*Short Report*

# Double-blind, randomized sham controlled study of deep-TMS add-on treatment for negative symptoms and cognitive deficits in schizophrenia

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**Abstract**

Negative symptoms and cognitive deficits are considered core symptoms of schizophrenia, yet treatment for them remains inadequate. Deep-transcranial magnetic stimulation (TMS) is a novel technology that enables non-invasive stimulation of deep layers of the prefrontal cortex. Preliminary evidence suggests that deep-TMS could be effective in the treatment of negative symptoms and cognitive deficits. The current study is the first double-blind, randomized sham-controlled study to examine the feasibility of deep-TMS add-on treatment for negative symptoms and cognitive deficits in schizophrenia. Twenty daily H1 deep-TMS treatments (20Hz, 120% MT) were delivered, in a double-blind, randomized sham-controlled design ($n$=30). Extensive clinical and cognitive assessments were carried out throughout the study and for an additional one month follow-up period. The results indicate that at the end of the treatment period, negative symptoms (as indicated by the Scale for the Assessment of Negative Symptoms (SANS)) significantly reduced in the TMS group (–7.7), but not in the sham group (–1.9). Differences between the groups were not statistically significant.

**Keywords**

Schizophrenia, negative symptoms, deep, TMS, transcranial magnetic stimulation

## Introduction

Negative symptoms are considered core symptoms of schizophrenia, and are possibly the most significant factor in patients' impaired functional recovery (Foussias and Remington, 2010). Antipsychotic medications often have little to no effect on negative symptoms, and may even have negative effects (Schneider et al., 2008).

Studies have consistently suggested that prefrontal dysfunction, particularly of the dorsolateral prefrontal cortex (DLPFC), is involved in the pathophysiology of negative symptoms, as well as in the cognitive deficits associated with schizophrenia (Hill et al., 2004; Potkin et al., 2002; Wolkin et al., 1992). Hypoactivation of the prefrontal cortex has been suggested as a primary abnormality in the disorder (Hill et al., 2004; Weinberger et al., 1996; Wolkin et al., 1992).

Transcranial magnetic stimulation (TMS) is a method of non-invasive brain stimulation that can modulate cortical excitability. High frequency TMS was shown to increase cortical excitability in healthy volunteers, and repeated TMS sessions have been demonstrated to induce long-lasting effects (Pell et al., 2011). It was thus hypothesized that activation of the prefrontal cortex via TMS could ameliorate hypofrontality in schizophrenia patients and alleviate negative symptoms (Geller et al., 1997). High frequency TMS targeted at prefrontal cortex (PFC) was shown to modulate dopamine release (Strafella et al., 2001), which may underlie negative symptoms amelioration (Heimer et al., 1997). Additionally, TMS was also shown to mediate changes in cortical inhibition, via inhibitory interneurons that use gamma-aminobutyric acid (GABA) as their principal neurotransmitter (de Jesus et al., 2013). Evidence suggest that high frequency TMS increases cortical inhibition (Daskalakis et al., 2006; de Jesus et al., 2013), particularly in subjects with reduced baseline inhibition (Daskalakis et al., 2006). Recently, high frequency TMS was also shown to selectively reduce excessive frontal gamma oscillatory activity in patients suffering from schizophrenia (Barr et al., 2011).

Recent reviews addressing the efficacy of TMS treatment for negative symptoms, however, reported mixed results, and called for improvement of stimulation protocols and techniques (Dlabac-de Lange et al., 2010; Slotema et al., 2010). It has been hypothesized that standard TMS coils deliver insufficient stimulation depth, and deeper stimulation could improve treatment results (Blumberger et al., 2010). To explore this possibility, a novel, deep-TMS coil was introduced in clinical studies (Zangen et al., 2005). While standard TMS coils induce an effective depth of approximately 1 cm, deep-TMS coils effectively reach a depth of

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3 cm without a significant increase in electric fields induced in superficial cortical regions (Zangen et al., 2005). The H1 version of the deep TMS coil is designed to stimulate deep layers of the PFC, particularly in the left hemisphere (Bersani et al., 2013).

A preliminary open-label study, which examined the effects of H1 deep-TMS, indicated improvement in negative symptoms, cognition and depression following 20 daily sessions. The effect was maintained at a two-week post-treatment follow-up (Levkovitz et al., 2011). The current study is the first double-blind, randomized sham-controlled study to examine the feasibility of deep-TMS add-on treatment for negative symptoms and cognitive deficits in schizophrenia.

