

Repetitive Transcranial Magnetic Stimulation for Working Memory Deficits in Schizophrenia: A Systematic Review of Randomized Controlled Trials

Li Li^{1,2}, Chaomeng Liu^{1,2}, Weigang Pan^{1,2}, Wen Wang^{1,2}, Wenqing Jin^{1,2}, Yanping Ren^{1,2}, Xin Ma^{1,2}

¹The National Clinical Research Center for Mental Disorders & Beijing Key Laboratory of Mental Disorders, Beijing An Ding Hospital, Capital Medical University, Beijing, People's Republic of China; ²Advanced Innovation Center for Human Brain Protection, Capital Medical University, Beijing, People's Republic of China

Correspondence: Yanping Ren; Xin Ma, the National Clinical Research Center for Mental Disorders & Beijing Key Laboratory of Mental Disorders, Beijing An Ding Hospital, Capital Medical University, NO. 5 Ankang Hutong, Xicheng District, Beijing, 100088, People's Republic of China, Email renyanping@ccmu.edu.cn; maxinanding@ccmu.edu.cn

Abstract: Working memory (WM) deficits are a significant component of neurocognitive impairment in individuals with schizophrenia (SCZ). Two previous meta-analyses, conducted on randomized controlled trials (RCTs), examined the effectiveness of repetitive transcranial magnetic stimulation (rTMS) in addressing WM deficits in individuals diagnosed with SCZ. However, the conclusions drawn from these analyses were inconsistent. Additionally, the commonly used random effects (RE) models might underestimate statistical errors, attributing a significant portion of perceived heterogeneity between studies to variations in study quality. Therefore, this review utilized both RE and quality effects (QE) models to assess relevant RCTs comparing TMS with sham intervention in terms of clinical outcomes. A comprehensive literature search was conducted using PubMed and Scopus databases, resulting in the inclusion of 13 studies for data synthesis. Overall, regardless of whether the RE or QE model was used, eligible RCTs suggested that the TMS and sham groups exhibited comparable therapeutic effects after treatment. The current state of research regarding the use of rTMS as a treatment for WM deficits in patients with SCZ remains in its preliminary phase. Furthermore, concerning the mechanism of action, the activation of brain regions focused on the dorsolateral prefrontal cortex and alterations in gamma oscillations may hold significant relevance in the therapeutic application of rTMS for addressing WM impairments. Finally, we believe that the application of closed-loop neuromodulation may contribute to the optimization of rTMS for WM impairment in patients with SCZ.

Keywords: working memory, schizophrenia, randomized controlled trials, repetitive transcranial magnetic stimulation, review

Introduction

Schizophrenia (SCZ), a profoundly debilitating psychiatric disorder, impacts ~21 million individuals worldwide.¹ This condition manifests with a diverse range of symptoms, including delusions, hallucinations, disorganized speech, abnormal psychomotor behavior, and negative symptoms.² Consequently, those diagnosed with SCZ face an elevated risk of premature mortality, contributing significantly to global disability.^{3,4} Cognitive impairments are widely recognized as the primary cause of functional deficits in individuals with SCZ.^{5,6} Consistent research findings indicate substantial deficits in working memory (WM) among individuals with SCZ, highlighting impairments in WM as a prevalent characteristic of the illness.⁷ Studies have further established a correlation between WM and functional outcomes, suggesting that WM deficits can serve as predictive indicators for functional outcomes.^{8,9} Therefore, addressing WM deficits should be prioritized as a key objective in treatment interventions aimed at enhancing functional outcomes for patients with SCZ.

WM is a crucial cognitive function that involves the temporary processing and storage of information, serving as a working platform for various advanced cognitive functions such as language, learning, understanding, problem-solving, and executive functions.¹⁰ Numerous studies have identified deficits in WM, including verbal and visual-spatial WM, among individuals with SCZ.¹¹ Various tasks and scales, including the n-back tool and subtests like the spatial span test and alphanumeric span test within the MATRICS Consensus Cognitive Battery (MCCB), are employed to evaluate the amelioration of WM deficits.¹² Despite the recognized importance of WM and its deficits in SCZ, current pharmacological interventions do not demonstrate efficacy in enhancing WM impairment in this population. Consequently, it is imperative to explore novel techniques and methodologies for addressing the cognitive deficit symptoms associated with SCZ, particularly those related to WM.

Repetitive transcranial magnetic stimulation (rTMS), a frequently employed experimental technique in the field of neuromodulation, is renowned for its non-invasive and non-intrusive nature. This intervention method can be categorized into two distinct types based on the frequency of stimulation: high-frequency (HF) stimulation (≥ 5 Hz) and low-frequency stimulation (≤ 1 Hz). It is hypothesized that HF stimulation can enhance local neuronal activity and excitability in the specific brain region, while low-frequency stimulation produces the opposite effect.¹³ The regulatory framework for rTMS encompasses key elements such as pulse number, pulse interval time, pulse intensity, stimulation mode, and stimulation target, and modifications to these variables can result in variations in the outcomes of stimulation.

Two recent meta-analyses, focusing on randomized controlled trials (RCTs), investigated the efficacy of rTMS in addressing WM deficits in individuals diagnosed with SCZ.^{14,15} However, the conclusions drawn from these analyses were inconsistent. A prior study reported that rTMS targeting the left dorsolateral prefrontal cortex (DLPFC) significantly improved WM impairments in patients with SCZ.¹⁴ In contrast, the other meta-analysis failed to identify any beneficial effects of rTMS.¹⁵ Additionally, Doi et al (2015) found that the use of random effects (RE) models might underestimate statistical errors,¹⁶ leading to a significant portion of perceived heterogeneity between studies being attributed to variations in study quality. Therefore, in this analysis, a quality effects (QE) model was employed for meta-analyses encompassing diverse studies. The QE model integrates data obtained from the rigorous assessment of included studies, giving preference to larger trials of superior quality and remaining robust against subjective judgments of quality.¹⁷ In this review, both RE and QE models were utilized to assess relevant RCTs comparing TMS with sham intervention in terms of clinical outcomes, to establish an evidence-based foundation for the utilization of TMS in treating WM deficits among patients with SCZ.

