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Adjunctive Intermittent Theta-Burst Stimulation for Schizophrenia: A Systematic Review and Meta-analysis of Randomized Double-Blind Controlled Studies

ABSTRACT

Objective: In order to determine whether intermittent theta-burst stimulation (iTBS) is a viable adjunct treatment for schizophrenia, a meta-analysis of double-blind, randomized clinical trials (RCTs) was performed.

Methods: Four independent researchers extracted and synthesized data from RCTs on adjunctive iTBS for patients suffering from schizophrenia. RevMan 5.3 software was used to calculate risk ratios (RRs) and standardized mean differences (SMDs) along with their 95% confidence intervals (CIs).

Results: Fifteen RCTs involving 671 patients with schizophrenia were included. Adjunctive iTBS was significantly superior to sham interventions for improvement in overall psychopathology (SMD = −0.75, 95% CI: −1.10, −0.41, I^2 = 64%, P < .0001), negative symptoms (SMD = −0.76, 95% CI: −1.18, −0.35, I^2 = 78%, P = .0003), and general psychopathology (SMD = −0.51, 95% CI: −0.88, −0.14, I^2 = 71%, P = .007), though no significant group difference was found regarding positive symptoms. Adjunctive iTBS also demonstrated superiority over control treatments in improving cognitive functions as measured by the Spatial Span Test (SMD = 0.83, 95% CI: 0.16, 1.49, I^2 = 73%, P = .02) and Montreal Cognitive Assessment (SMD = 0.49, 95% CI: 0.11, 0.88, I^2 = 0%, P = .01). Discontinuation rates (RR = 0.92, 95% CI: 0.57, 1.50, I^2 = 0%, P = .75) and adverse events were comparable between groups.

Conclusion: The use of iTBS in patients with schizophrenia appears to be effective in improving psychiatric symptoms and cognitive function. To substantiate these preliminary findings, future research involving larger participant cohorts is warranted.

Keywords: Intermittent theta burst stimulation, schizophrenia, meta-analysis, cognitive function

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Introduction

Schizophrenia is a severe mental illness affecting approximately 1% of the world's population[1] and accounts for 12.2% of global disability-adjusted life years worldwide according to the 2019 Global Burden of Disease Study Report.[2] A wide variety of disturbances are associated with schizophrenia, including positive symptoms (such as hallucinations or delusions), negative symptoms (such as avolition), and cognitive impairments. While antipsychotic medications constitute a treatment mainstay, approximately 33% of patients do not fully respond to pharmacotherapy.[3] For individuals who are unresponsive to pharmacological treatment, novel therapeutic approaches, such as non-invasive brain stimulation (NIBS) techniques, represent a viable alternative for the alleviation of symptoms.[4,5]

Several NIBS techniques have been tested in clinical practice as treatments for schizophrenia, including repetitive transcranial magnetic stimulation (rTMS),[6] electroconvulsive therapy (ECT)[7] and transcranial direct current stimulation (tDCS).[8] For example, ECT is a method used for patients with treatment-resistant schizophrenia; however, its utility is constrained by requirements for anesthesia and limitations imposed by cognitive side effects.[7] As a

non-invasive technique capable of modulating brain activity, rTMS has gained increasing interest. Accumulating studies have found that rTMS is safe and effective for schizophrenia. A recent meta-analysis of 57 studies involving 2633 schizophrenia patients revealed that rTMS had superior efficacy in alleviating negative symptoms compared with sham interventions.[6]

Theta burst stimulation (TBS) has also emerged as a specialized form of rTMS and potential therapeutic option for patients with schizophrenia.[9] In comparison to rTMS, TBS employs a reduced stimulation intensity and a shorter duration of stimulation. This approach not only facilitates more immediate and enduring impacts on synaptic plasticity but also enhances the modulation of functional connectivity within the right posterior parietal cortex.[10] Two distinct TBS stimulation approaches, continuous TBS (cTBS) and intermittent TBS (iTBS), have been observed to elicit differential effects. iTBS increases motor cortical excitability while cTBS elicits cortical inhibitory effects. This differential profile renders iTBS particularly influential in modulating synaptic plasticity. iTBS modulates cortical excitability across brain circuits by promoting the accumulation of the neurotransmitters, glutamate and γ-aminobutyric acid (GABA).[11]

Although iTBS has been recommended for major depressive disorder,[12,13] research on its efficacy in the field of schizophrenia is still in its infancy. While adjunctive iTBS is beneficial for older adults with schizophrenia in terms of cognitive function,[16] results of randomized controlled trials (RCTs) on the effects and safety of adjunctive iTBS (versus control interventions) have been mixed among patients with schizophrenia. Several studies have shown that iTBS over the left dorsolateral prefrontal cortex (L-DLPFC) can alleviate negative symptoms of schizophrenia.[14,15] Conversely, recent research revealed that active iTBS did not yield a notable improvement in negative symptoms when compared with sham stimulation.[28]

