RESEARCH ARTICLE

Efficacy of Adjunctive Use of Repetitive Transcranial Magnetic Stimulation in Patients with Schizophrenia with Prominent Negative Symptoms: A Randomized Controlled Trial

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Abstract

Aim: To explore the efficacy of adjunctive use of repetitive transcranial magnetic stimulation (rTMS) in patients with schizophrenia with prominent negative symptoms.

Materials and methods: It was a hospital-based, prospective, randomized, double-blind, sham-(placebo) controlled, interventional, two-armed trial, including 50 patients with predominant negative symptoms of schizophrenia who were divided into two groups of true and sham rTMS after TMS adult safety screening (TASS) screening and baseline Calgary Depression Scale for schizophrenia (CDSS), schedule for deficit syndrome (SDS), and scale for the assessment of negative symptoms (SANS) recording and weekly SDS and SANS application up till 4 weeks.

Results: There was greater reduction of negative symptoms in both SANS (9.04%) and SDS (9.75%) scales in true group as compared with sham group, where SANS and SDS scores were reduced by 1.32% and 0.48%, respectively.

Conclusion: The study is part of an emerging area of interest in the field of noninvasive techniques of brain stimulation, and the results are strongly persuading.

Clinical significance: This study suggests that the 10-Hz rTMS protocol is an efficacious, adjunctive, noninvasive, interventional strategy for treatment of negative symptoms of schizophrenia.

Keywords: Negative symptoms, Repetitive transcranial magnetic stimulation, Schizophrenia.

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Introduction

Schizophrenia is one of the most serious and debilitating mental illness. About 1% of the population suffers from schizophrenia in their lifetime worldwide.[1] The symptoms of schizophrenia are broadly divided into positive and negative symptoms. Blunted affect, alogia, asociality, anhedonia, and avolition (amotivation) are the negative symptoms of schizophrenia.

Since the ages of Emil Kraepelin, negative symptoms were recognized and included as "Emotional Dullness", and Eugen Bleuler referred them to as "Emotional deterioration". Kurt Schneider appreciated Bleuler's views but did not include it in his first-rank symptoms. That is why negative symptoms remained under-recognized and under-treated since those days.

"Expressive deficits" can be explained as a decrease in verbal output and expressiveness with blunted affect, which appears as diminished expressibility of emotions over the face, poor eye-to-eye contact, and reduced spontaneity in movement and behavior. The hallmark of another "Avolition/Amotivation" subdomain is a subjective reduction in interests, desires and goals, and a behavioral reduction in purposeful acts, with a lack of self-initiated social interactions.[2]

The primary negative symptoms are persistent deficit state, which suggests a poor prognosis, and they do not improve over time, while secondary negative symptoms are consequences of positive psychotic symptoms, depression, demoralization, or adverse effects of medication such as bradykinesia, tremors, and rigidity.[3,4] Other conditions giving rise to secondary negative symptoms may include chronic substance/alcohol use, high-dose antipsychotic medication, social deprivation, lack of stimulation, and hospitalization.

In people with established schizophrenia, negative symptoms are seen to a varying degree in up to three-quarters, with up

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to 20% having persistent primary negative symptoms.[5] The negative symptoms of schizophrenia are closely associated with poorer prognosis and bring in a significant amount of stress to the caregivers of the patient.[6,7]

Limited response to pharmacological agents and psychosocial interventions necessitates exploration of newer treatment modalities for negative symptoms. Repetitive transcranial magnetic stimulation (rTMS) is the latest noninvasive neuromodulation technique being applied in the field of neurology and psychiatry. It works on the principle of stimulating hypo-functional neuronal circuitry by generation of a small amount of electricity, enough to depolarize neurons in the brain through a rapidly changing magnetic field generated by the rTMS coil. Though the exact mechanism of action is not entirely clear, an established fact known is that brain excitability decreases by applying a low-frequency rTMS (1 Hz and lower) and increases by applying a high-frequency (HF) rTMS (HF rTMS) (5–20 Hz).[8] This mechanism is supposed to alter the functionality of the brain area being stimulated.