## Experimental procedure

### Subjects

Patients diagnosed by at least two psychiatrists as having schizophrenia/schizoaffective disorder (excluding manic type schizoaffective disorder; ICD-10 criteria) and displaying predominant negative symptoms were eligible for enrollment.

Thirty patients were recruited. Main admission criteria were: Positive and Negative Syndrome Scale (PANSS) negative subscale score ≥21, PANSS positive subscale score ≤24, no other axis-I disorder, use of antipsychotic medication two months prior to inclusion, no change in antipsychotics two months prior to inclusion, no use of medication lowering the seizure threshold (clozapine above 200 mg/day, bupropion, clomipramine, maprotiline, chlorpromazine), no drug or alcohol abuse in the year prior to admission.

### Study design

This study was a double-blind, randomized sham-controlled study ($n$ = 30), with a 2:1 ratio in favor of the active condition (the 2:1 ratio was chosen to facilitate patient recruitment). Power analysis was performed based on results of a pilot study (Levkovitz et al., 2011: reduction from baseline in Scale for the Assessment of Negative Symptoms (SANS) score of 15.6±7.72 when excluding for a single outlier) and assumed a placebo effect of 33%.

Daily TMS sessions were administered for four consecutive weeks using the H1 deep-TMS coil, followed by two additional visits at weeks 5 and 8.

### Clinical assessment

The primary outcome measure was change in the SANS total score from baseline (week 0) to the end of treatment period (week 4). Secondary outcome measures were changes from baseline to all time points (week 2, week 4 and two follow-up visits at weeks 5 and 8) in the following clinical measurements: SANS, PANSS (total, and negative subscale), Calgary Depression Scale for Schizophrenia (CDSS), Social and Occupational Functioning Assessment Scale (SOFAS), Cognitive Self Assessment (CSA), World Health Organization Quality of Life questionnaire (WHOQOL-BREF) and Clinical Global Impression – Severity scale (CGI-S). All the clinical evaluations were carried out by a single rater.

### Cognitive assessment

Neuropsychological performance was assessed (weeks 0, 4, 5) using the Cambridge Neuropsychological Test Automated Battery (CANTAB), and included four domains: *Psychomotor speed*: motor screening (MOT); reaction time (RTI); *Visuospatial memory*: pattern recognition memory (PRM); *Sustained attention*: rapid visual information processing (RVP); *Executive functions*: Stockings of Cambridge (SOC); spatial working memory (SWM).

### Study device and procedure

Stimulation was induced via Magstim Super Rapid stimulator (Magstim, UK) connected to an H1 deep-TMS coil (Brainsway, Israel). H1's main locus of stimulation is the left DLPFC. It is accompanied by weaker stimulation of the right DLPFC and lateral-medial axis in prefrontal and orbitofrontal regions (Roth et al., 2007). For specifics see Supplementary Appendix 1 online.

Motor threshold (MT) was defined as the lowest stimulation intensity able to produce motor-evoked potentials of the right abductor pollicis-brevis in 50% of the trials delivered. Coil placement for treatment was 5.5 cm anterior to this motor spot. Treatments were delivered at 120% intensity of MT, in trains of 20 Hz. Each session consisted of 42 two-second trains, divided by 20-second inter-train intervals.

### Statistical analysis

Baseline values and characteristics were compared with a t-test (continuous variables) or Fisher's exact test (dichotomous variables). Changes from baseline were modeled using repeated measures ANOVA as a function of baseline values (due to differences in baseline scores between the study groups), visit, group, and the visit × group interaction. Adjusted mean changes from baseline per group (active and sham) and the differences between groups are presented for each time point. $p$-values of ≤0.05 are considered significant. Nominal $p$-values are presented.

## Results

Twenty-eight subjects were analyzed for efficacy (two subjects were excluded from analyses due to stimulation intensity inadequacy, having received stimulation at intensities below 110% MT). Twenty-five subjects (83.33%) completed the treatment period; 19 subjects arrived at each of the follow-up visits. No differences were found between the active treatment group ($n$=20) and the sham group ($n$=10) in age, gender, duration of illness, age at first episode, family history of psychiatric conditions and number of hospitalizations. Demographic information is presented in Table 1.