Previous meta-analyses have concluded that adjunctive iTBS has demonstrable efficacy and safety in the treatment of schizophrenia.[16-19] A meta-analysis[17] of 13 studies (n = 524)[15,20-31] assessed the efficacy and safety of adjunctive iTBS among schizophrenia patients. However, one self-controlled trial[27] rather than an RCT was included,[17] potentially reducing the robustness of overall findings. Furthermore, 5 recent double-blind RCTs.[14,32-35]investigating the therapeutic impact of iTBS on schizophrenia were not included within Goh et al's meta-analysis.[17]

Our updated meta-analysis includes these 5 additional RCTs[14,32-35] to provide a more comprehensive evaluation of evidence regarding the use of iTBS for schizophrenia. Based on existing literature, our main hypothesis was that patients with schizophrenia would benefit from adjunctive iTBS treatment significantly more than control group participants would.

MAIN POINTS

- *Patients with schizophrenia benefit from adjunctive iTBS treatment.*
- *Adjunctive iTBS was superior to sham in terms of reducing total psychopathology, negative symptoms, and general psychopathology, but not positive symptoms.*
- *Adjunctive iTBS displayed comparatively enhanced effects on several specific cognitive functions.*
- *There were no significant group differences regarding discontinuation for any reason or adverse events.*

Material and Methods

Inclusion criteria

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,[36] the criteria for inclusion in our meta-analysis were established using the ***PICOS*** framework. ***P***articipants: individuals diagnosed with schizophrenia as their primary psychiatric diagnosis. ***I***ntervention: active iTBS combined with treatment as usual (TAU). There were no a priori restrictions on included iTBS treatment protocols regarding stimulation parameters and treatment durations. Comparison: sham iTBS plus TAU. Outcomes: The primary outcome evaluated was post-iTBS change in total psychopathology, as quantified by either the Positive and Negative Syndrome Scale (PANSS)[37] or Brief Psychiatric Rating Scale (BPRS).[38] Secondary outcomes comprised scores for positive symptoms, negative symptoms, and general psychopathology derived from the PANSS or BPRS, along with the Scale for the Assessment of Positive Symptoms (SAPS), the Scale for the Assessment of Negative Symptoms (SANS), cognitive functions, discontinuation rates, and adverse events. To minimize heterogeneity, PANSS subscale scores were prioritized when multiple measures were used to evaluate positive and negative symptoms. Study: Only double-blinded RCTs that tested the therapeutic effectiveness and safety profile of iTBS for individuals with schizophrenia were considered. Notably, one open-label study[39] and one study that administered only one iTBS session[27] were excluded from analyses. Two studies involving duplicate datasets were identified[23,34] but only the most comprehensive dataset was retained.[34] Finally, we excluded a study[40] that included a mixed schizophrenia and depression sample as well as case reports/series and reviews.

Search strategy

A systematic search for RCTs in English and Chinese was conducted independently by 4 researchers (XHY, KSW, NZ, and SYL) across several databases, including PubMed, Cochrane Library, PsycINFO, Embase, Chinese Journal Net, and WanFang, from inception dates of each database to August 11, 2023. The search strategy employed the following search terms: (intermittent theta burst stimulation OR (intermittent* AND theta burst stimulation) OR iTBS OR TBS OR theta burst transcranial magnetic stimulation OR transcranial theta burst stimulation) AND (schizophrenia [MeSH] OR schizophrenic disorder OR disorder, schizophrenic OR schizophrenic disorders OR schizophrenia OR dementia praecox). Moreover, in order to identify any additional RCTs that met the selection criteria, reference lists of included studies were manually searched, as well as relevant reviews and meta-analyses.

Data extraction

Data extraction and verification were performed independently by the same 4 researchers. Any discrepancies between them were resolved through a discussion with a senior researcher (WZ). Data on authorship details, iTBS protocols, study designs, and primary/secondary outcomes were collected using a standardized form. When data were incomplete or inaccessible, corresponding authors were contacted via email to request further information. In studies that

included at least 2 target sites, data from iTBS treatment at each site were extracted and analyzed independently versus the sham group.[41] With regard to continuous data, to prevent an artificial increase in the size of sham groups, totals from these groups were assigned to each active iTBS group, in accordance with the methodology employed in other meta-analyses.[42,43]

Statistical Analyses

For all meta-analyses, the data synthesis process was conducted utilizing a random-effects model according to Cochrane Collaboration guidelines.[44] RevMan version 5.30 software (Cochrane Collaboration, Plano Texas, TX, USA) was employed for data synthesis. For binary outcomes, we calculated risk ratios (RRs) with 95% confidence intervals (CIs). For continuous outcomes, we calculated standardized mean difference (SMD) values with 95% CIs. Studies were assessed for heterogeneity using Cochrane's Q and I^2 tests. Significant heterogeneity was denoted by a Q statistic less than 0.1 or an I^2 value of 50% or higher.[45] To better clarify possible sources of heterogeneity, we performed sensitivity analyses by removing one outlying study.[24] A publication bias analysis was conducted for the primary outcome using funnel plots and an Egger's test,[46] with a significance threshold of 0.05 based on 2-tailed P values. Data were analyzed using STATA Version 12 (Stata-Corp LP, College Station, TX, USA).