The pathophysiology of negative symptoms is considered to be because of the combined effect of hypometabolism in the prefrontal cortex, altered serotonin, and NMDA receptor functions. It indicates a strong association between the severity of negative symptoms and hypometabolism of the prefrontal cortex.[9] Evidences from animal studies found that the density of N-methyl-D-aspartate (NMDA) receptors was significantly increased with HF rTMS.[10] High-frequency rTMS also leads to serotonin receptors upregulation.[11] Elevation of dopamine levels in mesolimbic and mesostriatal pathways has also been evidenced in animal as well as human studies.[12] That is why it is expected that if rTMS improves perfusion and metabolism in the prefrontal cortex, negative symptoms shall also improve.[13] Since it's approval for treatment of depression by the FDA in 2008, rTMS has drawn the attention of researchers for exploring its efficacy in the negative symptoms. Many studies have suggested promising results for negative symptoms, but till date, relatively fewer studies have taken place and their results are not consistent. That is why more research is needed to explore and determine its efficacy for negative symptoms.

Materials and Methods

Patients were taken up for this study from the inpatient Department of Psychiatry at the Institute of Mental Health and Hospital, Agra, who were between the ages of 18 and 60 years, met the International Classification of Diseases, Tenth Revision-Diagnostic Criteria for Research criteria for schizophrenia, were voluntary and competent to consent for treatment, and able to pass the TMS adult safety-screening (TASS) questionnaire that is a safety questionnaire to prevent physical side effects due to rTMS administered by a psychiatrist only during the study.

The study was a double-blind randomized control trial with a follow-up period of 4 weeks. About 50 male patients with prominent negative symptoms were taken who were fit to initiate rTMS.

Patients who did not pass the TASS questionnaire, have a significant history of seizures, active suicidal intent, pregnant or may be pregnant, any significant neurological disorder or insult, an intracranial implant, and had changes in dose or initiation of any psychotropic medication in the 4 weeks prior to screening. Currently (or in the last 4 weeks), taking Lorazepam more than 2 mg daily (or equivalent) or any dose of an anticonvulsant due to the potential to limit rTMS efficacy or other psychiatric comorbidity or substance use except nicotine, caffeine, and tobacco, was excluded from the study. The principles enunciated in the Declaration of Helsinki and the Indian Council of Medical Research were complied with and the study was approved by the Ethical Review Committee of the Institution. The patient's sociodemographic and clinical details were recorded on structured performa.

rTMS Initiation

Patients were put on adequate doses of antipsychotics for at least 4 weeks and enrolled in the study when they were behaviorally stable. Medication doses were then recorded and subjects were divided into two groups. The first group was True rTMS group, and the second group was Sham rTMS (placebo) group. Randomization was by the odd and even method. Patients having odd intake serial numbers were assigned to the true rTMS group, and those having even intake serial numbers were assigned to the sham rTMS group. Double blinding was done, i.e., the rater and patient both were blinded.

Calgary Depression Scale for Schizophrenia (CDSS)—CDSS was used to assess depression independent of negative symptoms of schizophrenia. The schedule for deficit syndrome (SDS) and scale for assessment of negative symptoms (SANS) were applied at baseline and then weekly for up to 4 weeks till the termination of rTMS sessions and upon completion of the course of rTMS and then the results were compared between and within groups.

rTMS Protocol

High-frequency rTMS protocol was applied daily, which involved the application of 30 trains each for 5 seconds with 30 seconds intertrain intervals at 110% of the motor threshold and 10 Hz frequency to the left dorsolateral prefrontal cortex (DLPFC) area of the brain in every session for 4 weeks. Transcranial magnetic stimulation (TMS) machine used was Medicaid MedStim TMS stimulator. Sham group was given rTMS sessions with the same protocol using Sham Coil (placebo). Sham coil remains attached to TMS machine in the same manner as true coil, but it does not produce a magnetic impulse.

