Transcranial Magnetic Stimulation in the Treatment of Negative Symptoms of Schizophrenia

Olusegun Temitope Sodiya [1*] • Sujan Poudel [2, 3] • Akinkunmi Odutola [1] • Oluwafemi Popoola [4] • Habibat Salawu [5] • Daniel Gana [1] • Jide Jeje [6] • Temitope V. Arogundade [7] • Jinal Choudhari [8]

[1] Psychiatry and Behavioral Sciences, Tees, Esk and Wear Valleys NHS Foundation Trust, Darlington, United Kingdom
[2] Psychiatry and Behavioral Sciences, California Institute of Behavioral Neurosciences & Psychology, Fairfield, USA
[3] Division of Research & Academic Affairs, Larkin Community Hospital, South Miami, USA
[4] Psychiatry and Behavioral Sciences, North Staffordshire Combined Healthcare NHS Trust (NSCHT), Staffordshire, United Kingdom
[5] Psychiatry and Behavioral Sciences, Black Country Partnership Foundation Trust, Black Country, United Kingdom
[6] Psychiatry and Behavioral Sciences, Southern Health NHS Foundation Trust, Southampton, United Kingdom
[7] Psychiatry and Behavioral Sciences, Sheffield Health and Social care NHS Trust, Sheffield, United Kingdom
[8] Orthopedics, California Institute of Behavioral Neurosciences & Psychology, Fairfield, USA
sodiyaolusegun1@gmail.com

Abstract. The negative symptoms of schizophrenia are core components of schizophrenia that remain a clinical conundrum. It accounts for a large part of long-term disability and poor functional outcomes in patients with the disorder. The treatment options for the negative symptoms and cognitive deficits seen in schizophrenia continue to be limited despite recent psychopharmacology advancements. A functional abnormality in the prefrontal cortex (PFC) has been implicated in the pathogenesis of negative symptoms of schizophrenia, and non-invasive neurostimulation using repetitive transcranial magnetic stimulation has been mooted as an add-on treatment option in the amelioration of negative symptoms in schizophrenia. This study aims to review the published studies regarding Repetitive Transcranial Magnetic Stimulation (rTMS) to alleviate the negative symptoms of schizophrenia. 52 relevant articles were found from PubMed and Google Scholar using the following Mesh terms' Schizophrenia', 'Negative symptoms of schizophrenia, 'Transcranial magnetic stimulation, and 'Treatment' and 35 relevant articles were selected after a thorough screening process. The available evidence indicates that transcranial magnetic stimulation has found a root in the treatment of conditions such as depression, migraine, Obsessive-Compulsive Disorder (OCD), Post-Traumatic Stress Disorder (PTSD), and anxiety. There have been indicators from trials that Transcranial Magnetic Stimulation (TMS) could have a role in improving negative symptoms of schizophrenia, particularly when used as an adjunct to established pharmacological treatment. However, the current findings have been inconsistent with a relatively small sample size; hence larger multicenter studies may be required to prove the treatment significance before it becomes a mainstream and acceptable treatment option.

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1. Introduction & Background:

Schizophrenia is a chronic disabling mental disorder with an estimated one out of every hundred people affected worldwide (Adeosun, 2013). The core symptoms are broadly divided into positive and negative. The former can be described as an exaggeration or distortion of normal functioning and characterized by delusions, disorganized behavior, and hallucinations. The latter is characterized by a reduction or attenuation of normal behaviors with a significant impact on motivation and interest (Correll, & Schooler, 2020). Frequently observed negative symptoms include anhedonia, asociality, blunted effect, avolition, and psychomotor retardation (Correll, & Schooler, 2020). Despite advances in psychopharmacology, the negative symptoms of schizophrenia show limited response to both typical and atypical antipsychotics (Linsambarth et al., 2019).

Transcranial magnetic stimulation (TMS) is a procedure involving non-invasive stimulation of the human brain. The principles that underlie its use were suggested at least a century before its first development in 1985 (Barker et al., 1985). During a TMS procedure, an electrical current is conducted through a wire coil placed over the scalp inducing a substantive electrical field leading to depolarization of nerve cells resulting in the stimulation or disruption of brain activity (Iglesias, 2020). TMS may be