Assessment of Study Quality

Using the Cochrane risk of bias tool[47] and the Jadad scale,[48] 4 researchers (XHY, KSW, NZ, and SYL) independently assessed the quality of included RCTs. Randomized controlled trials scoring ≥3 on the Jadad scale were classified as high quality.[49] Quality assessments of primary and secondary outcome findings were conducted independently using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system.

Results

Study selection

A total of 453 articles were retrieved through database searches, with 2 additional articles[21,25] sourced from another meta-analysis.[17] After excluding irrelevant and duplicate studies, 331 articles were retained. Figure 1 shows the selection process for studies. Ultimately, 15 RCTs[14,15,20-22,24-26,28,29,31-35] were included.

Study characteristics

Table 1 shows a summary of participant characteristics and iTBS parameters from the 15 included RCTs. In total, 671 patients were included and randomized into an iTBS group (n = 348) versus a sham iTBS stimulation group (n = 323). Mean durations of illness for patients ranged from 3.8 to 33.2 years. iTBS treatment durations ranged from 5 days to 12 weeks, with total pulses ranging from 6000 to 57 600. Stimulus intensities were varied between 80% and 120% of the motor threshold, with a frequency of 50 Hz. Of the 15 included studies, 12 studies assessed iTBS applied to the L-DLPFC versus sham stimulation, 3 tested iTBS applied to the vermis of the cerebellum versus sham stimulation. Of the 15 included studies, one study[32] employed a 3-arm sham-controlled design, comparing iTBS applied to the left lateral parietal cortex (L-LPC) or right dorsolateral prefrontal cortex (R-DLPFC) versus sham stimulation.

Assessment of Study Quality

Of the 15 studies included (Figure 1), 13 were determined to be of high quality (Jadad score of 3 or above), while 2 were classified as low quality (Jadad score of 2). Figure 2 shows the Cochrane risk of bias of each included RCT. In accordance with the GRADE criteria, the aggregate evidence grades for 17 eligible meta-analysis outcomes were categorized as "low" (11.8%, 2/17), "moderate" (82.3%, 14/17), and "high" (5.9%, 1/17) (Supplementary Table 1).

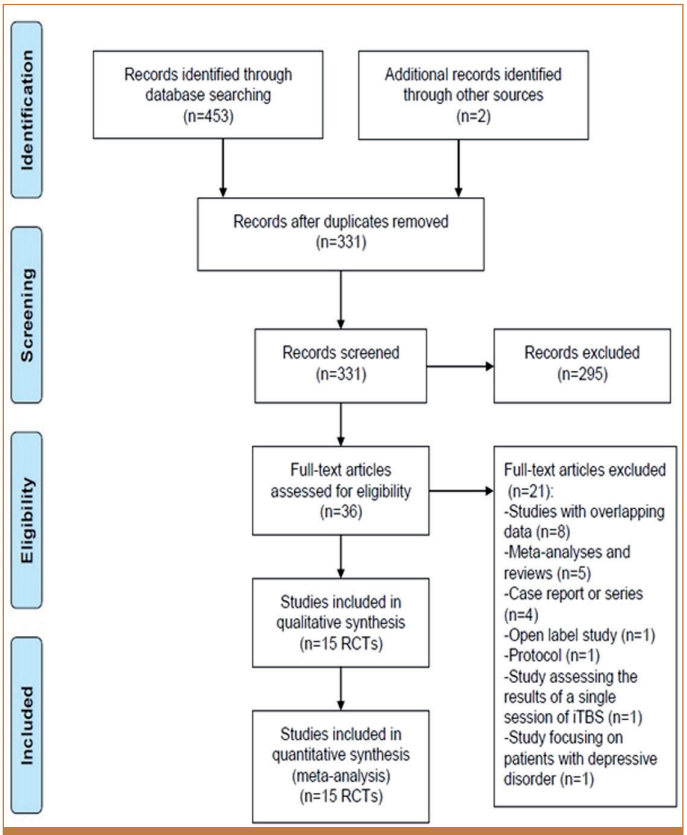

Figure 1. PRISMA flow diagram. RCTs, randomized clinical trials; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses.

Psychotic Psychopathology

Adjunctive active iTBS was more efficacious than sham iTBS for improving total psychopathology (SMD = −0.75, 95% CI: −1.10, −0.41, I^2 = 64%, P < .0001) as measured by the PANSS, improving negative symptoms (SMD = −0.76, 95% CI: −1.18, −0.35, I^2 = 78%, P = .0003), and improving general psychopathology related to cognitive dysfunctions (SMD = −0.51, 95% CI: −0.88, −0.14, I^2 = 71%, P = .007), as measured by the PANSS-negative symptoms subscale and the PANSS-general psychopathology subscale, respectively. Conversely, positive symptom improvements did not differ significantly between groups (SMD = 0.37, 95% CI: −0.29, 1.02, I^2 = 89%, P = .27) (Figure 3).