All treatments were performed under the supervision of psychiatrists trained in administration of TMS who had Basic and Advanced Cardiac Life Support certification. Transcranial magnetic stimulation was provided free of cost.

Analysis

The Statistical Package for the Social Sciences Version 16 (SPSS-16) was used for analysis.[14] Frequencies with percentages were calculated for the categorical variables. Mean and standard deviation were computed for the continuous variables. Comparisons were done by using *t*-tests and Chi-square tests.

Results

The demographic characteristics (age, duration of education, employment, religion, background, marital status, socioeconomic status, and family type) (Table 1) and clinical profile (age of onset, illness duration, family history, past history and response of rTMS, motor threshold, Simpson Angus baseline score, and CDSS baseline score) were also noted (Table 2). There were no significant group differences between true and sham group with respect to age, age of onset, total duration of illness, motor threshold, Simpson Angus baseline score, and CDSS baseline score (Supplementary Material, Table A1). There was a significant difference over both SANS and SDS scales when compared from baseline within the true

Table 1: Demographic characteristic

	True rTMS (n = 25)		*Sham rTMS (n = 25)*		
Demographic characteristic	*Mean*	*SD*	*Mean*	*SD*	
Age in years	34.08	7.455	34.8	8.078	*p-value*
Categorical variables	*Frequency*	*Percentage*	*Frequency*	*Percentage*	>0.05 (NS)
Education					
Uneducated	1	4	2	8	
Primary	2	8	2	8	
Middle school	13	52	9	36	
High school	5	20	2	8	
Intermediate	2	8	4	16	
Graduation	2	8	4	16	
Postgraduation and above	0	0	2	8	
	Mean	*SD*	*Mean*	*SD*	*p-value*
	3.57	4.43	3.57	2.58	>0.05 (NS)
Employment					
Unemployed	23	92	21	84	
Employed	2	8	4	16	
	Mean	*SD*	*Mean*	*SD*	*p-value*
	12.5	14.85	12.5	12.02	>0.05 (NS)
Religion					
Hindu	21	84	23	92	
Muslim	4	16	2	8	
	Mean	*SD*	*Mean*	*SD*	*p-value*
	12.5	12.02	12.5	14.85	>0.05 (NS)
Background					
Rural	16	64	16	64	
Urban	6	24	4	16	
Semi-urban	3	12	5	20	
	Mean	*SD*	*Mean*	*SD*	*p-value*
	8.33	6.81	8.33	6.66	>0.05 (NS)
Socio-economic status					
Low	20	80	20	20	
Middle	5	20	5	5	
	Mean	*SD*	*Mean*	*SD*	*p-value*
	12.5	10.61	12.5	10.61	>0.05 (NS)
Type of family					
Nuclear	3	12	5	20	
Joint	22	88	20	80	
	Mean	*SD*	*Mean*	*SD*	*p-value*
	12.5	13.44	12.5	10.61	>0.05 (NS)
Marital status					
Unmarried	17	68	15	60	
Married	7	28	8	32	
Divorced	1	4	0	0	
Separated	0	0	2	8	
	Mean	*SD*	*Mean*	*SD*	*p-value*
	6.25	7.8	6.25	6.75	>0.05 (NS)

NS, not significant

Table 2: Clinical characteristics

	True rTMS (n = 25)		*Sham rTMS (n = 25)*		
Clinical characteristics	*Mean*	*SD*	*Mean*	*SD*	*p-value*
Age of onset (years)	20.76	5.085	22.8	6.185	>0.05 (NS)
Illness duration (years)	13.68	7.256	12.44	6.971	>0.05 (NS)
Motor threshold	65.96	8.566	64.32	6.129	>0.05 (NS)
Simpson Angus baseline score	0.04	0.2	0	0	>0.05 (NS)
CDSS baseline score	1.08	1.038	1.36	1.114	>0.05 (NS)

(Contd...)