### Outcome measurements

*Primary outcome measure.* A statistically significant reduction in SANS score changes from baseline to end of treatment was observed in the active group but not in the sham group. Differences between the active and sham groups in the reduction of SANS scores from baseline to all time points (weeks 2, 4, 5, 8) were not statistically significant (Figure 1).

**Table 1.** Sample demographics and characteristics for the active and sham groups.

| Variable | | Active (*N*=20) | Sham (*N*=10) | *p*-value |
|---|---|---|---|---|
| **Gender** | Male (%) | 13 (65) | 8 (80) | 0.6749[a] |
| | Female (%) | 7 (35) | 2 (10) | |
| **Age, years** | Mean (SD) | 33.1 (11.31) | 35.9 (11.00) | 0.5169[b] |
| **Age at first episode, years** | Mean (SD) | 21.0 (9.84) | 25.9 (8.31) | 0.2067[b] |
| **Family history of psychiatric conditions** | Yes (%) | 6 (30) | 4 (40) | 0.6872[a] |
| | No (%) | 10 (50) | 3 (30) | |
| | Unknown (%) | 4 (20) | 3 (30) | |
| **Number of hospitalizations** | Mean (SD) | 3.2 (3.39) | 2.6 (2.84) | 0.6629[b] |

[a]Fisher's exact test.
[b]*t*-test.

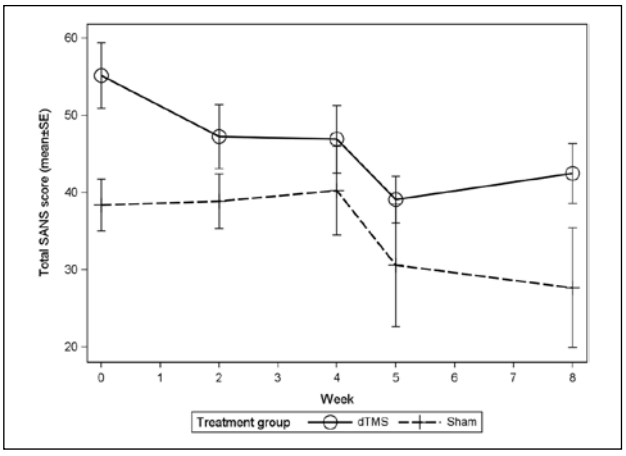


**Figure 1.** Scale for the Assessment of Negative Symptoms (SANS) mean total score (±standard error) at weeks 0, 2, 4, 5 (one-week follow-up) and 8 (one-month follow-up) in both treatment groups.

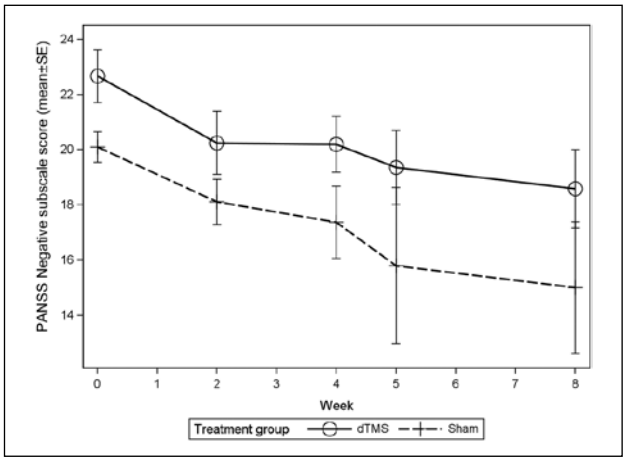


**Figure 2.** Positive and Negative Syndrome Scale (PANSS) mean negative subscale score (±standard error) at weeks 0, 2, 4, 5 (one-week follow-up) and 8 (one-month follow-up) in both treatment groups.

The analysis was repeated separately for all SANS subscales at the end of treatment periods, with similar results (comparison of the adjusted means at the end of the treatment period: affective flattening $p$=0.13; alogia $p$=0.49; avolition–apathy $p$=0.50; anhedonia–asociality $p$=0.79; attention $p$=0.10).

A higher 'response to treatment' rate (defined as a change from baseline SANS score of at least 20% (Mogg *et al.*, 2007)) was found at end of treatment in the active (10/16, 62.5%) than in the sham (3/9, 33.3%) group, but this difference was not statistically significant (Fisher's exact test $p$ =0.2262).