In sensitivity analyses, significant effects were retained for total psychopathology (I^2 = 45%; P < .0001), PANSS-negative symptoms (I^2 = 66%; P = .0005), and PANSS-general psychopathology (I^2 = 12%; P = .002), after removing one outlying study.[24] Similarly, the null effect for positive symptoms (I^2 = 22%; P = .16) did not differ significantly between groups when the outlying study[24] was excluded.

Cognitive Functions

Regarding specific cognitive functions, adjunctive active iTBS resulted in greater improvements than sham iTBS with respect to visuospatial working memory, as measured by the Spatial Span

Table 1. Participant Characteristics and iTBS Parameters of Each Included Studies

Study (country)	Sample size (n)[a]	Diagnostic criteria -Diagnosis (%)	-Illness duration (years) [a]-Male (%)[a]	Mean age: years (range)[a]	Trial duration	Intervention versus control groups; dose (mg/day)	Target site	-Intensity (% MT) -Frequency (Hz)	-Train duration (s) -Intertrain duration (s)	-Total sessions -Pulse per session -Total pulses	Jadad score
Basavaraju et al, 2021 (India)	Total:60 iTBS:30 Sham:30	-DSM-V -SCZ (100)	-NR -NR	NR	5 d	1. Active iTBS + APs; NR 2. Sham iTBS + APs; NR	The cerebellar vermis area VII-B	-100 -50	-2 -8	-10 -600 -6000	5
Bation et al, 2021 (France)	Total:22 iTBS:12 Sham:10	-DSM-IV-TR -SCZ (100)	-16.0 -95.5	42.0 (22-65)	10 d	1. Active iTBS + APs; CPZ-equ=325 2. Sham iTBS + APs; CPZ-equ=389	L-DLPFC	-80 -50	-2 -8	-20 -990 -19 800	5
Cen et al, 2020 (China)	Total:18 iTBS:10[b] Sham:8	-DSM-V -SCZ (100)	-3.8 -72.2	24.7 (18-50)	20 d	1. Active iTBS + APs; CPZ-equ=606 2. Sham iTBS + APs; CPZ-equ=594	R-DLPFC or L-LPC[b]	-80 -50	-2 -8	-20 -600 -12 000	3
Chauhan et al, 2021 (India)	Total:36 iTBS:19 Sham:17	-ICD-10 -TRS (100)	-14.6 -41.7	40.6 (18-59)	5 d	1. Active iTBS + APs; CPZ-equ=608 2. Sham iTBS + APs; CPZ-equ=568	The vermal part of cerebellum	-80 -50	-2 -8	-10 -600 -6000	4
Chen et al, 2011 (China)	Total:46 iTBS:24 Sham:22	-DSM-IV -SCZ (100)	-NR -64.3	38.4 (18-55)	4 w	1. Active iTBS + APs[c]; NR 2. Sham iTBS + APs[c]; NR	L-DLPFC	-80 -50	NR	-20 -2400 -48 000	5
Chen et al, 2023 (China)	Total:41 iTBS:25 Sham:16	-ICD-10 -SCZ (100)	-9.5 -46.3	37.4 (18-50)	12 w	1. Active iTBS + APs; NR 2. Sham iTBS + APs; NR	L-DLPFC	-85~100 -50	-2 -8	-96 -600 -57600	3
Jin et al, 2023 (China)	Total:66 iTBS:34 Sham:32	-DSM-V -SCZ (100)	-8.6 -56.1	47.5 (18-65)	4 w	1. Active iTBS + OLA; 12 2. Sham iTBS + OLA; 12	L-DLPFC	-120 -50	-NR -8	-60 -600 -36 000	5
Kazemi et al, 2013 (Iran)	Total:10 iTBS:5 Sham:5	-DSM-IV-TR -SCZ (100)	-4.1 -NR	27.1 (18-50)	NR	1. Active iTBS + APs; NR 2. Sham iTBS + APs; NR	L-DLPFC	-80 -50	-2 -8	-20 -NR -NR	2
Wang et al, 2020 (China)	Total:50 iTBS:25 Sham:25	-DSM-IV -SCZ (100)	-NR -NR	NR (18-52)	2 w	1. Active iTBS + APs; NR 2. Sham iTBS + APs; NR	L-DLPFC	NR	NR	NR	2
Wang et al, 2022 (China)	Total:59 iTBS:33 Sham:26	-DSM-IV -TRS (100)	-4.6 -44.1	24.0 (18-52)	2 w	1. Active iTBS + APs; CPZ-equ=759 2. Sham iTBS + APs; CPZ-equ=670	L-DLPFC	-80 -50	-2 -8	-42 -600 -25 200	4
Zhao et al, 2014 (China)	Total:48 iTBS:24 Sham:24	-DSM-IV -SCZ (100)	-NR -45.7	47.2 (20-55)	4 w	1. Active iTBS + APs[d]; NR 2. Sham iTBS + APs[d]; NR	L-DLPFC	-80 -50	-NR -NR	-20 -2400 -48 000	5
Zhao et al, 2021 (China)	Total:52 iTBS:26 Sham:26	-ICD-10 -SCZ (100)	-33.2 -66.7	63.3 (59-71)	4 w	1. Active iTBS + APs; CPZ-equ=495 2. Sham iTBS + APs; CPZ-equ=527	L-DLPFC	-100 -50	-NR -NR	-20 -600 -12000	5
Zhen et al, 2015 (China)	Total:60 iTBS:30 Sham:30	-DSM-IV -SCZ (100)	-7.5 -43.9	43.4 (18-55)	4 w	1. Active iTBS + APs[c]; NR 2. Sham iTBS + APs[c]; NR	L-DLPFC	-80 -50	-2 -8	-20 -600 -12 000	5
Zheng et al, 2012 (China)	Total:39 iTBS:19 Sham:20	-CCMD-3 -SCZ (100)	-32.3 -100.0	56.0 (NR)	5 d	1. Active iTBS + APs[e]; NR 2. Sham iTBS + APs[e]; NR	L-DLPFC	-80 -50	-2 -8	-5 -1200 -6000	5

