Deep transcranial magnetic stimulation add-on for treatment of negative symptoms and cognitive deficits of schizophrenia: a feasibility study

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Abstract

Treatment for negative symptoms and cognitive deficits, core elements of schizophrenia, remains inadequate. Stimulation of the prefrontal cortex via transcranial magnetic stimulation (TMS) yields only moderate results, possibly due to limited stimulation depth. Deep-TMS enables deeper and wider stimulation than before. This preliminary study is the first to examine deep-TMS as a possible add-on treatment for negative symptoms and cognitive deficits of schizophrenia. The effect of 20 daily deep-TMS sessions (20 Hz, 120% motor threshold) over the prefrontal cortex of 15 patients indicated improvement in cognition and negative symptoms that was maintained at 2-wk post-treatment follow-up.

Introduction

Negative symptoms and cognitive deficits are considered core symptoms of schizophrenia (Kuperberg & Heckers, 2000) and treatment for these indications remains inadequate (Keefe *et al.* 1999).

A growing body of evidence suggests that repetitive transcranial magnetic stimulation (rTMS) can alleviate negative symptoms of schizophrenia via excitatory stimulation of the dorsolateral prefrontal cortex (DLPFC) (Blumberger *et al.* 2010). Attempts to treat negative symptoms with TMS have been guided by knowledge of frontal pathology in schizophrenia (Stanford *et al.* 2008). Hypofrontality, particularly of

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DLPFC correlates with both negative symptoms and cognitive deficits (Andreasen *et al.* 1997) and has been suggested as a primary abnormality in the disorder (Weinberger *et al.* 1996). It was hypothesized that high-frequency rTMS, which increases cortical excitability in healthy volunteers, might reverse prefrontal hypo-activity in schizophrenia patients (Jin *et al.* 2006). It has been demonstrated that activation of the prefrontal cortex (PFC) modulates dopamine release (Strafella *et al.* 2001) which may underlie improvement of negative symptoms (Heimer *et al.* 1997). High-frequency TMS was also shown to induce acute increases in neuronal excitability, and repeated sessions were shown to induce long-lasting effects (Pell *et al.* 2011).

However, even though specific parameters (such as treatment duration and frequency) have been found to improve clinical outcomes (Dlabac-de Lange *et al.* 2010), recent reviews (Blumberger *et al.* 2010; Freitas *et al.* 2009; Stanford *et al.* 2008), reported moderate improvement of negative symptoms. Moreover, despite recent data suggesting that such stimulation can

improve cognitive performance (Barr *et al.* 2009), no studies have focused on the effect of an extensive TMS protocol, applied to the DLPFC, on cognition in patients with schizophrenia. It should be noted that cognitive evaluations have been included in four relevant studies (Fitzgerald *et al.* 2008; Mogg *et al.* 2007; Novak *et al.* 2006; Schneider *et al.* 2008); however, relative to the present study, they were all lower in stimulation intensity, duration and frequency, and all included less extensive cognitive evaluations.

Standard rTMS coils induce an effective field in depth of approximately 1 cm (Roth *et al.* 2002). It was hypothesized that deeper stimulation could improve results (Blumberger *et al.* 2010). Recently, a novel, deep-TMS H1 coil was introduced in clinical studies, inducing a magnetic field with greater depth and distribution (Roth *et al.* 2007; Zangen *et al.* 2005). This version of the H coil is designed to stimulate deeper layers of the PFC, especially in the left hemisphere, and effectively reaches a depth of 3 cm without a significant increase of electric fields induced in superficial cortical regions (Roth *et al.* 2007).

The current preliminary study is the first safety and feasibility investigation into deep-TMS as an add-on treatment for negative symptoms and cognitive deficits in schizophrenia.

Methods

Subjects

Patients diagnosed as having schizophrenia (DSM-IV criteria) and displaying predominant negative symptoms were eligible for enrolment. The main inclusion criteria were age 18–65 yr, Positive and Negative Syndrome Scale (PANSS) negative score ⩾21, PANSS positive score ⩽24, stability on antipsychotics, and naïve to TMS (patients who had previously experienced rTMS were excluded from the study). The main exclusion criteria were another Axis I disorder(s), any known risk factor for seizures, substance abuse disorder and suicide risk. The study period ran from 2006 to 2009. Ethical approval was given by the Institutional Review Board (IRB) committee of the Shalvata Mental Health Center and informed consent was obtained from patients.

Study design

Daily TMS sessions were conducted for four consecutive weeks, using the H1 deep-TMS coil (inducing bilateral stimulation in the PFC with greater depth and intensity in the left hemisphere) totalling 20 sessions (visits 1–20). Follow-up assessments were conducted 2 wk post-treatment (visit 21). Clinical efficacy assessments were conducted at baseline, visits 5, 10, 15, 20 and 21.