Table 2: *(Contd...)*

	True rTMS (n = 25)		*Sham rTMS (n = 25)*		
Clinical characteristics	*Mean*	*SD*	*Mean*	*SD*	
Categorical variables	*Frequency*	*Percentage*	*Frequency*	*Percentage*	*p-value*
Family history of mental illness					
Present	4	16	2	8	
Not present	21	84	23	92	
	Mean	*SD*	*Mean*	*SD*	*p-value*
	12.5	12.02	12.5	14.84	>0.05 (NS)
History of past rTMS					
No	24	96	24	96	
Yes	1	4	1	4	
	Mean	*SD*	*Mean*	*SD*	*p-value*
	12.5	16.26	12.5	16.26	>0.05 (NS)
Response to past rTMS					
Unknown	1	4	1	4	
Not applicable	24	96	24	96	
	Mean	*SD*	*Mean*	*SD*	*p-value*
	12.5	16.26	12.5	16.26	>0.05 (NS)

NS, not significant

Table 3: Paired samples *t*-test within true group over SANS and SDS scales

True group	*Mean*	*N*	*p*
SANS score baseline	72.12	25	0.01** (S)
SANS score week 4	65.60	25	
SDS score baseline	17.64	25	0.01** (S)
SDS score week 4	15.92	25	

Table 3 shows that there was significant difference over both SANS and SDS scales when compared from baseline within true group at statistical significance level 0.01. **Statistically significant of *p*-value < 0.05. S, significant

group at a statistical significance level 0.01 (Table 3), but there was no significant difference between the true and sham group over SANS and SDS scales across the 4-week duration (Supplementary Material, Tables A2 and A3). There was more reduction over SANS and SDS scores in the true group as compared with the sham group (Figs 1 and 2). There was a greater reduction of negative symptoms in both SANS (9.04%) and SDS (9.75%) scales in the true group as compared with the sham group where SANS and SDS scores were reduced by 1.32% and 0.48%, respectively (Fig. 3).

Discussion

This paper presents a study that was conducted at the Institute of Mental Health and Hospital, Agra, from June 2019 to October 2020, with the aim to evaluate the efficacy of HF rTMS as an adjunctive intervention along with antipsychotics, on negative symptoms of schizophrenia. The study was a hospital-based, prospective, randomized, double-blind, sham-(placebo) controlled, interventional, two-armed trial. The study is part of an emerging area of interest in the field of noninvasive techniques of brain stimulation, and was conducted with an intention to contribute to the body of literature on the topic.

Numerous studies utilizing rTMS have been conducted to treat negative symptoms of schizophrenia.[10,15] The Positive and Negative Syndrome Scale (PANSS) has been frequently utilized to evaluate negative symptoms. However, in this study, we used scales specifically designed for negative symptoms, namely SANS and SDS.

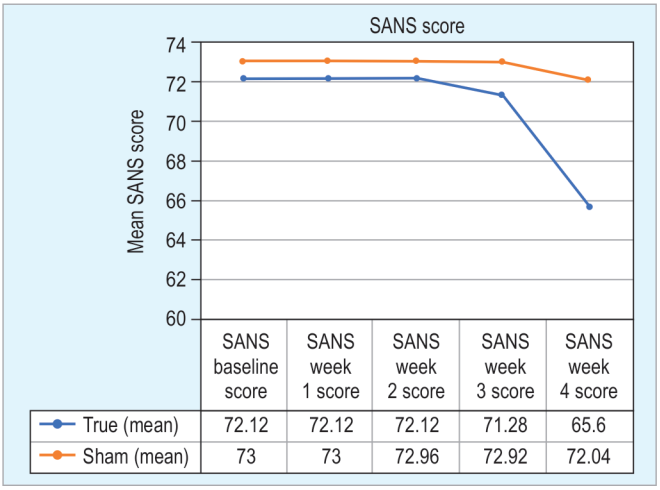


Fig. 1: Shows that there was more reduction over SANS scores in the true group as compared with sham group