### *Secondary outcome measures*

*Clinical.* Improvement from baseline to end of treatment was observed for CGI, PANSS total (trend) and SOFAS (trend) in the treatment group but not in the sham (differences between the groups not statistically significant). Differences between the groups' mean change from baseline to all time points, namely, PANSS negative subscale (Figure 2), CDSS (Figure 3), PANSS total score, SOFAS, CSA, WHOQOL-BREF and CGI-S, were not statistically significant (baseline to end of treatment period: Table 2. Baseline to all time points: Supplementary Appendix 2 online).

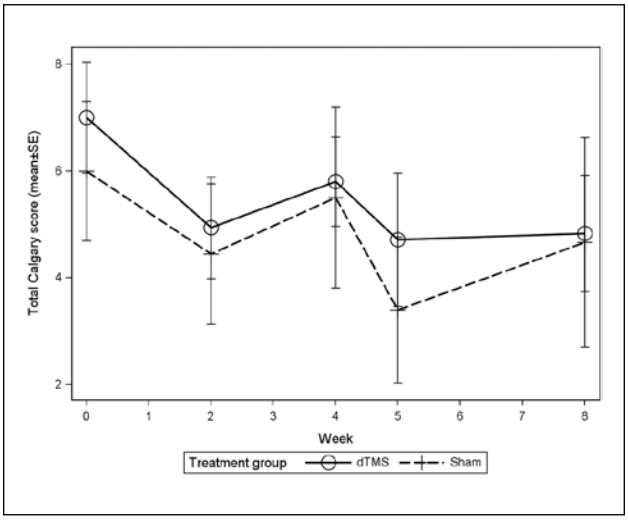


**Figure 3.** Calgay Depression Scale (CDSS) mean total score(±standard error) at weeks 0, 2, 4, 5 (one-week follow-up) and 8 (one-month follow up) in both treatment groups.

**Table 2.** Adjusted mean changes from baseline to the end of treatment period for all clinical parameters in the active and the sham groups, and differences between them.

| Parameter | | | Estimate | Standard error | *p*-value | 95% CI |
|---|---|---|---|---|---|---|
| **SANS** | Adjusted means of the changes | Active | −7.716 | 3.313 | 0.0289 | (−14.567; −0.866) |
| | | Sham | −1.945 | 4.607 | 0.6766 | (−11.443; 7.553) |
| | Difference | | −5.771 | 5.881 | 0.3356 | (−17.871; 6.328) |
| **PANSS** | Adjusted means of the changes | Active | −6.257 | 3.261 | 0.0677 | (−13.008; 0.494) |
| | | Sham | −2.695 | 4.440 | 0.5498 | (−11.877; 6.487) |
| | Difference | | −3.562 | 5.527 | 0.5256 | (−14.993; 7.869) |
| **PANSS (negative)** | Adjusted means of the changes | Active | −2.393 | 0.813 | 0.0075 | (−4.080; −0.707) |
| | | Sham | −3.083 | 1.127 | 0.0119 | (−5.416; −0.750) |
| | Difference | | 0.690 | 1.417 | 0.6311 | (−2.240; 3.619) |
| **CDSS** | Adjusted means of the changes | Active | −1.282 | 0.850 | 0.1466 | (−3.051; 0.487) |
| | | Sham | −1.165 | 1.161 | 0.3271 | (−3.581; 1.250) |
| | Difference | | −0.117 | 1.441 | 0.9362 | (−3.115; 2.881) |
| **SOFAS** | Adjusted means of the changes | Active | 4.774 | 2.382 | 0.0578 | (−0.172; 9.721) |
| | | Sham | −0.269 | 3.291 | 0.9355 | (−7.080; 6.542) |
| | Difference | | 5.044 | 4.117 | 0.2327 | (−3.465; 13.552) |
| **CSA** | Adjusted means of the changes | Active | 1.147 | 1.059 | 0.2907 | (−1.052; 3.346) |
| | | Sham | 1.075 | 1.683 | 0.5289 | (−2.390; 4.539) |
| | Difference | | 0.072 | 2.076 | 0.9724 | (−4.198; 4.343) |
| **WHOQOL** | Adjusted means of the changes | Active | 0.816 | 2.884 | 0.7802 | (−5.214; 6.846) |
| | | Sham | 3.504 | 3.909 | 0.3803 | (−4.631; 11.638) |
| | Difference | | −2.688 | 4.941 | 0.5922 | (−12.964; 7.589) |
| **CGI** | Adjusted means of the changes | Active | −0.323 | 0.139 | 0.0294 | (−0.611; −0.036) |
| | | Sham | 0.114 | 0.190 | 0.5534 | (−0.279; 0.508) |
| | Difference | | −0.438 | 0.236 | 0.0763 | (−0.926; 0.050) |

PANSS: Positive and Negative Syndrome Scale; CDSS: Calgary Depression Scale for Schizophrenia; SOFAS: Social and Occupational Functioning Assessment Scale; CSA: cognitive self-assessment; WHOQOL: World Health Organization Quality of Life questionnaire; CGI: Clinical Global Impression

Distribution of study parameters in the treatment and the sham groups at each measured time point can be found in Supplementary Appendix 3 online.