Materials and Methods

Data Sources and Search Terms

A systematic search was conducted in the PubMed and Scopus databases, utilizing Boolean operators to combine the search terms “repetitive transcranial magnetic stimulation”, “TMS”, “deep TMS”, and “theta burst stimulation” with “working memory”, “WM”, “cognitive impairments”, and “cognitive function”. The search covered the period from the inception of the databases until October 10, 2023, and was restricted to English-language publications. The search was specifically limited to RCTs involving patients diagnosed with SCZ. Additionally, potentially relevant articles were identified through a manual search of the reference lists of the included articles. The titles and abstracts were reviewed by the authors (LL and CL) to ensure they met the selection criteria. In instances where there was a disagreement regarding inclusion, the opinion of the third author (WP) was sought.

Inclusion and Exclusion Criteria

The predetermined inclusion criteria were as follows: (1) adult participants meeting the diagnostic criteria for SCZ, confirmed through the Structured Clinical Interview for DSM-IV or DSM-V; (2) inclusion of control groups with two or more groups, with mandatory inclusion of the sham stimulation group; (3) utilization of TMS in more than one session; (4) inclusion of studies with more than five patients; (5) requirement for cognitive function assessment involving WM. Exclusions encompassed abstracts, systematic reviews, meta-analyses, studies involving healthy volunteers, non-human studies, and studies conducted in languages other than English.

The information extracted from each study included: (1) sample characteristics, including size, age, gender composition, and adverse events; (2) details about the TMS technique employed, such as coil position, settings, duration, and number of sessions; (3) information about the control group or condition used; and (4) the scales or tasks utilized to assess WM.

Quality Assessment

The risk of bias for each RCT was evaluated using a modified version of the 10-item Physiotherapy Evidence Database (PEDro) scale. This scale assessed factors such as allocation concealment, randomization, eligibility criteria, baseline similarity of groups, blinding of subjects and assessors, dropout rates below 15%, handling of missing data, inter-group comparisons, variability data, and point measures.^{18,19} Notably, items related to therapist-blinding, which do not apply to TMS studies, were excluded from the analysis. Additionally, as emphasized by Maher et al²⁰ this analysis did not consider eligibility criteria when assigning scores. The articles were evaluated on a 9-point scale, where a higher score indicated a higher quality of the study.

Statistical Analysis

The statistical analysis in this study utilized MetaXL, a Microsoft Excel add-in specifically designed for meta-analysis. Within MetaXL, the study quality scores obtained from the PEDro scale were transformed into a Quality Index (Qi), ranging from 0 to 1. This transformation was achieved by dividing the obtained score by the highest possible score in the study. The resulting Qi facilitated the classification of study quality as poor (0.33–0.55), adequate (0.56–0.77), or good (0.78–1.0).²¹ Higher scores on the Qi indicated superior study quality. The QE model, employed in data synthesis, incorporated the study's quality score, giving more weight to studies with higher quality scores in the meta-analysis.

The effect index for continuous variables was determined through the calculation of standardized mean difference (SMD) and 95% confidence intervals (CIs). The I^2 statistic was used to assess the extent of heterogeneity, with values of 25%, 50%, and 75% indicating mild, moderate, and high heterogeneity, respectively.¹⁹ To evaluate publication bias, the Doi plot and Luis Furuya-Kanamori (LFK) index were employed. The Doi plot, offering improved asymmetry visualization compared to the funnel plot, was used for this purpose.²² Additionally, LFK indices were utilized to categorize asymmetry levels as none, mild, and high, corresponding to values below 1, between 1 and 2, and above 2, respectively. A sensitivity analysis was also conducted by systematically excluding individual studies to assess their impact on the overall findings.

Results

Study Retrieval and Features

The review process was independently conducted by two authors, namely CL and WW, and a visual representation of the trial identification process is depicted in Figure 1. The systematic review covered a total of 13 RCTs.^{23–35} Among these, three trials were conducted in China, three in Germany, and the remaining studies took place in India, the Netherlands, the United States, Turkey, Israel, and the Czech Republic. Regarding the stimulus paradigm, 10 studies utilized rTMS, 2 employed intermittent theta-burst stimulation (iTBS), and 1 used deep transcranial magnetic stimulation (dTMS). Details about stimulation frequency, stimulation site, total pulses, duration, and evaluation methods for WM are presented in Table 1.

Assessment of Study Quality

Table 2 provides an overview of the methodological quality of the 13 included RCTs, assessed using the PEDro program. The quality scores ranged from 6 to 9 points, with a mean score of 7.31. The PEDro scale consists of 10 items, beginning with “Eligibility criteria” and followed by “Random allocation”. Notably, all nine studies included in the meta-analysis satisfactorily met both of these criteria. The use of “intention-to-treat” analysis, crucial for addressing missing data, was observed in only two studies. Additionally, this study evaluated the Qi for each RCT, as determined by the PEDro score. The Qi values varied from 0.67 to 1, with a mean of 0.81, indicating a commendable level of quality.