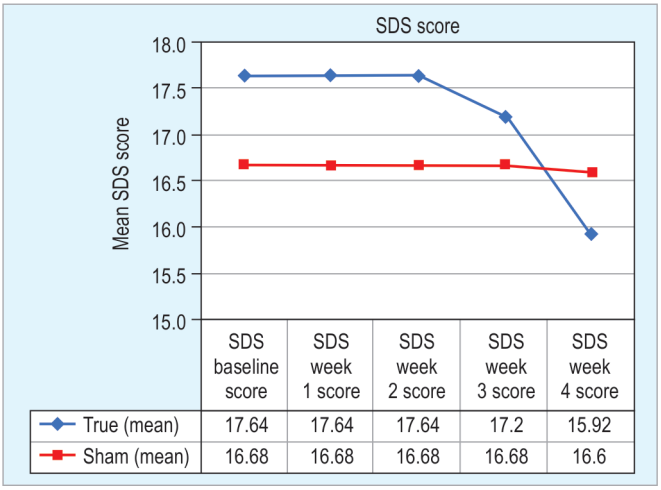


Fig. 2: Shows that there was more reduction in SDS scores in true group as compared with sham group

The presence of deficit syndrome in a patient ensures the existence of significant negative symptoms. Assessment of negative symptoms requires careful observation, and although the SANS is a sensitive and specific scale for negative symptoms, it is time-consuming and requires experience. On the other hand, the SDS is a short and easy-to-apply scale that can be used by moderately experienced raters who are relatively new to the field of behavioral sciences. Both scales measure similar domains of negative symptoms.

A meta-analysis by Osoegawa et al.[16] in 2018 analyzed 30 rTMS-based studies on negative symptoms and found that the sample sizes ranged from 11 to 157 with a mean of 36.21. The sample size in our study is greater than this mean value, indicating that it is in line with other studies. In our study, 50 patients were randomized equally into true and sham groups, and double-blinding was used to increase authenticity and reduce bias. Previous studies found major improvement in the negative symptoms when rTMS was applied over the DLPFC area[10,15] and also the pathophysiology of negative symptoms considered due to hypometabolism in the prefrontal region leads us to choose the DLPFC region to apply rTMS.

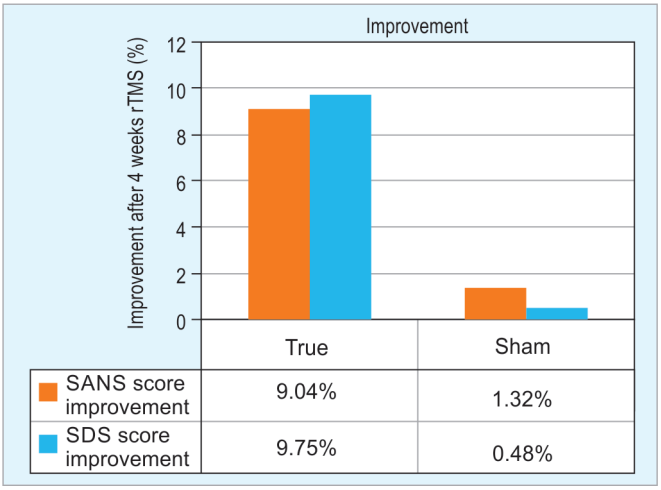


Fig. 3: Shows that there was greater reduction of negative symptoms in both SANS (9.04%) and SDS (9.75%) scales in true group as compared with sham group where SANS and SDS scores were reduced by 1.32% and 0.48%, respectively

Sociodemographic variables, such as age, sex, education, marital status, religion, type of family, age of onset, occupation, rural/urban background, substance abuse, total duration of illness, co-morbidities, and history of mental illness in the family, may affect study results and prognosis. In this study, both groups were comparable with respect to these factors and did not show significant differences in these variables. Therefore, it is expected that these factors will not significantly influence the outcome measures of the study.