used as single or multiple stimuli per second, with variation in sites, intensities, and magnetic field orientation. Repetitively applied TMS, as used in treatment studies, is usually referred to as rTMS (Fitzgerald & Daskalakis, 2008). It has been demonstrated that rTMS involves varieties of neuronal and non-neural mechanisms that might be fully responsible for the range of observed effects (Fitzgerald & Daskalakis, 2008). Prefrontal cortical dysfunction appears to be the significant perpetuating factor for negative symptoms of schizophrenia (Wolkin et al., 1992). Some studies have also confirmed that repetitive Transcranial Magnetic Stimulation (rTMS) can modulate neuronal activity, leading to improvement of symptoms or decreased negative symptoms in patients with schizophrenia (Linsambarth et al., 2019; Barker et al., 1985). Also, rTMS applied over the left dorsolateral prefrontal cortex (DLPFC) has been proposed adjuvant to pharmacological therapy of negative symptoms in schizophrenia (Linsambarth et al., 2019). The functional hypofrontality hypothesis in schizophrenia has created new frontiers that electrotherapy applied to the prefrontal cortex may effectively treat negative symptoms of schizophrenia (Franchi et al., 2015). Repetitive transcranial magnetic stimulation (rTMS) is already approved in some countries for major depressive disorder. Because of its success in treating depression, there has been tremendous interest in its application in other neuropsychiatry areas (d'Alfonso et al., 2002).

Most of the published articles have emphasized the efficacy of TMS in reducing symptoms in patients with treatment-resistant depression and auditory hallucinations when the stimulation is applied over the DLPFC (Fitzgerald & Daskalakis, 2008; Psomiades et al., 2017).

The most extensive literature for rTMS application in schizophrenia has focused on low-frequency stimulation to reduce the intensity of persistent refractory auditory hallucinations (d'Alfonso et al., 2002). Although there have been studies that indicate that rTMS could play a role in augmenting cognitive function by alleviating the negative symptoms of schizophrenia, the findings from these studies have been limited and inconsistent due to the small sample size (Fitzgerald & Daskalakis, 2008; d'Alfonso et al., 2002). This lends credence to the urgent need for further research on the efficacy of rTMS on negative symptoms, including multicenter studies to consider the value of these options (Psomiades et al., 2017).

The aim of this study is to have a better understanding of the rTMS role to alleviate the negative symptoms of schizophrenia and to identify its efficacy as a potential source of treatment. For this review article, we conducted a literature search using PubMed and Google Scholar databases. A total of 52 articles were found after using Keywords such as 'Schizophrenia,' 'Negative Symptoms of Schizophrenia,' 'Transcranial magnetic stimulation, and 'Treatment.' The Keywords were used individually and in combination to gather the relevant articles. After a thorough screening process, we selected 35 relevant articles. We included the studies published within 21 years, human studies, and written in the English language. Types of studies included were randomized controlled trials, meta-analysis, review articles, and observational studies.

2. Literature Review:

2.1. Dilemma

It is noteworthy to state that positive symptoms have been effectively managed over the years to a large extent with available antipsychotics (Correll, & Schooler, 2020). The advent of second-generation antipsychotics played a pivotal role in the treatment of schizophrenia because of its more safety profile, and fewer extrapyramidal side effects. However, the same cannot be said for the negative symptoms as the treatment options remain limited despite advances in the psychopharmacology of schizophrenia (Correll, & Schooler, 2020).

Contrary to the positive symptoms of schizophrenia, such as auditory hallucinations, disorganized speech, and, delusions which respond relatively well to standard treatment, there has been significant drawback with the negative symptoms (Correll, & Schooler, 2020; Barker et al., 1985). Unfortunately, even the introduction of clozapine and other newer antipsychotics have not achieved many remissions of these negative symptoms (Fitzgerald & Daskalakis, 2008). This problem contributes immensely to the disability and healthcare costs associated with schizophrenia (Fitzgerald & Daskalakis, 2008).

2.2. Efficacy of rTMS

Several trials have explored the use of rTMS methods for the treatment of negative symptoms of schizophrenia. A study was done by Linsambarth et al. involving 16 patients with schizophrenia who were under successful pharmacological control of positive symptoms and predominantly negative symptoms. Repetitive deep transcranial magnetic stimulation (dTMS) with a frequency of 18Hz was administered to the prefrontal cortex (PFC) of these 16 patients. The effects of dTMS on negative symptoms were measured using the Positive and Negative Syndrome Scale (PANSS) and Scale for the Assessment of Negative Symptoms (SANS). The results showed that repetitive dTMS treatment induced significant improvement in negative symptoms assessed using the above scales (Linsambarth et al., 2019).