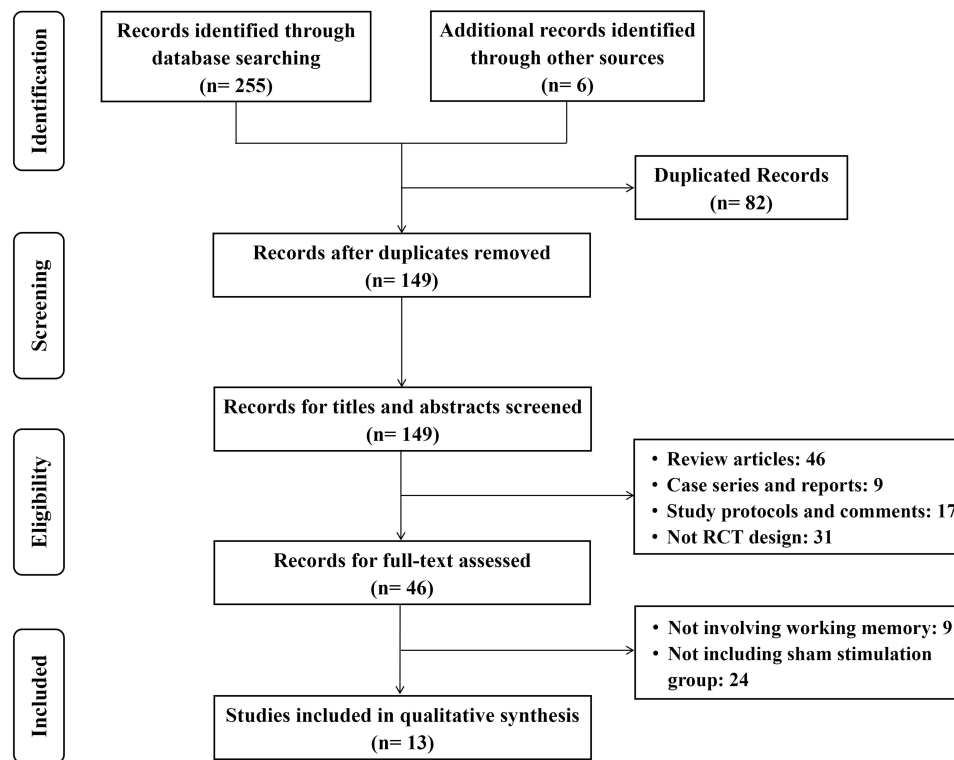


Figure 1 Flow diagram of trial identification and selection.

Meta-Analysis of TMS versus Sham Stimulation

Concerning WM performance before and after the intervention, all 13 RCTs reported outcomes comparing TMS to sham stimulation. In the aggregate, the differences between the TMS groups and sham groups (SMD = 0.89, 95% CI: -0.25–2.04, $P < 0.05$, $I^2 = 53%$, RE model; SMD = 0.70, 95% CI: -0.77–2.17, $P < 0.05$, $I^2 = 53%$, QE model) were not statistically significant (Figure 2), suggesting comparable therapeutic effects between both groups with moderate heterogeneity across studies. In the sensitivity analysis, whether utilizing the RE or QE model, excluding any individual RCT did not result in a change of more than 0.3 in the pooled SMD or an increase of more than 20% in the I^2 value. Moreover, an LFK index of 4.53 in the Doi plot indicated the presence of significant publication bias (Supplementary Figure 1).

Additionally, this review compared the results of the two groups under different stimulus parameters using the QE model. Unfortunately, the pooled SMD indicated that both groups exhibited comparable therapeutic effects at specific stimulation sites (left DLPFC or bilateral DLPFC), stimulus frequencies (10 Hz or 20 Hz), and total pulse counts ($\leq 30,000$ or 30,000). Further details can be found in Supplementary Table 1.

Discussion

This study compared the therapeutic effects of TMS and sham stimulation on WM deficits reported in RCTs in patients with SCZ. Regardless of whether the RE or QE model was employed, the eligible RCTs indicated that the TMS and sham groups demonstrated comparable therapeutic effects post-treatment.

rTMS

The prevailing paradigm in current research aimed at improving WM performance in individuals with SCZ is rTMS, particularly HF rTMS at 10 Hz and 20 Hz. In the case of 20 Hz rTMS, Barr et al (2013) conducted an RCT with a limited sample size.²³ The study involved 27 patients diagnosed with chronic SCZ, randomly assigned to either the rTMS treatment group or the sham-stimulation group. The bilateral DLPFC was targeted for stimulation using 20 Hz rTMS, and WM was assessed through the n-back task. After a four-week intervention, the findings showed a significant

Table 1 Characteristics of Randomized Controlled Trials Included in This Review

| Study | | Arms | N | Age (SD) | Cortical Target | Hz/(% MT) | Total Pulses | No. of Sessions | Scales/ Tasks for Working Memory | SMD |
|--|-----------------|------|----|---------------|---------------------------|--------------|--------------|-----------------|-----------------------------------|-------|
| Reference | Location | | | | | | | | | |
| Barr et al (2013) ²³ | Canada | rTMS | 13 | 41.15 (12.01) | BLDLPFC | 20 Hz (90%) | 30,000 | 20 | N-back task | 12.49 |
| | | Sham | 14 | 49.00 (12.42) | | | | | | |
| Basavaraju et al (2021) ²⁴ | India | iTBS | 30 | 37.17 (9.90) | Midline cerebellar vermis | 50 Hz (100%) | 6000 | 10 | Spatial span test | 0.20 |
| | | Sham | 30 | 34.17 (8.06) | | | | | | |
| Dlabac-de Lange et al (2015) ²⁵ | The Netherlands | iTBS | 16 | 41.80 (11.60) | BLDLPFC | 10 Hz (90%) | 60,000 | 15 | Verbal learning test | 3.90 |
| | | Sham | 16 | 32.30 (9.70) | | | | | | |
| Francis et al (2019) ²⁶ | United States | rTMS | 9 | 23.4 (3.10) | BLDLPFC | 20 Hz (110%) | 12,000 | 10 | BACS digit sequencing | -0.76 |
| | | Sham | 10 | 22.3 (2.00) | | | | | | |
| Guleken et al (2020) ²⁷ | Turkey | rTMS | 11 | 36.45 (8.58) | BLDLPFC | 20 Hz (90%) | 40,000 | 20 | Digit span task | 0.38 |
| | | Sham | 10 | 34.40 (12.11) | | | | | | |
| Guse et al (2013) ²⁸ | Germany | rTMS | 13 | 37.00 (NR) | LDLPFC | 10 Hz (110%) | 15,000 | 15 | N-back task | -4.20 |
| | | Sham | 12 | 36.00 (NR) | | | | | | |
| Hasan et al (2016) ³⁰ | Germany | rTMS | 73 | 36.40 (10.60) | LDLPFC | 10 Hz (110%) | 15,000 | 15 | Digit span test | 0.73 |
| | | Sham | 78 | 35.50 (9.00) | | | | | | |
| Prikryl et al (2012) ³¹ | Czech Republic | rTMS | 19 | 30.47 (9.19) | LDLPFC | 10 Hz (110%) | 22,500 | 15 | Verbal fluency test | 9.80 |
| | | Sham | 11 | 34.55 (10.57) | | | | | | |
| Rabany et al (2014) ²⁹ | Israel | dTMS | 20 | 33.10 (11.31) | LDLPFC | 20 Hz (120%) | NR | 20 | Cambridge Neuropsychological Test | 0.13 |
| | | Sham | 10 | 35.90 (11.00) | | | | | | |
| Wang et al (2022) ³² | China | iTBS | 33 | 23.79 (5.33) | LDLPFC | 50 Hz (80%) | 25,200 | 42 | N-back task | 6.49 |
| | | Sham | 26 | 24.15 (4.62) | | | | | | |
| Wölwer et al (2014) ³³ | Germany | rTMS | 18 | 34.30 (NR) | LDLPFC | 10 Hz (110%) | 10,000 | 10 | D2 attention task | -0.60 |
| | | Sham | 14 | 34.40 (NR) | | | | | | |

