post RM (2011). Daily left prefrontal repetitive transcranial magnetic stimulation for acute treatment of medication-resistant depression. *American Journal of Psychiatry* **168**, 356–364.

Gershon AA, Dannon PN, Grunhaus L (2003). Transcranial magnetic stimulation in the treatment of depression. *American Journal of Psychiatry* **160**, 835–845.

Giel R, Nienhuis FJ (1996). *SCAN-2.1: Schedules for Clinical Assessment in Neuropsychiatry (in Dutch)*. WHO: Geneva/ Groningen.

Glahn DC, Ragland JD, Abramoff A, Barrett J, Laird AR, Bearden CE, Velligan DI (2005). Beyond hypofrontality: a quantitative meta-analysis of functional neuroimaging studies of working memory in schizophrenia. *Human Brain Mapping* **25**, 60–69.

Gonul AS, Kula M, Esel E, Tutus A, Sofuoglu S (2003). A Tc-99 m HMPAO SPECT study of regional cerebral blood flow in drug-free schizophrenic patients with deficit and non-deficit syndrome. *Psychiatry Research* **123**, 199–205.

Goyal N, Nizamie SH, Desarkar P (2007). Efficacy of adjuvant high frequency repetitive transcranial magnetic stimulation on negative and positive symptoms of schizophrenia: preliminary results of a double-blind sham-controlled study. *Journal of Neuropsychiatry and Clinical Neurosciences* **19**, 464–467.

Grant DA, Berg EA (1948). A behavioral analysis of degree of reinforcement and ease of shifting to new responses in a Weigl-type card-sorting problem. *Journal of Experimental Psychology* **38**, 404–411.

Hajak G, Marienhagen J, Langguth B, Werner S, Binder H, Eichhammer P (2004). High-frequency repetitive transcranial magnetic stimulation in schizophrenia: a combined treatment and neuroimaging study. *Psychological Medicine* **34**, 1157–1163.

Holi MM, Eronen M, Toivonen K, Toivonen P, Marttunen M, Naukkarinen H (2004). Left prefrontal repetitive transcranial magnetic stimulation in schizophrenia. *Schizophrenia Bulletin* **30**, 429–434.

Ikezawa K, Iwase M, Ishii R, Azechi M, Canuet L, Ohi K, Yasuda Y, Iike N, Kurimoto R, Takahashi H, Nakahachi T, Sekiyama R, Yoshida T, Kazui H, Hashimoto R, Takeda M (2009). Impaired regional hemodynamic response in schizophrenia during multiple prefrontal activation tasks: a two-channel near-infrared spectroscopy study. *Schizophrenia Research* **108**, 93–103.

Jandl M, Bittner R, Sack A, Weber B, Gunther T, Pieschl D, Kaschka WP, Maurer K (2005). Changes in negative symptoms and EEG in schizophrenic patients after repetitive transcranial magnetic stimulation (rTMS): an open-label pilot study. *Journal of Neural Transmission* **112**, 955–967.

Jin Y, Kemp AS, Huang Y, Thai TM, Liu Z, Xu W, He H, Potkin SG (2012). Alpha EEG guided TMS in schizophrenia. *Brain Stimulation* **5**, 560–568.

Jin Y, Potkin SG, Kemp AS, Huerta ST, Alva G, Thai TM, Carreon D, Bunney Jr WE (2006). Therapeutic effects of individualized alpha frequency transcranial magnetic stimulation (alphaTMS) on the negative symptoms of schizophrenia. *Schizophrenia Bulletin* **32**, 556–561.

Kapur S, Remington G, Zipursky RB, Wilson AA, Houle S (1995). The D_2 dopamine receptor occupancy of risperidone and its relationship to extrapyramidal symptoms: a PET study. *Life Sciences* **57**, 103–107.

Karow A, Pajonk FG (2006). Insight and quality of life in schizophrenia: recent findings and treatment implications. *Current Opinion in Psychiatry* **19**, 637–641.

Kay SR, Fiszbein A, Opler LA (1987). The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophrenia Bulletin* **13**, 261–276.

Kirkpatrick B, Fenton WS, Carpenter Jr WT, Marder SR (2006). The NIMH-MATRICS consensus statement on negative symptoms. *Schizophrenia Bulletin* **32**, 214–219.

Kirkpatrick B, Strauss GP, Nguyen L, Fischer BA, Daniel DG, Cienfuegos A, Marder SR (2011). The brief negative symptom scale: psychometric properties. *Schizophrenia Bulletin* **37**, 300–305.

Klein E, Kolsky Y, Puyerovsky M, Koren D, Chistyakov A, Feinsod M (1999). Right prefrontal slow repetitive transcranial magnetic stimulation in schizophrenia: a double-blind sham-controlled pilot study. *Biological Psychiatry* **46**, 1451–1454.

Klemm E, Danos P, Grünwald F, Kasper S, Moller HJ, Biersack HJ (1996). Temporal lobe dysfunction and correlation of regional cerebral blood flow abnormalities with psychopathology in schizophrenia and major depression – a study with single photon emission computed tomography. *Psychiatry Research* **68**, 1–10.