A metanalysis was done by Dlabac-de Lange et al. involving nine randomized controlled trials (RCTs) assessing the therapeutic efficacy of prefrontal rTMS for negative symptoms in schizophrenia. It is seen that the overall mean weighted effect size for rTMS versus sham rTMS was small to medium and statistically significant (d‘ ‰=‘ ‰0.43; 95% CI, 0.05-0.80). It also showed that studies with a longer duration of treatment of more than three weeks had a larger mean effect size when compared

to studies with shorter durations d‘ ‰=‘ ‰0.58 (95% CI, 0.19-0.97) and d‘ ‰=‘ ‰0.32 (95% CI, −0.3 to 0.95), respectively. This meta-analysis conclusion supports a further study of rTMS as a potential treatment for negative symptoms of schizophrenia (Dlabač-de Lange et al., 2010).

A Randomized Control Trial was done by Prikryl et al. involving twenty-two patients who have been stabilized on antipsychotic medications with prominent negative symptoms. The patients were divided into two cohorts; eleven were treated with active rTMS and the other half with ineffective sham rTMS (control subjects). The group treated with active rTMS showed a statistically significant decrease of negative symptoms (approximately 29% reduction in the PANSS negative symptoms subscale and 50% reduction in the SANS). A decrease of negative symptoms was also identified in the sham rTMS but to a lesser extent than active rTMS (about 7% in negative subscale PANSS and 13% in SANS). They concluded that the augmentation of rTMS with medications enabled the patient to experience a significant decrease in the severity of negative symptoms (Prikryl et al., 2007).

A randomized controlled trial was done by Dlabac-de Lange et al. in the Netherlands using 24 patients diagnosed with schizophrenia with moderate to severe negative symptoms. They were randomized to a three-week (15 working days) course of active or sham rTMS. All patients performed the Tower of London task during the Functional MRI (fMRI) scanning, both pre-treatment and post-treatment, and differences in brain activation between the two groups were compared non-parametrically. They concluded that treatment with rTMS over the DLPFC might increase task-related activation in frontal areas in patients and consequently alleviate negative symptoms of schizophrenia. They also advised that the effects of different rTMS parameters and fMRI tasks targeting relevant brain circuitry deserve further investigations (Dlabac-de Lange et al., 2015).

Four different RCTs used primary outcome measures as PANSS and SANS, whereas secondary outcome measures as Clinical Global Impression (CGI) and the Udvalg for Klinker Under Sogelser(UKU) side effect rating scale. They found that treatment with high-frequency rTMS for six weeks significantly improved the active group's negative symptoms compared to the sham group (Gan et al., 2015; Quan et al., 2015; Dlabac-de Lange et al., 2015; Prikryl et al., 2013).

Three RCTs using PANSS, SANS, and brief psychiatric rating scale (BPRS) as the primary outcome showed a statistically significant decrease of negative symptoms. They concluded that the augmentation of rTMS with medications enabled patients to experience a substantial reduction in the severity of the negative symptoms of schizophrenia, and mutual comparison demonstrated a more significant decrease in negative symptoms in favor of real rTMS in contrast to sham rTMS (Schneider et al., 2008; Jin et al., 2006).

2.3. Differential effect of rTMS on Positive and Negative symptoms

In an RCT by Wobrock et al., 175 patients with schizophrenia and predominantly negative symptoms were divided into two treatment groups. The first group was treated with active rTMS and the second with sham rTMS. The study found no significant difference in improvement in negative symptoms between the two groups at day 21 (p =0 .53, effect size = .09) or subsequently through day 105. Although there was a small statistical improvement in positive symptoms in the active rTMS group (p = .047, effect size = 0.30), which was limited to day 21. They concluded that the application of active 10Hz rTMS to the left dorsolateral prefrontal cortex (DLPFC) was not superior compared to sham rTMS in improving negative symptoms (Wobrock et al., 2015).

A review article by Prikryl et al. pointed out that the effect size of the high-frequency repetitive rTMS over the left prefrontal cortex in treating negative symptoms of schizophrenia is thought to be mild to moderate effect. This paper concluded that despite the promising results of some rTMS studies, the potential of rTMS for the treatment of negative symptoms is currently relatively unclear and suggested large multicenter studies (Prikryl et al., 2013).

A meta-analysis was done by He et al. involving thirteen studies and seven studies with 1 Hz and 10Hz, respectively. They found that auditory hallucinations improved in studies with 1Hz compared to the sham rTMS group (SMD = −0.29, 95%CI = −0.57 to −0.01). Studies with 10 Hz found that negative symptoms improvement did not differ significantly between the real rTMS and sham rTMS groups. They found that although there may be a therapeutic effect for 1Hz rTMS on auditory hallucinations of schizophrenia, this further needs to be confirmed by large-scale randomized controlled trials (He et al., 2017).