(Continued)

Table I (Continued).

| Study | | Arms | N | Age (SD) | Cortical Target | Hz/(% MT) | Total Pulses | No. of Sessions | Scales/ Tasks for Working Memory | SMD |
|---------------------------------|----------|--------------|----|---------------|-----------------|--------------|--------------|-----------------|----------------------------------|----------------------------|
| Reference | Location | | | | | | | | | |
| Xiu et al (2020) ³⁴ | China | rTMS (10 Hz) | 40 | 50.70 (9.00) | LDLPFC | 10 Hz (110%) | 48,000 | 40 | RBANS Immediate memory | 2.40 (10Hz) 9.80 (20Hz) |
| | | rTMS (20Hz) | 40 | 52.00 (10.10) | | 20 Hz (110%) | 64,000 | 40 | | |
| | | Sham | 40 | 54.70 (6.40) | | | | | | |
| Zhuo et al (2019) ³⁵ | China | rTMS | 33 | 28.97 (7.40) | LDLPFC | 20 Hz (90%) | 40,000 | 20 | MCCB WMS-III Spatial Span | -1.88 |
| | | Sham | 27 | 30.63 (8.25) | | | | | | |

Abbreviations: %MT, Percentage of motor threshold. Stimulation techniques; dTMS = Deep transcranial magnetic stimulation; iTBS, Intermittent theta-burst stimulation; rTMS, repetitive transcranial magnetic stimulation; BL, Bilateral dorsolateral prefrontal cortex; DLPPFC, Dorsolateral prefrontal cortex; BACS, Brief Assessment of Cognition; NR, No record; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; TMT-A, Trail making task-part A; TMT-B, Trail making task-part B; MCCB, MATRICS Consensus Cognitive Battery; WMS, Working Memory Spatial Span; SMD, standardized mean difference in the quality effects model.

Table 2 Methodological Quality Scores for All RCTs According to the Modified Physiotherapy Evidence Database Scale

| References | Item 1 | Item 2 | Item 3 | Item 4 | Item 5 | Item 6 | Item 7 | Item 8 | Item 9 | Item 10 | Sum Score | Qi |
|--|--------|--------|--------|--------|--------|--------|--------|--------|--------|---------|-----------|------|
| Barr et al (2013) ²³ | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 7 | 0.78 |
| Basavaraju et al (2021) ²⁴ | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 9 | 1.00 |
| Dlabac-De Lange et al (2015) ²⁵ | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 8 | 0.89 |
| Francis et al (2019) ²⁶ | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 8 | 0.89 |
| Guleken et al (2020) ²⁷ | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 8 | 0.89 |
| Guse et al (2013) ²⁸ | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 6 | 0.67 |
| Hasan et al (2016) ³⁰ | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 7 | 0.78 |
| Prikryl et al (2012) ³¹ | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 8 | 0.89 |
| Rabany et al (2014) ²⁹ | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 6 | 0.67 |
| Wang et al (2022) ³² | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 8 | 0.89 |
| Wölwer et al (2014) ³³ | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 7 | 0.78 |
| Xiu et al (2020) ³⁴ | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 6 | 0.67 |
| Zhuo et al (2019) ³⁵ | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 7 | 0.78 |

Notes: Item 1, eligibility criteria; Item 2, random allocation; Item 3, concealed allocation; Item 4, groups similar at baseline; Item 5, subject blinding; Item 6, assessor blinding; Item 7, less than 15% dropouts; Item 8, missing data management (intention-to-treat analysis); Item 9, between-group statistical comparisons; Item 10, point measures and variability data. Qi, quality index. A column designation of 1 indicates explicitly described and present in details. A column designation of 0 indicates absent, inadequately described, or unclear. In addition, eligibility criteria were not considered for scoring.