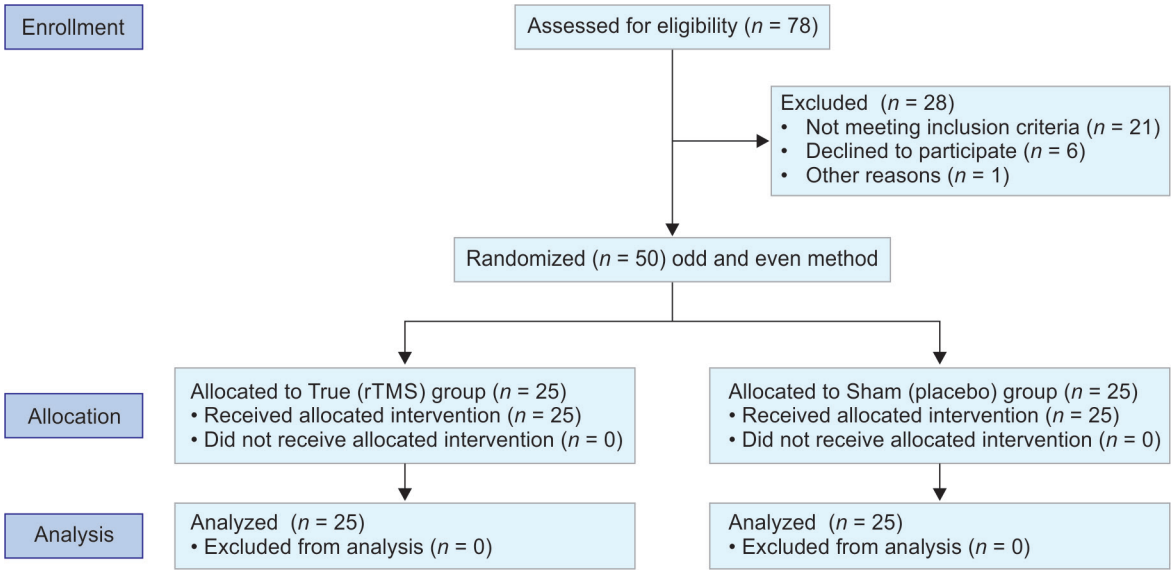
Outcome Measures

The study involved pre- and postinterventional comparisons within an experimental group. The results were statistically significant. The negative symptom scores were compared between the true and sham groups after 4 weeks of rTMS intervention. While the true group showed greater improvement than the sham group, the difference between the two groups was not statistically significant. The experimental group showed a significant improvement in the baseline score, with a 9.04% improvement over the SANS scale and 9.75% improvement over the SDS scale after 4 weeks of rTMS intervention also this improvement would have limited by monotonous daily routine and inpatient ward and hospital environment during a longer stay in the hospital as it provides limited activities of interest for patients than a nonrestricted home environment. In contrast, the sham group showed only a 1.32% improvement over SANS scale and 0.48% improvement over SDS scale, indicating a significant difference in improvement between the two groups (Flowchart 1).

The graph of negative symptom assessment scores (SANS and SDS) shows a trend of further improvement in the experimental group, which would have been statistically significant if rTMS intervention continued for a duration longer than the current study.

The salient feature of the study was the absence of dropouts since the patients were taken from the male inpatient department (IPD) of the institute, where chronic patients with schizophrenia stay for longer than a month. Prolonged hospitalization in IPD is

Flowchart 1: CONSORT 2010 flow diagram



preferred over the outpatient department (OPD) as hospitalized patients share the same psychobiological environment. The large capacity of the IPD section allowed for frequent availability of patients with negative symptoms of schizophrenia, which facilitated the intake of patients and ensured that all sessions were completed without any dropouts in any group in the study.

In our study, follow-up after 4 weeks of rTMS intervention was lacking due to which we could not assess the delayed effect of HF rTMS.