Three RCTs with two treatment arms for each study showed no significant difference between the active rTMS and sham rTMS on all subscales of the PANSS and CGI. They all concluded that active rTMS failed to show superiority over sham stimulation in treating schizophrenic symptoms (Novak et al., 2006; Fitzgerald et al. 2008)

Three different studies showed variable results with some degree of improvements seen on domains such as verbal fluency, visual-spatial working memory, and auditory hallucinations. Their conclusions summarized that although rTMS has demonstrated some promise in treating schizophrenia, more research is required as the potential of rTMS for treating negative symptoms is currently relatively unclear (Zheng et al. 2012; Prikryl & Kucerova, 2013; Blumberger et al. 2010).

From the studies, repetitive Transcranial Magnetic Stimulation (rTMS), non-invasive neurostimulation showed mixed outcomes of effectiveness in improving the negative symptoms of schizophrenia (Fitzgerald et al. 2008; Zheng et al. 2012).

Some of the studies found negative or opposed results (Novak et al., 2006; Wobrock et al., 2015). But the majority of the studies demonstrated an overall positive effect of rTMS ranging from small and medium-range to incredibly significant (Linsambarth et al., 2019; Wagner et al., 2019; Cohen et al., 1999; Jandl et al., 2005) [Table 1]. The negative and mixed outcomes of rTMS are shown in the table below (Fitzgerald et al. 2008; Zheng et al. 2012) [Table 2].

Table 1: Table showing positive findings of repetitive transcranial magnetic stimulation

Study	Subjects	Frequency	Intensity of Rmt (%)	Duration of Days	Measures of Outcome	Results
PARALLEL (Sham Controlled)	**POSITIVE RESULTS**					
Wagner et al. (2019)	26			15	PANSS	Active rTMS may be more effective than Sham rTMS.
Prikryl et al. (2007)	22	10Hz	110	15	PANSS and SANS	Significantly greater reduction in negative symptoms in the real rTMS compared within the sham group.
Dlabac et al. (2015a)	24	10Hz			PANSS – negative subscale	Found a significant increase in brain activity in the active group.
Gan et al. (2015)	70	10Hz	100	10	PANSS TESS VAS score	Observed a significant reduction in negative symptoms in the active group.
Prikryl et al. (2013)	40	10Hz	110	15	SANS	Found a reduction in negative symptoms in the active group.
Quan et al. (2015)	117			20	PANSS SANS CGI UKU side effect rating scale	Significant reduction in the active group as compared to the sham group.
Dlabac et al. (2015b)	32	10Hz		21	PANSS SANS	Significant improvement of the SANS in the active group. No difference in PANSS scores.
CROSSOVER STUDIES- POSITIVE RESULTS						
Rollnik et al. (2000)	12	20Hz	80	10	BPRS BDI STAI	Significant reduction in BPRS scores.
Jin et al. (2006)	17	Alpha TMS (8–13Hz) 3Hz 20Hz	80	10	PANSS MADRS SARS	Alpha frequency rTMS resulted in a significant reduction of negative symptoms.
OPEN STUDIES						
Linsambarth et al. (2019)	16	18Hz			SANS and PANSS	Repetitive rTMS treatment induced significant improvement.
Cohen et al. (1999)	6	20Hz	80	10	PANSS WCST	Significant but minimal improvement in negative symptoms.
Jandl et al. (2005)	10	10Hz		5	SANS	Significant reduction in SANS rating score.

RMT- Resting Motor Threshold, PANSS- Positive and Negative Syndrome Scale, rTMS- Repetitive Transcranial Magnetic Stimulation, SANS- Scale for the Assessment of Negative Symptoms, TESS- Treatment Emergent Symptom Scale, VAS- Visual Analogue Scale, CGI- Clinical Global Impression, UKU- Udvalg for Klinske Undersogelser, CGI-clinical global impression, TESS- Treatment Emergent Side Effect Scale, BPRS-Brief Psychiatric Rating Scale, & BDI- Beck Depression Inventory, State-Trait Anxiety inventory, MADRS- Montgomery-Asberg Depression rating scale, and WCST- Wisconsin card sorting test.

Table 2: Table showing the negative and mixed outcomes of rTMS

PARALLEL (Sham Controlled)	NEGATIVE AND MIXED RESULTS					
Fitzgerald & Daskalakis, (2008)	20	10Hz	110	15	SANS	A trend for greater reduction in the autistic preoccupation scale of the PANSS scale for the active group was observed; however, there was no significant difference between active and sham groups on the SAN scale.
Wobrock et al. (2015)	175	10Hz		21		No statistically significant difference in the active and sham groups.
Novak et al. (2006)	16	20Hz	90	10	PANSS CGI MADRS and Neuropsychological tests	No significant effect or rTMS between the active and sham groups.
Saba et al. (2006)	18	1Hz	80	10	PANS CGI	No difference between the active and sham groups.
Zheng et al. (2012)	80	10Hz 20Hz			PANSS Visuospatial working memory test Verbal fluency test	The effects of the rTMS on cognitive function and psychotic symptoms vary according to the changes in stimulus parameters.