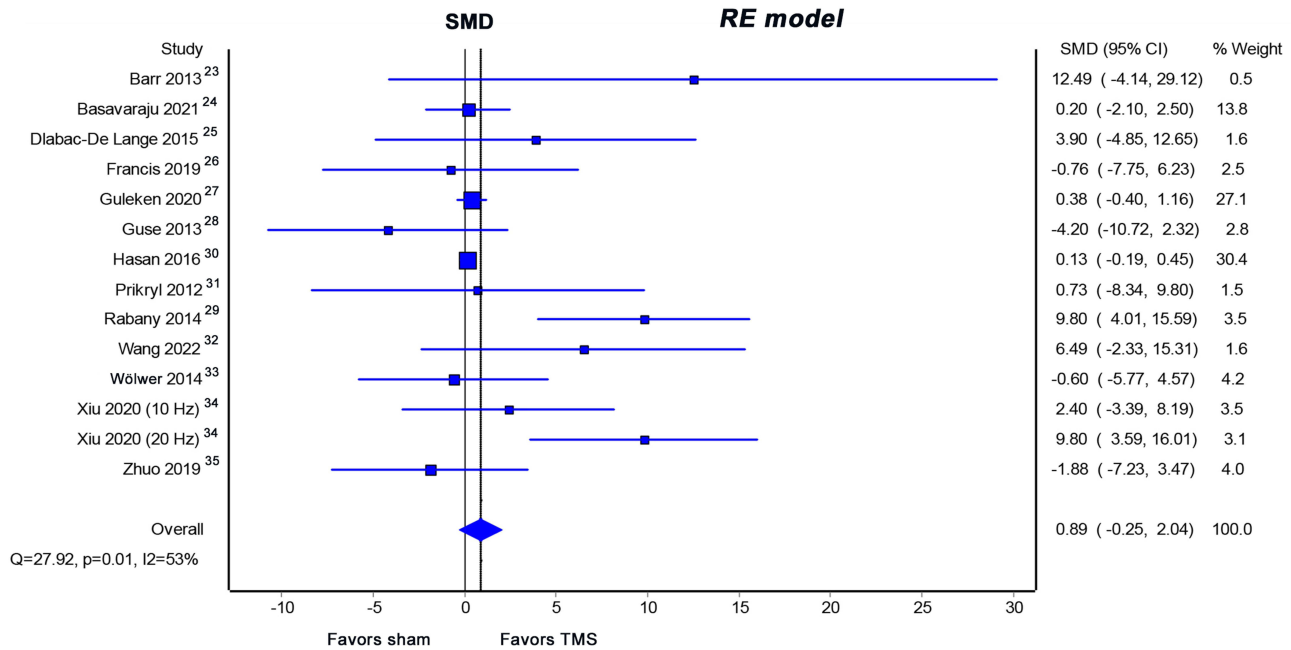
improvement in the accuracy of the 3-back task among participants receiving rTMS treatment compared to those in the sham-stimulation group. Subsequently, Francis et al (2019)²⁶ replicated the research methodology outlined by Barr et al (2013),²³ targeting bilateral DLPFC as the stimulation site. Neural cognition was assessed using the Brief Assessment of Cognition in Schizophrenia, with a primary focus on the digit sequencing task as a WM measure. The results indicated that following a 2-week treatment period, rTMS significantly enhanced neural cognition across various dimensions, as evidenced by improvements in symbol coding, semantic and letter fluency, and the token motor task. However, no notable improvement in WM was observed. This lack of improvement in WM may be attributed to the insufficient sensitivity of the digit sequencing subtest when compared to traditional paradigms such as the n-back task.

Guleken et al (2020) recently demonstrated that a five-week application of 20 Hz rTMS stimulation on the bilateral DLPFC holds promise for enhancing attention, verbal WM, and information processing speed in individuals diagnosed with SCZ.²⁷ Conversely, Zhuo et al (2019) argued that a four-week adjunctive treatment of 20 Hz rTMS stimulation, specifically targeting the left DLPFC, may effectively improve negative symptoms in patients with SCZ³⁵ but may not impact cognitive functions such as information processing speed, verbal learning, visual learning, and spatial WM. It is crucial to acknowledge that the assessment of WM varied across studies, and the potential influence of a placebo effect should be considered, as indicated by recent meta-analyses.^{15,36}

In our meta-analysis, no significant difference was observed between left rTMS and bilateral rTMS applied to the DLPFC in treating WM impairment in patients with SCZ. Barr et al (2013) suggested that rTMS targeting the DLPFC may enhance the recall and recollection processes necessary for the desired responses mediated by this brain region.²³ Notably, the body of evidence supporting hypoactivity in the left DLPFC in individuals with SCZ surpasses that for hypoactivity in the right DLPFC.²⁵ Research findings indicate that rTMS applied at the left DLPFC, but not the right DLPFC, could modulate dopamine release in brain regions, aligning with the dopamine hypothesis concerning cognitive impairments observed in individuals with SCZ.^{37,38} Consequently, utilizing HF rTMS targeting the left DLPFC appears to be a reasonable and suitable approach for addressing WM deficits. However, there remains a lack of consensus regarding the precise region within the DLPFC that should be targeted for stimulation.

In addition to the use of 20 Hz, some investigations also included the application of 10 Hz rTMS. Prikryl et al (2012) conducted a randomized controlled double-blind study involving 30 male individuals diagnosed with SCZ exhibiting negative symptoms.³¹ The intervention consisted of administering 10 Hz rTMS stimulation targeting the left DLPFC over 3 weeks, with WM assessed using a verbal fluency task. The study findings revealed that, in comparison to sham