The graph of SANS and SDS scores, across time, in our study, suggests that there is a dormant phase of 3–4 weeks duration, after which the effect of rTMS intervention starts to appear. Researchers who applied rTMS sessions for 3 weeks or lesser duration were not sufficient for producing any beneficial effect.[17,18]

Limitations of this Study

Only male patients were included and female subjects were not present in the study, so the results cannot be generalized to the whole population, a 4-week duration of medication may behaviorally stabilize patients but may not resolve the secondary negative symptoms completely and may lead to overscoring of primary negative symptoms, and all the patients were given stimulation at the left DLPFC, irrespective of handedness of the patients, sample size was small, neuro-navigation methods were not used to stimulate the exact area of brain, and lack of follow-up for successive weeks due to which any delayed effect or adverse effect could not be assessed. The impact of rTMS over cognitive symptoms was not assessed, so it was difficult to assess whether the improvement in cognitive symptoms has any contribution to improvement in SANS, CDSS, PANSS, and SDS scales.

Conclusion

This study suggests that the 10 Hz rTMS protocol is an efficacious, adjunctive, noninvasive, interventional strategy for treatment of negative symptoms of schizophrenia if applied after screening out the risk factors for adverse events related to rTMS.

Clinical Significance

The study results are suggestive of greater improvement in negative symptoms when medications are given along with rTMS therapy over the left DPFC than pharmacotherapy alone, which shows that augmenting rTMS is promising for prominent negative symptoms.

Supplementary Material

The cited supplementary file is available on the website of https://www.ijpp.in/.

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Appendix

Table A1 shows that there were no significant group differences between true and sham group with respect to age, age of onset, total duration of illness, motor threshold, Simpson Angus baseline score, and CDSS baseline score

Table A2 shows that there was no significant difference between the true and sham groups over SANS scales across the 4-week duration

Table A3 shows that there was no significant difference between the true and sham groups over SDS scales across the 4-week duration

Table A1: Independent *t*-test (clinical variables)

Group	*Mean*	*Std. deviation*	*t*	*p*
Age (years)				
True	34.08	7.455	–0.328	0.745 (NS)
Sham	34.80	8.078		
Age of onset (years)				
True	20.76	5.085	–1.274	0.209 (NS)
Sham	22.80	6.185		
Total duration of illness				
True	13.68	7.256	0.616	0.541 (NS)
Sham	12.44	6.971		
Motor threshold				
True	65.96	8.566	0.779	0.440 (NS)
Sham	64.32	6.129		
Simpson Angus baseline score				
True	0.04	0.200	1.000	0.322 (NS)
Sham	0.00	0.000		
CDSS baseline score				
True	1.08	1.038	–0.920	0.362 (NS)
Sham	1.36	1.114		

Table A2: Independent *t*-test (SANS scale)

Group	*Mean*	*Std. deviation*	*T*	*p*
SANS baseline				
True	72.12	16.154	–0.193	0.847 (NS)
Sham	73.00	16.016		
SANS week 1				
True	72.12	16.154	–0.193	0.847 (NS)
Sham	73.00	16.016		
SANS week 2				
True	72.12	16.154	–0.184	0.854 (NS)
Sham	72.96	16.048		
SANS week 3				
True	71.28	15.015	–0.373	0.711 (NS)
Sham	72.92	16.083		
SANS week 4				
True	65.60	9.504	–1.681	0.099 (NS)
Sham	72.04	16.624		

Table A3: Independent *t*-test (SDS scale)

Group	*Mean*	*Std. deviation*	*t*	*p*
SDS baseline				
True	17.64	3.510	0.974	0.335 (NS)
Sham	16.68	3.461		
SDS week 1				
True	17.64	3.510	0.974	0.335 (NS)
Sham	16.68	3.461		
SDS week 2				
True	17.64	3.510	0.974	0.335 (NS)
Sham	16.68	3.461		
SDS week 3				
True	17.20	3.014	0.567	0.574 (NS)
Sham	16.68	3.461		
SDS week 4				
True	15.92	2.159	–0.839	0.405 (NS)
Sham	16.60	3.428		