All subjects received active treatment (there was no sham control condition), and the clinical rater was not blind to the treatment. Cognitive performance was assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB, visits 1, 10, 20, 21) which included four domains: psychomotor speed (reaction time), visuospatial memory (spatial recognition memory), sustained attention (rapid visual information processing) and executive functions [Stockings of Cambridge (SOC), spatial working memory, spatial span and intra-/extra-dimensional shift].

The primary outcome measures were defined as change in the Scale for the Assessment of Negative Symptoms (SANS) and CANTAB results from baseline (visit 1) to the primary efficacy time-point at the end of treatment (visit 20). Secondary outcome measures were negative symptoms and cognitive performance at follow-up and the following clinical measurements: PANSS, Calgary Depression Scale (CDS), Social and Occupational Functioning Assessment Scale (SOFAS), cognitive self-assessment (CSA) and Clinical Global Impression – Severity scale (CGI-S). Safety was assessed by interviews, daily inspections of the scalp, a self-graded headache intensity visual analog scale (VAS; scored from 0 to 10), blood pressure and pulse rate measurements (visits 1, 10, 20).

Study device

Magnetic field induction was by a Magstim Super Rapid stimulator (Magstim, UK) connected to an H1 coil (deep-TMS, Israel). Motor threshold (MT) was defined as the lowest intensity of stimulation able to produce motor-evoked potentials of the right abductor pollicis brevis of at least $50 \mu V$ in 5/10 trials. Coil placement for treatment was 5 cm anterior to this motor spot. Daily treatments were delivered at 120% intensity of MT, in trains of 20 Hz. Each daily session consisted of 42 trains of 2 s (40 pulses each), with a 20-s inter-train interval.

Statistical analysis methods

Baseline characteristics of the participants are presented using descriptive statistics. The change from baseline to week 4 in clinical rating scales was estimated from repeated-measures analysis of variance models (SAS PROC MIXED). For each rating scale, the change from baseline was modelled as a function of time in weeks and the baseline value. Linearity was assessed by comparing the -2 log likelihood of two

models, week entered as a continuous variable and week entered as a categorical variable. The differences were found to be statistically significant; thus, it was assumed that the change from baseline follows a non-linear pattern and the models chosen were those with week entered as a categorical variable. LSMeans of the adjusted mean change from baseline at each visit were estimated together with a 95% CI and a test for the significance of the change from baseline at each week.

To examine the possibility of a relationship between cognitive performance at baseline and improvement of negative symptoms, Spearman's correlation coefficients (r_s) were calculated for cognitive performance scores at baseline *vs.* PANSS negative scores. Similarly, to examine the possibility of a relationship between negative symptoms on the one hand and measures of cognition at baseline and/or cognitive improvement on the other we calculated Spearman's correlation coefficients for PANSS negative, *vs.* cognitive performance scores at baseline, and *vs.* cognitive changes from baseline to visit 20.

Results

Fifteen subjects (11 males, 73.3%) met the inclusion/exclusion criteria, and 10 (66.7%) completed the 4-wk treatment (visit 20). Eight of those 10 subjects arrived at the 2-wk follow-up (visit 21; there was a 3-month follow-up point, which only four subjects attended, data not presented due to the small sample). Four subjects withdrew from the study (none attributed their withdrawal to side-effects). One patient was excluded from the study (see Safety and tolerability section below).

Baseline characteristics of study patients

The subjects included had the following baseline characteristics (mean ± S.D.): age (32.73 ± 11.18 yr), education (12.40 ± 1.72 yr), age at first episode (24.86 ± 10.69 yr), age at first hospitalization (25.93 ± 13.69 yr), and number of prior hospitalizations (2.29 ± 2.20). The subjects had the following baseline PANSS scores (mean ± S.D.): total (91.73 ± 15.34), positive (14.40 ± 4.66), negative (24.07 ± 6.28), and general (50.47 ± 6.95) (Supplementary Table S1, online).

Primary endpoints

A significant change throughout the study period was observed in the participants' SANS scores: there was a mean decrease of 16.82% (11.8 ± 3.28 points) after 4 wk, with a 95% CI of −18.73 to −4.82 ($p = 0.0025$). Response was defined as a change from baseline SANS score of at least 20% at 4 wk (Mogg *et al.* 2007). Seventy percent of the subjects who completed the entire course of treatment responded to the treatment. Inclusion of subjects who dropped out into the calculation of responders would have yielded a 46.67% response rate. The SANS subscale scores over time, and all subscales except for 'alogia' reached a level of significance by end of treatment (see Supplementary material, available online).

Cognitive improvement was found in executive functions (SOC, $p = 0.04$; spatial span, $p = 0.03$; spatial working memory, $p = 001$), and sustained attention (rapid visual information processing, $p = 0.01$). There were no changes in psychomotor speed (reaction time), visuospatial memory (spatial recognition memory) and one of the executive functions tasks (i.e. intra-/extra-dimensional shift) (Table 1).