A



B

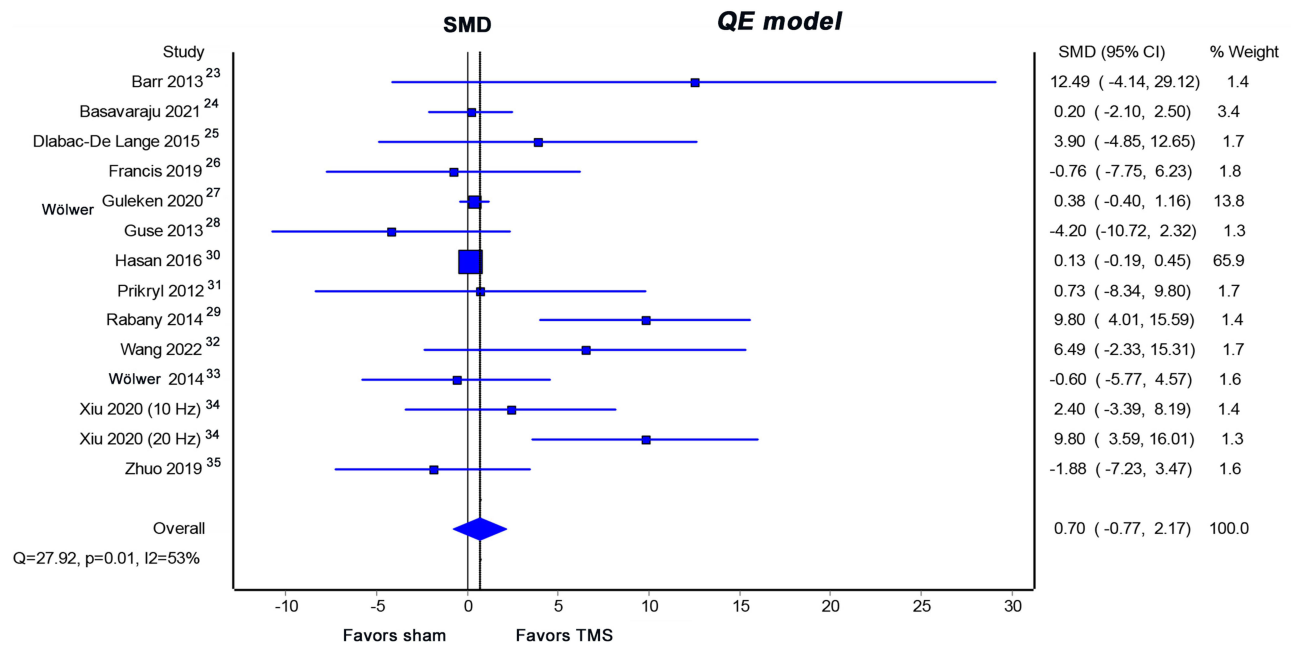


Figure 2 Meta-analysis of TMS vs sham stimulation for WM deficits. **(A)** random effects (RE) model; **(B)** quality effects (QE) model. **Abbreviation:** SMD, standardized mean difference.

stimulation, the implementation of rTMS treatment did not lead to enhancements in participants' WM. This conclusion was consistent with the research findings of Guse et al (2013).²⁸

Subsequently, Hasan et al (2016) conducted a multi-center RCT with a larger sample size, comprising 156 individuals diagnosed with SCZ.³⁰ Similarly, they demonstrated that 10 Hz rTMS stimulation of the left DLPFC for 3 weeks did not result in improvements in the cognitive functions of the patients. Interestingly, a recent study investigated the effects of rTMS with different frequencies under neuro-navigation on the cognitive function of individuals diagnosed with SCZ.³⁴ Considering the DLPFC's substantial size, which may not have been accurately targeted in most prior studies, a neuro-navigation system was employed to ensure precise targeting and monitoring in rTMS studies. This involves aligning the subject's head with

a standardized brain.^{39,40} The results indicated that after 8 weeks of stimulation of the left DLPFC, 20 Hz rTMS showed greater potential for enhancing WM in patients compared to the 10 Hz frequency.

iTBS

As a novel rTMS protocol, iTBS is characterized by three 50 Hz intra-plexus pulses repeated for 200 ms. These intra-plexus pulses are replicated at 5 Hz to mimic the theta rhythm. The stimulation unit comprises 10 bursts, followed by an 8-second interval, and this pattern is reiterated every 10 seconds.⁴¹ In contrast to traditional rTMS, iTBS provides substantial reductions in treatment time and medical costs, rendering it highly promising for a broad spectrum of clinical applications.¹⁹

The treatment of visual-spatial WM deficits in treatment-resistant SCZ (TRS) currently lacks satisfactory options. Wang et al (2022) utilizing neuro-navigation equipment to target the left DLPFC, randomly assigned patients with TRS to either receive iTBS or sham treatment over two weeks.³² The primary outcome measure was the accuracy of n-back target responses, with a specific emphasis on 3-back accuracy. The results revealed that the iTBS group demonstrated significant improvements in n-back accuracy compared to the sham group, particularly in terms of 3-back accuracy. Consequently, the researchers concluded that iTBS intervention may represent a promising and innovative approach for addressing visual-spatial deficits in TRS.

The predominant focus of research has centered on investigating the impact of HF rTMS, specifically applied to the DLPFC. Despite showing potential in addressing negative symptoms, the overall body of evidence supporting its effectiveness remains limited.^{42,43} Considering the cerebellum's involvement in cognitive processes, emotional regulation, motivation, and social functioning,⁴⁴ an RCT was conducted to recruit individuals with SCZ displaying at least a moderate severity of negative symptoms.²⁴ Participants were randomly assigned to receive either real or sham iTBS under magnetic resonance imaging (MRI)-guided neuro-navigation, with a specific focus on targeting the cerebellar vermis area VII-B. Unfortunately, the application of cerebellar vermis iTBS did not result in any improvements in the negative symptoms and WM performance of the patients with SCZ. The author hypothesized that this lack of improvement may be attributed to the relatively short duration of the treatment. Furthermore, frequent evaluations may have inadvertently enhanced the effectiveness of the placebo. Animal studies have provided evidence of cerebellar projections to the anterior cingulate cortex (ACC), involving intermediary structures such as the ventral tegmental area,⁴⁴ as well as cerebellar regulation of prefrontal dopamine.⁴⁵ The involvement of the cerebellum in dopamine signaling and ACC activity suggest that the cerebellum interacts with other brain structures in emotional functions. This highlights the significance of the cerebellum in higher-order functions and positions it as a potential target for addressing TRS the negative symptoms of SCZ, due to its mood-enhancing effects.⁴⁶

dTMS

The hypothesis underlying the introduction of dTMS proposed that standard TMS coils might not sufficiently penetrate deep brain regions. Therefore, dTMS, with a reach of ~3 cm, was primarily designed to enhance negative symptoms.^{47,48} In a preliminary open-label study, positive outcomes were observed in alleviating negative symptoms and depression after 20 daily sessions of H1 dTMS. Moreover, cognitive enhancements were noted in spatial WM and sustained attention.⁴⁹ Rabany et al (2014) explored the potential of using dTMS as an adjunctive treatment for negative symptoms and cognitive deficits in individuals with SCZ.²⁹ Participants underwent twenty daily sessions of H1 20 Hz dTMS treatment, with comprehensive clinical and cognitive assessments conducted throughout the study and during a one-month follow-up period. Unfortunately, no significant differences were observed between the groups in terms of changes in scores on the spatial WM test at any of the time points. In conclusion, the application of dTMS for addressing cognitive impairment in SCZ is still in its early stages and requires further investigation.