Table 1. Participant Characteristics and iTBS Parameters of Each Included Studies (*Continued*)

Study (country)	Sample size (n)[a]	Diagnostic criteria -Diagnosis (%)	-Illness duration (years) -Male (%)[a]	Mean age: years (range)[a]	Trial duration	Intervention versus control groups; dose (mg/day)	Target site	-Intensity (% MT) -Frequency (Hz)	-Train duration (s) -Intertrain duration (s)	-Total sessions -Pulse per session -Total pulses	Jadad score
Zhu et al,2021 (China)	Total:64 iTBS:32 Sham:32	-ICD-10 -SCZ (100)	-15.6 -50.0	35.3 (18-50)	2 w	1. Active iTBS + APs; CPZ-equ=464 2. Sham iTBS + APs; CPZ-equ=487	The vermal part of cerebellum	-100 -50	-2 -8	-10 -600 -6000	5

[a]Available data were extracted based on the mean baseline value of each included trial.
[b]Of the 10 patients who received iTBS with the same parameters, 6 patients were treated in the R-DLPFC and 4 were treated in the L-LPC.
[c]Including risperidone, olanzapine, aripiprazole, quetiapine, or clozapine.
[d]Including risperidone, olanzapine, or quetiapine.
[e]Including risperidone, olanzapine, aripiprazole, quetiapine, clozapine, or chlorpromazine.
APs, antipsychotics; CCMD-3, Chinese Classification and Diagnostic Criteria of Mental Disorders 3rd edition; CPZ-equ, chlorpromazine equivalents; d, days; DB, double blind; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders 4th edition; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders 4th edition, Text-Revision; DSM-V, Diagnostic and Statistical Manual of Mental Disorders 5th edition; ICD-10, International statistical classification of diseases and related health problems 10th revision; iTBS, intermittent theta burst stimulation; L-DLPFC, left dorsolateral prefrontal cortex; L-LPC, left lateral parietal cortex; MT, motor threshold; NR, not reported; OLA, olanzapine; R-DLPFC, right dorsolateral prefrontal cortex; s, seconds; SCZ, schizophrenia; TRS, treatment-resistant schizophrenia; w, weeks.

Figure 2. Cochrane risk of bias. +: low risk of bias; –: high risk of bias; ?: unclear risk of bias.

Test (SMD = 0.83, 95% CI: 0.16, 1.49, I^2 = 73%, P = .02) and Montreal Cognitive Assessment (MoCA) (SMD = 0.49, 95% CI: 0.11, 0.88, I^2 = 0%, P = .01) (Table 2). However, adjunctive active iTBS did not outperform sham iTBS on other specific cognitive measures, including Forward Digit Span, Stroop Inference Test, Backward Digit Span, Trail Making A, Trail Making B, or Verbal Fluency Test performance.

Discontinuation Rate and Adverse Events

Within the study dataset, 55 patients discontinued, including 27 from the iTBS group and 28 from sham iTBS group. The iTBS group did not significantly differ from the sham iTBS group in terms of discontinuation rates for any reason (RR = 0.92, 95% CI: 0.57, 1.50, I^2 = 0%, P = .75). Adverse reactions, including headaches, dizziness, and numbness, and exacerbations of positive symptoms, did not differ significantly between interventions (all Ps > .05).

Publication Bias

There was no evidence for publication bias based on the highly symmetrical funnel plots for included studies. Similarly, Egger's test found no significant publication bias concerning total psychopathology (P = .80; Supplementary Figure 1).