Ko JH, Monchi O, Ptito A, Bloomfield P, Houle S, Strafella AP (2008). Theta burst stimulation-induced inhibition of dorsolateral prefrontal cortex reveals hemispheric asymmetry in striatal dopamine release during a set-shifting task: a TMS-[^{11}C]raclopride PET study. *European Journal of Neuroscience* **28**, 2147–2155.

Kole MH, Fuchs E, Ziemann U, Paulus W, Ebert U (1999). Changes in 5-HT1A and NMDA binding sites by a single rapid transcranial magnetic stimulation procedure in rats. *Brain Research* **826**, 309–312.

Lahti AC, Holcomb HH, Medoff DR, Weiler MA, Tamminga CA, Carpenter Jr WT (2001). Abnormal patterns of regional cerebral blood flow in schizophrenia with primary negative symptoms during an effortful auditory recognition task. *American Journal of Psychiatry* **158**, 1797–1808.

Lako IM, Bruggeman R, Knegtering H, Wiersma D, Schoevers RA, Slooff CJ, Taxis K (2012). A systematic review of instruments to measure depressive symptoms in patients with schizophrenia. *Journal of Affective Disorders* **140**, 38–47.

Lako IM, van den Heuvel ER, Knegtering H, Bruggeman R, Taxis K (2013). Estimating dopamine D_2 receptor occupancy for doses of 8 antipsychotics: a meta-analysis. *Journal of Clinical Psychopharmacology* **33**, 675–681.

Lane HY, Chang YC, Liu YC, Chiu CC, Tsai GE (2005). Sarcosine or D-serine add-on treatment for acute exacerbation of schizophrenia: a randomized, double-blind, placebo-controlled study. *Archives of General Psychiatry* **62**, 1196–1204.

Leucht S, Pitschel-Walz G, Abraham D, Kissling W (1999). Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo. A meta-analysis of randomized controlled trials. *Schizophrenia Research* **35**, 51–68.

Liemburg E, Castelein S, Stewart R, van der Gaag M, Aleman A, Knegtering H, Genetic Risk and Outcome of Psychosis (GROUP) Investigators (2013). Two subdomains of negative symptoms in psychotic disorders: established and confirmed in two large cohorts. *Journal of Psychiatric Research* **47**, 718–725.

Lisanby SH, Gutman D, Luber B, Schroeder C, Sackeim HA (2001). Sham TMS: intracerebral measurement of the induced electrical field and the induction of motor-evoked potentials. *Biological Psychiatry* **49**, 460–463.

Lisanby SH, Maddox JH, Prudic J, Devanand DP, Sackeim HA (2000). The effects of electroconvulsive therapy on memory of autobiographical and public events. *Archives of General Psychiatry* **57**, 581–590.

Loo CK, McFarquhar TF, Mitchell PB (2008). A review of the safety of repetitive transcranial magnetic stimulation as a clinical treatment for depression. *International Journal of Neuropsychopharmacology* **11**, 131–147.

Loo CK, Mitchell PB (2005). A review of the efficacy of transcranial magnetic stimulation (TMS) treatment for depression, and current and future strategies to optimize efficacy. *Journal of Affective Disorders* **88**, 255–267.

Mennemeier M, Triggs W, Chelette K, Woods A, Kimbrell T, Dornhoffer J (2009). Sham transcranial magnetic stimulation using electrical stimulation of the scalp. *Brain Stimulation* **2**, 168–173.

Milev P, Ho BC, Arndt S, Andreasen NC (2005). Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: a longitudinal first-episode study with 7-year follow-up. *American Journal of Psychiatry* **162**, 495–506.

Mogg A, Purvis R, Eranti S, Contell F, Taylor JP, Nicholson T, Brown RG, McLoughlin DM (2007). Repetitive transcranial magnetic stimulation for negative symptoms of schizophrenia: a randomized controlled pilot study. *Schizophrenia Research* **93**, 221–228.

Montgomery SA, Asberg M (1979). A new depression scale designed to be sensitive to change. *British Journal of Psychiatry* **134**, 382–389.

Murphy BP, Chung YC, Park TW, McGorry PD (2006). Pharmacological treatment of primary negative symptoms in schizophrenia: a systematic review. *Schizophrenia Research* **88**, 5–25.

Novak T, Horacek J, Mohr P, Kopecek M, Skrdlantova L, Klirova M, Rodriguez M, Spaniel F, Dockery C, Hoschl C (2006). The double-blind sham-controlled study of high-frequency rTMS (20 Hz) for negative symptoms in schizophrenia: negative results. *Neuro Endocrinology Letters* **27**, 209–213.

Potkin SG, Alva G, Fleming K, Anand R, Keator D, Carreon D, Doo M, Jin Y, Wu JC, Fallon JH (2002). A PET study of the pathophysiology of negative symptoms in schizophrenia. Positron emission tomography. *American Journal of Psychiatry* **159**, 227–237.