The majority of RCTs in this study claimed adherence to published safety application guidelines for administering rTMS therapy.^{50,51} Generally, rTMS treatment is well-tolerated, although common occurrences of earache, headache, tinnitus, discomfort at the application site, fatigue, gum sensation, muscle twitching, and increased heart rate have been reported. These adverse reactions are typically of mild intensity, brief duration, and reversible. Moreover, as the frequency of treatments increases, the aforementioned adverse reactions tend to progressively diminish or cease entirely. Epilepsy is considered the most profound adverse reaction to TMS treatment; however, none of the 13 RCTs encompassed in this study identified any instances of such symptoms. It is noteworthy to mention that Basavaraju et al (2021) discovered that among the participants who underwent real iTBS targeting the cerebellar vermis, two individuals

exhibited indications suggestive of mania/hypomania during the trial. Conversely, none of the participants who received sham iTBS displayed similar symptoms.²⁴

Potential Neural Mechanisms of TMS in the Treatment of WM Deficits

Multiple lines of evidence consistently indicate that alterations in the DLPFC play a central role in the impaired WM performance observed in individuals with SCZ.⁵² In a study by Wang et al (2022) functional MRI (fMRI) revealed that the iTBS group exhibited increased fractional amplitude of low-frequency fluctuations (fALFF) in the right occipital areas and decreased fALFF in the right precuneus while performing a visual-spatial WM n-back task.³² Previous research has also reported a general reduction in cortical thickness in the low-level visual areas, particularly the lateral occipital cortex, among patients with SCZ, which has been associated with abnormal visual processing. Importantly, this reduction in activation is most pronounced during high WM loads.⁵³ Moreover, the heightened requirement for attentiveness in individuals diagnosed with SCZ may lead to the failure of the top-down executive control network, primarily centered around the DLPFC, to maintain stable WM representations, making them more vulnerable to distraction.^{54,55}

Following a two-week intervention of iTBS on the left DLPFC, the heightened activity in the visual cortex (increased fALFF) may enable patients to process visual stimuli more effectively by converting sensory information into relatively stable WM. This process ensures and enhances the accuracy of visual information.⁵⁶ The precuneus, a crucial element of the default mode network associated with task negativity, exhibited decreased activity to facilitate cognitive processing linked to WM. Leveraging the brain's capacity for recovery, a two-week course of iTBS has the potential to aid individuals with TRS in restoring their cognitive functioning through compensatory mechanisms targeting distant regions within specific cognitive circuits.

Gamma oscillation refers to rhythmic synchronous brain activity with a frequency of ~40 Hz, falling within the range of 25–100 Hz. This phenomenon plays a crucial role in promoting synaptic plasticity and regulating neural networks, particularly in higher cognitive functions such as sensory feature integration, selective attention, and WM.⁵⁷ Previous investigations have shown that the amplitude of frontal gamma oscillations increases in proportion to the cognitive load imposed by WM tasks.^{58,59} Importantly, individuals with SCZ exhibit an inability to increase this amplitude in response to heightened WM demands.^{60,61}

In a study by Barr et al (2011), the impact of 20 Hz rTMS on gamma oscillatory activity during the n-back task was investigated in individuals with SCZ compared to healthy controls (HCs).⁶² Before receiving rTMS, patients exhibited elevated gamma oscillatory activity across WM load. Following active rTMS, patients experienced a decrease in frontal gamma oscillatory activity, while HCs demonstrated an increase in activity during the 3-back task. These divergent effects of rTMS on gamma oscillatory activity may be attributed to differential alterations in gamma-aminobutyric acid (GABA)ergic activity. A previous study indicated that the effects of rTMS on GABAA receptor-mediated inhibition can vary depending on baseline levels.⁶³ Given that GABAA inhibitory post-synaptic potentials play a role in generating gamma oscillations, these findings can be used to explain the diverse effects of rTMS on gamma oscillatory activity in both individuals with SCZ and HCs. Specifically, rTMS was found to suppress gamma oscillatory activity in patients with SCZ who exhibited higher levels of baseline gamma activity, while enhancing activity in HCs with lower levels of baseline gamma activity. These effects may also be associated with homeostatic plasticity, a mechanism that regulates neuronal activity to ensure it remains within a beneficial physiological range, playing a crucial role in maintaining neuronal stability.

This study has some limitations. Firstly, the inclusion of 13 RCTs that utilized TMS as an augmentation treatment alongside medications has hindered our ability to elucidate the therapeutic effect of TMS in isolation. Secondly, a moderate level of heterogeneity was observed among the studies included in this meta-analysis, as various stimulus protocols, such as rTMS, dTMS, and iTBS, were employed to assess the therapeutic effects of TMS compared to sham treatment for WM deficits. Lastly, the limited number of studies investigating the neural mechanisms underlying TMS as a treatment for WM deficits in patients with SCZ hampers the generalizability of our findings.

Conclusion and Prospect

The research landscape regarding the use of rTMS for treating WM deficits in patients with SCZ is currently in its early exploratory stages. Although certain studies have indicated a potentially significant positive impact of rTMS on WM in individuals with SCZ, further replication is needed, and the existing evidence is not sufficient to draw definitive conclusions. This study offers two notable advantages compared to previous retrospective reviews on the same topic.

First, the use of the QE model, incorporating the study's quality score, allowed us to integrate the latest evidence related to the treatment of WM impairment by TMS. Second, prioritizing both clinical efficacy and safety, we conducted a comprehensive examination of the potential mechanism of action underlying the therapeutic effects of TMS for WM deficits in individuals diagnosed with SCZ. Moving forward, additional well-designed and rigorously conducted studies are essential to establish the efficacy and safety of rTMS in addressing WM deficits in the context of SCZ.