Secondary endpoints

Improvement in SANS was maintained at follow-up ($p = 0.0014$). PANSS scores of patients changed significantly by end of treatment ($p < 0.0001$), as did CGI-S ($p = 0.0107$), CDS ($p = 0.0001$) and SOFAS ($p < 0.0001$). They all maintained a significant improvement at follow-up. CSA improvement did not reach significance ($p = 0.0993$) (Table 2).

Cognitive improvement at follow-up was maintained in rapid visual information processing ($p < 0.001$), and achieved significance in intra-/extra-dimensional shift ($p = 0.0065$). To examine the possibility that the improvement in negative symptoms was mediated by improvement in depressive symptoms and vice versa, we analysed both the adjusted mean changes in SANS scores when adjusting for CDS scores and the adjusted mean changes in CDS scores when adjusting for SANS scores: these adjustments did not change the results at the primary endpoints ($p = 0.0005$ and $p < 0.0001$, respectively).

A correlation between PANSS negative score and the executive functions test, SOC, was revealed for both PANSS-N score at baseline *vs.* cognitive baseline scores, and PANSS-N at baseline *vs.* cognitive changes from baseline to visit 20 (at baseline: $r_s = -0.55$, $p = 0.04$; change from baseline: $r_s = 0.68$, $p = 0.03$). Patients with greater PANSS negatives scores at baseline showed poor performance in SOC, but had greater improvement in this test after the treatment. On the other hand, no correlation was found between cognitive performance at baseline and improvement of negative symptoms (Supplementary Table S2, online).

Table 1. CANTAB tests: adjusted mean change (LSmeans) at end of treatment (visit 20) of study patients

Parameter	Estimate	S.E.	d.f.	*t* value	Pr > |*t*|	95% CI
Psychomotor speed						
MOT mean latency	1.49	0.86	14	1.72	0.1065	−0.36 to 3.34
Sustained attention						
RVP A	0.05	0.01	16	5.07	**0.0001**	0.03 to 0.07
Visuospatial memory						
SRM % correct	−7.85	5.03	16	−1.56	0.1380	−18.52 to 2.81
Executive functions						
SWM between errors	−13.53	5.09	16	−2.66	**0.0172**	−24.31 to −2.74
SWM strategy	−4.00	1.04	16	−3.86	**0.0014**	−6.20 to −1.80
SSP span length	0.86	0.35	10	2.47	**0.0331**	0.08 to 1.63
IED stages completed	0.26	0.35	16	0.73	0.4783	−0.49 to 1.00
IED total errors	−3.03	7.79	16	−0.39	0.7025	−19.53 to 13.48
SOC initial thinking time, 5 moves	−0.35	1.91	16	−0.19	0.8553	−4.40 to 3.69
SOC subsequent thinking time, 5 moves	0.02	0.10	16	0.19	0.8521	−0.20 to 0.24
SOC problems solved	1.35	0.60	15	2.25	**0.0400**	0.07 to 2.64

CI, Confidence interval; MOT, motor screening; RVP A, rapid visual processing – sensitivity to errors; SRM, spatial recognition memory; SWM, spatial working memory; SSP, spatial span; IED, intra-/extra-dimensional shift; SOC, Stockings of Cambridge.

Table 2. Clinical measurements scores adjusted mean change from baseline per week (LSmeans) of study patients

Parameter	Week	Estimate	S.E.	d.f.	*t* value	Pr > |*t*|	95% CI
SANS	4	−11.77	3.28	16	−3.59	**0.0025**	−18.72 to −4.82
	6	−14.19	3.67	16	−3.87	**0.0014**	−21.97 to −6.42
PANSS	4	−16.50	3.12	17	−5.29	**<0.0001**	−23.08 to −9.92
	6	−20.97	3.28	17	−6.39	**<0.0001**	−27.90 to −14.04
CGI-S	4	−0.50	0.17	17	−2.87	**0.0107**	−0.87 to −0.13
	6	−0.67	0.18	17	−3.66	**0.0020**	−1.06 to −0.28
CDS	4	−4.22	0.84	17	−5.04	**0.0001**	−5.98 to −2.45
	6	−5.07	0.89	17	−5.71	**<0.0001**	−6.94 to −3.20
SOFAS	4	6.89	1.21	17	5.71	**<0.0001**	4.34 to 9.43
	6	7.34	1.27	17	5.77	**<0.0001**	4.66 to 10.02
CSA	4	2.15	1.23	15	1.76	0.0993	−0.46 to 4.77
	6	2.43	1.23	15	1.98	0.0657	−0.18 to 5.04

SANS, Scale for the Assessment of Negative Symptoms; PANSS, Positive and Negative Syndrome Scale; CGI-S, Clinical Global Impression – Severity scale; CDS, Calgary Depression Scale; SOFAS, Social and Occupational Functioning Assessment Scale; CSA, cognitive self-assessment.