Prikryl R, Kasparek T, Skotakova S, Ustohal L, Kucerova H, Ceskova E (2007). Treatment of negative symptoms of schizophrenia using repetitive transcranial magnetic stimulation in a double-blind, randomized controlled study. *Schizophrenia Research* **95**, 151–157.

Prikryl R, Ustohal L, Prikrylova Kucerova H, Kasparek T, Venclikova S, Vrzalova M, Ceskova E (2013). A detailed analysis of the effect of repetitive transcranial magnetic stimulation on negative symptoms of schizophrenia: a double-blind trial. *Schizophrenia Research* **149**, 167–173.

Rabany L, Weiser M, Werbeloff N, Levkovitz Y (2011). Assessment of negative symptoms and depression in schizophrenia: revision of the SANS and how it relates to the PANSS and CDSS. *Schizophrenia Research* **126**, 226–230.

Rey A (1958). *L'examin clinique en psychologie (The examined clinical psychology)*. Presses universitaires de France: Paris.

Sabri O, Erkwoh R, Schreckenberger M, Cremerius U, Schulz G, Dickmann C, Kaiser HJ, Steinmeyer EM, Sass H, Buell U (1997). Regional cerebral blood flow and negative/positive symptoms in 24 drug-naive schizophrenics. *Journal of Nuclear Medicine* **38**, 181–188.

Sachdev P, Loo C, Mitchell P, Malhi G (2005). Transcranial magnetic stimulation for the deficit syndrome of schizophrenia: a pilot investigation. *Psychiatry and Clinical Neurosciences* **59**, 354–357.

Sanfilipo M, Lafargue T, Rusinek H, Arena L, Loneragan C, Lautin A, Rotrosen J, Wolkin A (2002). Cognitive performance in schizophrenia: relationship to regional brain volumes and psychiatric symptoms. *Psychiatry Research* **116**, 1–23.

Schmand B, Bakker D, Saan R, Louman J (1991). The Dutch Reading Test for Adults: a measure of premorbid intelligence level. *Tijdschrift voor gerontologie en geriatrie* **22**, 15–19.

Schneider AL, Schneider TL, Stark H (2008). Repetitive transcranial magnetic stimulation (rTMS) as an augmentation treatment for the negative symptoms of schizophrenia: a 4-week randomized placebo controlled study. *Brain Stimulation* **1**, 106–111.

Schutter DJ, van Honk J (2006). A standardized motor threshold estimation procedure for transcranial magnetic stimulation research. *Journal of ECT* **22**, 176–178.

Selemon LD, Mrzljak J, Kleinman JE, Herman MM, Goldman-Rakic PS (2003). Regional specificity in the neuropathologic substrates of schizophrenia: a morphometric analysis of Broca's area 44 and area 9. *Archives of General Psychiatry* **60**, 69–77.

Shad MU, Tamminga CA, Cullum M, Haas GL, Keshavan MS (2006). Insight and frontal cortical function in schizophrenia: a review. *Schizophrenia Research* **86**, 54–70.

Shi C, Yu X, Cheung EF, Shum DH, Chan RC (2014). Revisiting the therapeutic effect of rTMS on negative symptoms in schizophrenia: a meta-analysis. *Psychiatry Research* **215**, 505–513.

Shioiri T, Kato T, Inubushi T, Murashita J, Takahashi S (1994). Correlations of phosphomonoesters measured by phosphorus-31 magnetic resonance spectroscopy in the frontal lobes and negative symptoms in schizophrenia. *Psychiatry Research* **55**, 223–235.

Sibon I, Strafella AP, Gravel P, Ko JH, Booij L, Soucy JP, Leyton M, Diksic M, Benkelfat C (2007). Acute prefrontal cortex TMS in healthy volunteers: effects on brain ^{11}C-alphaMtrp trapping. *NeuroImage* **34**, 1658–1664.

Slotema CW, Blom JD, Hoek HW, Sommer IE (2010). Should we expand the toolbox of psychiatric treatment methods to include repetitive transcranial magnetic stimulation (rTMS)? A meta-analysis of the efficacy of rTMS in psychiatric disorders. *Journal of Clinical Psychiatry* **71**, 873–884.

Strafella AP, Paus T, Barrett J, Dagher A (2001). Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. *Journal of Neuroscience* **21**, RC157.

Strous RD, Maayan R, Lapidus R, Stryjer R, Lustig M, Kotler M, Weizman A (2003). Dehydroepiandrosterone augmentation in the management of negative, depressive, and anxiety symptoms in schizophrenia. *Archives of General Psychiatry* **60**, 133–141.

van den Burg W, Saan RJ, Deelman BG (1985). *15-Woordentest. Provisional Manual (15 - Word Test Provisional Manual)*. University Hospital: Groningen.

Verhage F (1983). *Revised Scoring Method*. University Hospital: Groningen.

Wechsler D (1997). *Wechsler Adult Intelligence Scale*, 3rd edn. Psychological Corp.: San Antonio, TX.

Wolkin A, Sanfilipo M, Wolf AP, Angrist B, Brodie JD, Rotrosen J (1992). Negative symptoms and hypofrontality in chronic schizophrenia. *Archives of General Psychiatry* **49**, 959–965.