Recent advancements in neuroimaging methodologies have enabled precise targeting of TMS based on individual functional connectivity.⁶⁴ For example, a study by Brady et al (2019) demonstrated that applying rTMS to the cerebellum node led to alterations in the cerebellar association network among patients with SCZ.⁶⁵ The authors utilized fMRI to identify the network associated with the severity of negative symptoms, including the cerebellum node. They then investigated the connectivity between the DLPFC and the cerebellum, administering rTMS to the cerebellum node, which resulted in a notable improvement in negative symptoms. Importantly, the symptomatic improvement positively correlated with the change in DLPFC-cerebellar functional connectivity. Considering the close relationship between WM impairment in SCZ and disruption of the frontoparietal network,⁶⁶ individually defined network-based rTMS treatment could offer a novel therapeutic approach for SCZ.

Moreover, utilizing multivariate and data-driven methodologies can enhance our understanding of intricate brain biology and enable individual-level prediction of disease progression.⁶⁷ Previous studies have primarily employed univariate statistical group comparisons or regression analyses with relatively straightforward models to examine the structural and functional disparities in the brain associated with SCZ. However, relying solely on these uncomplicated analyses poses challenges in comprehending the intricate brain pathophysiology of this disorder. To gain a deeper understanding of the disease's pathogenesis in relation to clinical symptoms and treatment response, future investigations on rTMS for SCZ should employ diverse modalities to assess patients and conduct multivariate analysis.⁶⁸

Exploring various rTMS intervention programs for WM deficits and determining the most effective intervention parameters should be pursued as the next research direction. In recent years, the concept of closed-loop neuromodulation has emerged as a method for identifying localized and network-level irregularities within the brain in real-time through the utilization of fMRI or electroencephalogram (EEG). Additionally, this technique aims to simultaneously neuromodulate and address these abnormalities. A closed-loop neuromodulation system focuses on the endophenotypes assessed by fMRI or EEG and adaptively adjusts stimulation parameters to optimize these indicators, transitioning them from pathological to healthy states⁶⁹ (refer to Figure 3). Furthermore, alongside neuroimaging, it is imperative to investigate

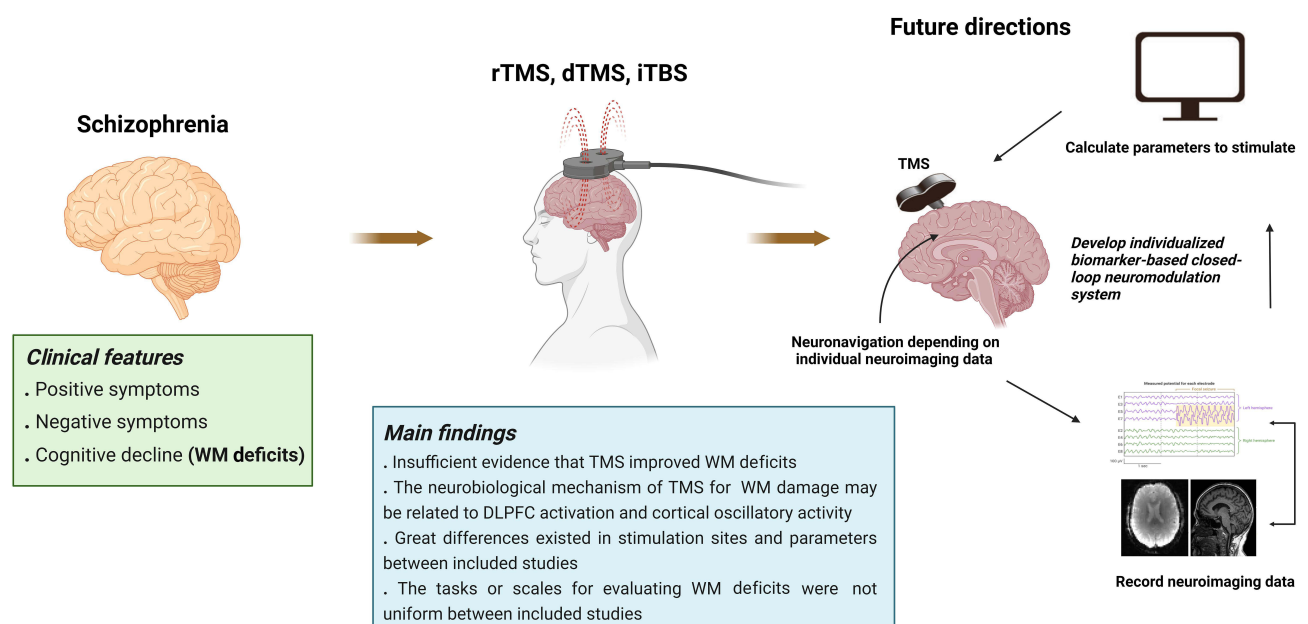


Figure 3 Research findings and future directions.

Abbreviations: WM, working memory; TMS, transcranial magnetic stimulation; rTMS, repetitive TMS; dTMS, deep TMS; iTBS, intermittent theta-burst stimulation; DLPFC, dorsolateral prefrontal cortex.

the biological ramifications of rTMS through a comprehensive examination of various dimensions, including gene regulation, molecular interactions, and neurophysiology. With enrichment and in-depth research, rTMS is expected to become an important means to improve WM deficits in SCZ.

Ethics Approval

Ethics approval was not required, as all data were gathered from previous published studies.

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Author Contributions

Each author has made a substantial contribution to the research presented, encompassing various aspects such as conception, study design, execution, data acquisition, analysis and interpretation. Additionally, they have actively participated in the drafting, revising, and critical review of the article, ultimately providing their final approval for publication. Furthermore, the authors have collectively agreed upon the journal to which the article has been submitted and acknowledge their accountability for all facets of the work.

Disclosure

The authors report no conflicts of interest in this work.

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