Discussion

In accordance with our comprehensive literature review, this paper represents the largest meta-analysis to date of the therapeutic efficacy of iTBS as an adjunctive treatment for schizophrenia. Based on 15 RCTs (n = 671), adjunctive iTBS was found to be superior to control group interventions in terms of alleviating overall psychopathology, negative symptoms, and general psychopathology as measured by the PANSS, although there was no significant group difference for positive symptom reductions. In addition, adjunctive iTBS displayed comparatively enhanced effects on select specific cognitive functions, particularly the Spatial Span Test and MoCA. Finally, no

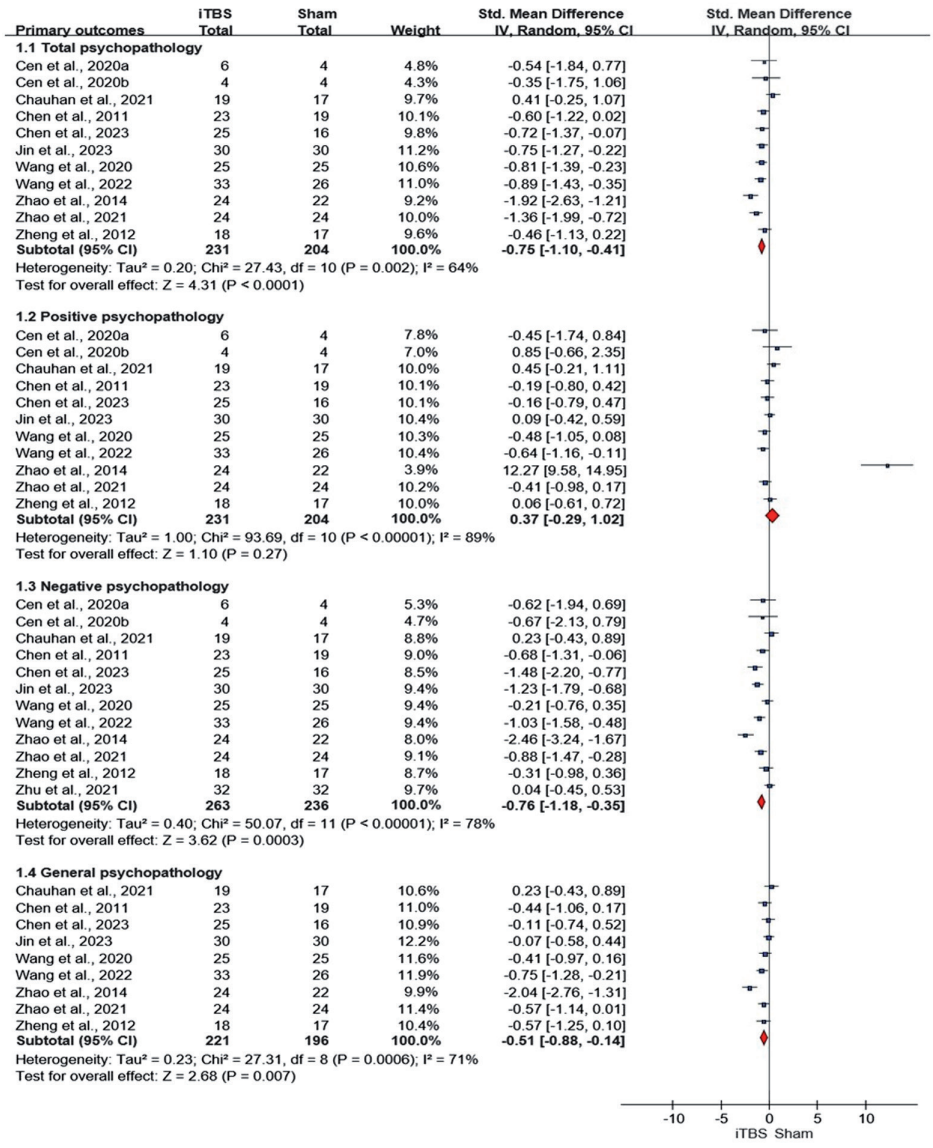

Figure 3. Adjunctive iTBS for patients with schizophrenia: forest plot for improvement in symptoms assessed by the PANSS. CI, confidence interval; PANSS, Positive and Negative Syndrome Scale.

significant intervention differences were detected concerning treatment discontinuation rates for any reason or adverse events. Taken together, these findings indicate that adjunctive iTBS represents a viable and efficacious therapeutic option for patients suffering from schizophrenia.

We found that patients with schizophrenia who underwent adjunctive iTBS treatment exhibited notable improvements in overall psychopathological symptoms, including total psychopathology, negative symptoms, and general psychopathology, compared with sham stimulation group cohorts. These findings are consistent with and bolster the contentions of prior meta-analyses[17,18] highlighting the potential utility of iTBS as an adjunctive treatment for schizophrenia. One therapeutic mechanism underlying iTBS effects in treating schizophrenia may involve modulation of L-DLPFC activity, potentially alleviating psychotic symptoms.[22] However, our findings differ from those of another meta-analysis[19] that included only English language articles and found no significant iTBS versus sham intervention differences in negative symptoms. This discrepancy may be attributed to selection criteria differences that resulted in the inclusion of different samples for analysis. In light of this discrepancy, more RCTs with larger sample sizes are required to conclusively elucidate the efficacy of adjunctive iTBS treatment for negative symptoms.