*Cognitive.* No differences were found between the groups in score changes in any of the cognitive tests from baseline to any of the time points, apart from one SOC measure (subsequent times for five move problems) at week 4 (Supplementary Appendix 4 online).

## Discussion

The current study examined the efficacy of H1 deep-TMS in the treatment of negative symptoms and cognitive deficits of schizophrenia (120% MT; 20 sessions). SANS and CGI scores improved in the active treatment group and not in the sham group, but no differences were found between the treatment groups. A second measurement of negative symptoms (PANSS-negative) indicated improvement in both treatment and sham groups, with no difference between the groups. No differences were found between the groups in all other parameters as well; namely, change from baseline in severity of: depression, social and occupational functioning, quality of life, clinical global impression and various cognitive measurements. It should be noted that despite randomization, the two groups differed in the severity of negative symptoms (and additional clinical variables) at baseline.

These results stem from the following: First, the sample size tested was insufficient to detect statistically significant differences between the groups. Second, H1-coil deep-TMS could be less effective in the treatment of negative symptoms of schizophrenia, possibly due to its distribution of stimulation: the H1 coil has a wider ipsilateral distribution of stimulation compared with standard figure of eight and round coils (Roth et al., 2007). Additionally, while H1's main locus of stimulation is the left DLPFC, it is accompanied by weaker stimulation of the contralateral DLPFC, as well as additional areas (lateral-medial axis in prefrontal and orbitofrontal regions (Roth et al., 2007)), creating a more distributed and somewhat bilateral stimulation. To date, most studies that examined the effect of rTMS stimulation on negative symptoms targeted the left DLPFC (Barr et al., 2012), and the effects of different stimulation patterns are yet to be ascertained. Recent studies that aimed to examine bilateral stimulation, however, did not find it effective in the treatment of negative symptoms (Barr et al., 2012; Fitzgerald et al., 2008), possibly suggesting a partial explanation of the results of the current study.

Third, the active treatment group had more severe negative symptoms at baseline than the sham group, possibly affecting results. We are unaware of studies addressing the question of the

effect of baseline severity on TMS results in negative symptoms; however, we cannot rule out the possibility of such an effect.

Fourth, a recent meta-analysis performed by Dlabac-de Lange et al. indicated that a stimulation frequency of 10 Hz is superior to that of 20 Hz (used in the current study) in reducing the negative symptoms of schizophrenia (10 Hz: Cohen's-*d*=0.63, 95% confidence interval (CI) 0.11–1.15; 20 Hz: Cohen's-*d* = 0.43; 95% CI 0.05–0.80) (Dlabac-de Lange et al., 2010). It has been suggested that the superiority of 10 Hz rTMS may be related to the fact that it lies within the peak alpha frequency band, which has been shown to be related to the occurrence and severity of negative symptoms (Jin et al., 1995, 1998, 2006).

Other possible explanations include the study's population (e.g. deficit and non-deficit negative symptoms were not distinguished, and a floor effect cause by insufficient severity of symptoms at baseline), other sub-optimal stimulation parameters (number of trains, pulses, sessions etc.) and abnormal neural plasticity reported in patients with schizophrenia (Daskalakis et al., 2008).

In conclusion, the current study did not find a difference between H1 deep-TMS and sham stimulation in the treatment of negative symptoms of schizophrenia. However, a significant reduction in SANS score was achieved in the active treatment group. To better examine the full potential of deep-TMS treatment for negative symptoms of schizophrenia a large-scale study is due. Future studies are also advised to use 10 Hz stimulation frequency and stimulate the left DLPFC exclusively. In addition, further research should examine the effect of baseline severity on the outcome of TMS treatment for negative symptoms.

## Conflict of interest

Yechiel Levkovitz and Lisa Deutsch are consultants to Brainsway Ltd.

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