SANS- SANS- Scale for the Assessment of Negative Symptoms, PANSS- Positive and Negative Syndrome Scale, CGI- Clinical Global Impression, MADRS- Montgomery-Asberg Depression Rating Scale.

2.4. What to expect during TMS treatment?

Transcranial magnetic stimulation (TMS) is a non-invasive treatment that does not need anesthesia and can be done on an outpatient basis. As shown in the figure, a purpose-made electromagnetic coil is held against the scalp to induce electric currents in the brain's implicated area, which in the case of schizophrenia would be the cerebral cortex and DLPFC. These magnetic fields are similar to those found in magnetic resonance imaging (MRI) (Repetitive transcranial magnetic stimulation for depression, 2015). The treatment has shown to be a safe and well-tolerated procedure to effectively treat patients with depression or other neuropsychiatric disorders (Transcranial Magnetic Stimulation (TMS) Therapy, 2020). The clinician may sometimes use imaging to help target specific areas of the brain (Repetitive transcranial magnetic stimulation for depression, 2015).

During the TMS procedure, patients are awake and will hear a clicking sound and feel a knocking or tingling sensation on the head [Figure 1]. A typical course includes daily sessions lasting 20 to 40 minutes (5 times per week) for 4 to 6 weeks. Sometimes, some patients may occasionally return for maintenance treatment following the initial treatment course (Transcranial Magnetic Stimulation (TMS) Therapy, 2020).

Unlike ECT, TMS does not affect memory or clarity, and the person can return straight back to their routine activities as no downtime is needed to recover. However, TMS is not free of side effects, and the most common side effects are painful scalp sensations, facial twitching, and headache. An uncommon side effect is a seizure, and it has been reported in less than 0.001% (Transcranial Magnetic Stimulation (TMS) Therapy, 2020; Repetitive transcranial magnetic stimulation (rTMS), 2020).

TMS therapy has been approved in the United States for the treatment of depression (Transcranial Magnetic Stimulation (TMS) Therapy, 2020). Also, Food and drug administration has authorized it to be used to treat OCD, migraine, and bipolar depression. It has been approved for migraine and depression by the National Institute for Health care and Excellence (NICE) in the United Kingdom (Repetitive transcranial magnetic stimulation (rTMS), 2020).

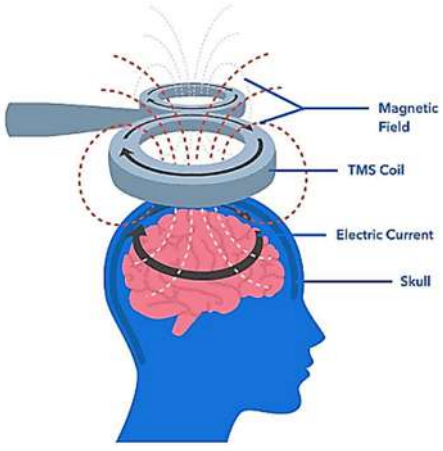

Figure 1. TMS Procedure.

3. Conclusions

There is substantial evidence from this review pointing to the relevance of repetitive transcranial magnetic stimulation(rTMS) in alleviating the negative symptoms of schizophrenia, but the approval for the treatment of this condition is currently limited. It has only been applicable for the treatment of depression in most countries so far. While it is difficult to clearly say whether the improvements obtained are specific to negative symptoms or attributable to the antidepressant effects of rTMS, some of the studies found that rTMS induced significant improvements in negative symptoms compared to sham rTMS using both PANSS and SANS scales. The potential benefits of rTMS in treating negative symptoms of schizophrenia can be explored more through the method of neuronavigation, such as positron emission tomography, magnetoencephalography, and functional magnetic resonance imaging. A better understanding of brain connectivity in schizophrenic patients is crucial to provide breakthrough treatment options in the future. In addition, larger multicentre studies are required to overcome the limited generalizability of current mixed findings resulting from small sample sizes. Also, further investigations are necessary to look at the effects of rTMS on different parts of the brain.

Corresponding Author:
Olusegun Temitope Sodiya, MBChB.
Tees, Esk and Wear Valleys NHS Foundation Trust, Darlington, United Kingdom
E-mail: sodiyaolusegun1@gmail.com

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