Patients receiving iTBS also demonstrated superior performance on the general psychopathology subscale of the PANSS which reflects various cognitive deficits as well as performance on specific cognitive tasks including the Spatial Span Test and MoCA, albeit no significant differences were observed for other specific cognitive domains (e.g., auditory attention and working memory, planning, impulse control). This pattern suggests that iTBS may have selectively beneficial effects on cognitive functions among people with schizophrenia.

Table 2. Adjunctive iTBS for Patients with Schizophrenia: Secondary Outcomes

Variables	Number of Studies (Sample Size)	RRs/ SMDs	95% CI [Lower, Upper]	I^2 (%)	*P*
Cognitive function:					
Verbal Fluency Test	2 (85)	0.02	[−0.41, 0.44]	0	.93
Forward Digit Span	2 (107)	0.22	[−0.82, 1.27]	86	.68
Backward Digit Span	2 (107)	0.19	[−0.19, 0.57]	0	.34
Trail Making A	2 (110)	−0.21	[−0.62, 0.20]	16	.32
Trail Making B	2 (110)	−0.28	[−0.66, 0.10]	0	.14
Stroop Interference Test	2 (110)	−0.10	[−0.48, 0.27]	0	.59
Digital Span Test	2 (92)	0.26	[−0.20, 0.72]	18	.26
Spatial Span Test	3 (148)	0.83	[0.16, 1.49]	73	**.02**
MoCA	2 (109)	0.49	[0.11, 0.88]	0	**.01**
Discontinuation rate:					
Discontinuation due to any reasons	10 (493)	0.92	[0.57, 1.50]	0	.75
Adverse events:					
Headache	5 (254)	1.52	[0.80, 2.88]	0	.20
Dizziness	2 (124)	1.89	[0.64, 5.55]	18	.25
Exacerbation of positive symptoms	2 (68)	0.18	[0.02, 1.43]	0	.10

Bolded values are $P < .05$.
CI, confidence interval; iTBS, intermittent theta burst stimulation; MoCA, Montreal Cognitive Assessment; RRs, risk ratios; SMDs, standardized mean differences.

Previous meta-analyses have demonstrated the efficacy of certain NIBS techniques, such as transcranial alternating current stimulation (tACS)[50] and tDCS,[8] in improving cognitive functions for patients with schizophrenia. The present meta-analysis extends these findings by demonstrating that iTBS has similar potential for improving particular cognitive functions. However, previous meta-analyses and systematic reviews on the cognitive effects of iTBS on patients with schizophrenia have yielded mixed findings.[16,17] A systematic review concluded that iTBS results in the enhancement of cognitive functions in elderly patients with schizophrenia.[16] In contrast, a previous meta-analysis found no iTBS versus control group differences on multiple cognitive parameters.[17] Notably, sample sizes across meta-analyses for cognitive functions have been small and typically based on only 2 to 3 RCTs (n = 85-148). Thus, there is a pressing need for further research with larger samples to determine more conclusively whether iTBS has reliable effects on cognitive functions in patients diagnosed with schizophrenia.

In terms of safety, patients receiving iTBS treatment showed a slightly higher frequency of adverse reactions, including headache and dizziness, compared with control group patients. However, this difference did not reach statistical significance. A systematic review, dedicated to examining the general safety profile of TBS in the broader population, revealed that a small proportion of participants encountered mild adverse events.[51] Another review of research on various psychiatric disorders, including schizophrenia, depression, nicotine and cocaine addiction, and obsessive-compulsive disorder, concluded that TBS has consistent minor side effects with no occurrences of seizures or manic episodes.[52] Taken together, these findings are reassuring and underscore a favorable safety profile for iTBS as a therapeutic adjunctive intervention.

Limitations

Our meta-analysis has several limitations. First, although the overall sample size (n = 671) exceeded that of past published meta-analyses on schizophrenia,[16-19] sample sizes for particular outcomes, particularly cognitive dysfunctions, were relatively small. Therefore, future RCTs with larger samples specifically focusing on the effects of adjunctive iTBS on cognitive symptoms of schizophrenia are needed. Second, significant heterogeneity was found for meta-analyses on different outcomes (I^2 = 64% to 89%). However, all meta-analytic results for psychotic psychopathology (I^2 = 12% to 66%) were replicated after removing one outlying study.[24] Therefore, heterogeneity can be partially attributed to study differences in sample characteristics and methodology. As RCTs accumulate, future meta-analyses should examine potential moderators of variable findings between studies as one means of clarifying subgroups for whom iTBS is more and less beneficial. Third, the RCTs included in this meta-analysis focused only on relatively short-term effects and safety of iTBS as an adjunct treatment for schizophrenia (from 5 days to 12 weeks). Therefore, it is important to investigate the long-term effects and safety of adjunctive iTBS in schizophrenia in the future via the inclusion of multi-year follow-ups. Finally, due to insufficient information provided in the included studies, the confounding effects of other interventions, specifically psychotropic drugs, could not be examined. To address this shortcoming, researchers should endeavor to fully report sample medication details, as a matter of course, in future RCTs of iTBS.