Safety and tolerability

The average degree of headache on a scale of 1–10 (VAS) was 2.8 and 1.2 on visits 1 and 20, respectively. No change was observed in blood pressure or pulse measurements (average 125/79 mmHg and 77.11 beats per minute at baseline, and 120/75 mmHg and 67.57 beats per minute at visit 20). Inspections of the scalp revealed no damage. One patient (male, 28 yr) receiving 5 mg/d olanzapine, 20 mg/d Recital, 1 mg/d Lorivan, developed a short tonic-clonic seizure with no incontinence during the fifth session. The patient recovered after a few minutes without neurological deficits apart from tiredness. However, seizures induced intentionally via rTMS (magnetic seizure therapy – MST) were suggested as an alternative to ECT in the treatment of depressive symptoms, with fewer side-effects (Spellman *et al.* 2008).

Discussion

This preliminary study is the first to examine the effect of add-on deep-TMS stimulation of prefrontal regions in the treatment of cognitive deficits and negative symptoms of schizophrenia. The results suggest that H coil deep-TMS to these regions can induce a positive therapeutic effect on both negative symptoms and cognitive deficits of schizophrenia when used as an adjunct to antipsychotic medication. The improvement in negative symptoms was suggested by an improvement in the SANS over time, as well as improvement in the PANSS negative subscale. Seventy percent of patients who completed treatment were responders, having achieved a ⩾20% improvement in negative symptoms.

The cognitive assessments suggested an improvement in cognitive deficits in frontal and frontoparietal-related tasks, both for executive functions (SOC, spatial span, spatial working memory) and sustained attention (rapid visual information processing). No change was found in a test of fronto-striatal function (intra-/extra-dimensional set shift) and a parietal function task (spatial recognition memory). Taken together, these findings suggest that excitatory TMS to the PFC might improve frontal lobe-related cognitive functions, and does not improve cognitive functions associated with the striatal and parietal areas.

It should be noted, however, that due to the lack of a sham control group, the improvements found in the cognitive measurements may be attributed to a learning effect, although our previous study using these assessments (Levkovitz *et al.* 2009) did not show a learning effect in a control group tested in a similar time-course. Nevertheless, this issue requires further investigation in a large sham-controlled, double-blinded study.

The strong positive correlation found between the negative symptoms score at baseline and the improvement in executive functions, indicates that stronger negative symptoms at baseline may predict a bigger improvement of executive functions in response to deep-rTMS over the PFC. On the other hand, the lack of correlation between cognitive performance at baseline and improvement of negative symptoms indicates that measurement of executive function at baseline can not be used at this time as a predictor for potential effectiveness of deep-rTMS for negative symptoms (however, future larger studies, should explore this option).

Due to small sample size it is not within the scope of the current study to determine whether or not cognitive improvement stemmed from improvement in negative/depressive symptoms (and/or additional possible explanations). Future, larger studies should better characterize responsive populations with regards to these parameters. Nevertheless, the current study is the first to suggest a possible cognitive improvement which can be maintained following extensive prefrontal stimulation via TMS in schizophrenia patients.

Improvement in depressive symptoms was indicated by an improvement over time in the CDS, at the social and occupational level (SOFAS), and in general condition (CGI-S). The effect lasted for at least 2 wk. There was no indication that CSA had been changed.

The short seizure induced in the fifth treatment day in one of the patients receiving olanzapine (5 mg/d) implies that caution should be used when using high-intensity and high-frequency parameters of stimulation in such patients. It is important to note that antipsychotics lower the threshold for a seizure and can even induce seizures without rTMS (Pisani *et al.* 2002). Furthermore, intentional TMS seizure induction (MST) was suggested as a therapeutic tool, and has been shown to alleviate depressive symptoms (Lisanby & Peterchev, 2009). The risk for seizures may be reduced in future studies by monitoring EEG patterns during the rTMS treatment in patients receiving high-intensity and high-frequency rTMS combined with such medications (Rotenberg, 2010). It is too early at this stage to determine whether deep-TMS is more likely to induce seizures than standard TMS.

The design of the current study has several limitations: its small sample size and add-on design prevent ruling out a possible placebo effect and expectancy bias, as well as the possibility of improvement having been the result of other factors, such as the natural course of the illness. Nevertheless, given the chronic and persistent nature of negative symptoms and cognitive deficits that characterize schizophrenia, together with the lack of any currently available satisfactory therapeutic options, the results of this pilot study seem to point to a possible new treatment that needs to be further examined. In light of this pilot study, a randomized controlled study seems desirable.

Note

Supplementary material accompanies this paper on the Journal's website (http://journals.cambridge.org/pnp).

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