Conclusion

This meta-analysis demonstrated that iTBS significantly improves total psychopathology, negative symptoms, and general psychopathology related to cognitive dysfunctions as well as certain specific cognitive functions among patients with schizophrenia. However, the beneficial effects did not extend to positive symptoms. To substantiate these preliminary findings, future research involving larger participant cohorts and more complete reporting of study details is warranted.

Data Availability Statement: *The data that support the findings of this study are available from the corresponding author upon reasonable request.*

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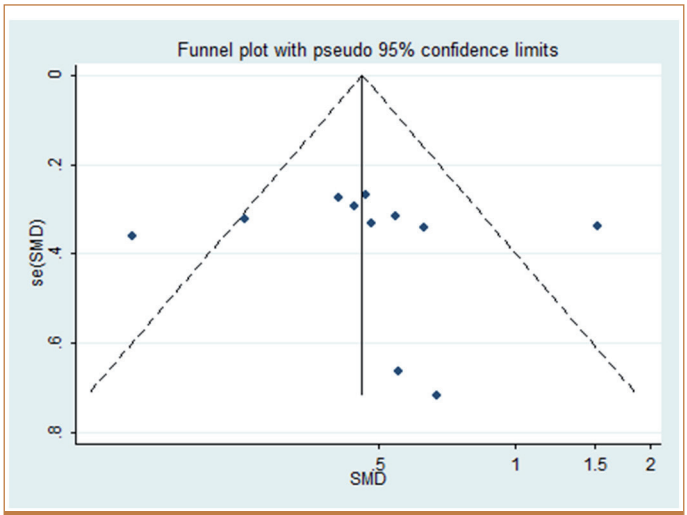
Supplementary Table 1. GRADE analyses: iTBS for schizophrenia

Primary and *secondary outcomes*	N (subjects)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Overall quality of evidence[a]
Total psychopathology	10 (435)	No	Serious[b]	No	No	Undetected	No	+/+/+/-; Moderate
Positive psychopathology	10 (435)	No	Serious[b]	No	No	Undetected	No	+/+/+/-; Moderate
Negative psychopathology	11 (499)	No	Serious[b]	No	No	Undetected	No	+/+/+/-; Moderate
General psychopathology	9 (417)	No	Serious[b]	No	No	Undetected	No	+/+/+/-; Moderate
The improvement of depressive symptoms at post- iTBS measured by HAMD	2 (109)	No	No	No	Serious[c]	Undetected	No	+/+/+/-; Moderate
The improvement of anxiety symptoms at post- iTBS measured by HAMA	2 (109)	No	No	No	Serious[c]	Undetected	No	+/+/+/-; Moderate
Verbal Fluency Test	2 (85)	No	No	No	Serious[c]	Undetected	No	+/+/+/-; Moderate
Forward Digit Span	2 (107)	No	Serious[b]	No	Serious[c]	Undetected	No	+/+/-/-; Low
Backward Digit Span	2 (107)	No	No	No	Serious[c]	Undetected	No	+/+/+/-; Moderate
Trail Making A	2 (110)	No	No	No	Serious[c]	Undetected	No	+/+/+/-; Moderate
Trail Making B	2 (110)	No	No	No	Serious[c]	Undetected	No	+/+/+/-; Moderate
Stroop Interference Test	2 (110)	No	No	No	Serious[c]	Undetected	No	+/+/+/-; Moderate
Digital Span Test;	2 (92)	No	No	No	Serious[c]	Undetected	No	+/+/+/-; Moderate
Spatial Span Test	3 (148)	No	Serious[b]	No	Serious[c]	Undetected	No	+/+/-/-; Low
MoCA	2 (109)	No	No	No	Serious[c]	Undetected	No	+/+/+/-; Moderate
Discontinuation due to any reason	10 (493)	No	No	No	No	Undetected	No	+/+/+/+; High
Headache	5 (254)	No	No	No	Serious[c]	Undetected	No	+/+/+/-; Moderate
Dizziness	2 (124)	No	No	No	Serious[c]	Undetected	No	+/+/+/-; Moderate
Exacerbation of positive symptoms	2 (68)	No	No	No	Serious[c]	Undetected	No	+/+/+/-; Moderate

[a]GRADE Working Group grades of evidence: High quality=further research is very unlikely to change our confidence in the estimate of effect. Moderate quality=further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality=further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality=we are very uncertain about the estimate.
[b]Meta-analytic results presented a serious inconsistency when I^2 values were greater than 50% or $P < .1$ in the Q statistics.
[c]For continuous outcomes, N<400. For dichotomous outcomes, N < 300.
HAMA = Hamilton Anxiety Scale; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; HAMD = Hamilton Depression Scale; iTBS = intermittent theta burst stimulation; MoCA = Montreal Cognitive Assessment.



Supplementary Figure 1. Funnel plot evaluating publication bias across studies on total psychopathology in schizophrenia.