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Systematic Review

Efficacy of Noninvasive Brain Stimulation in Treating General Psychopathology Symptoms in Schizophrenia: A Meta-Analysis

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Abstract

Objectives: Noninvasive brain stimulation (NIBS) has been shown to effectively alleviate negative and positive symptoms in patients with schizophrenia. However, its impact on depressive symptoms and general psychopathology symptoms (GPSs), which are crucial for functional outcomes, remains uncertain. We aimed to compare the efficacy of various NIBS interventions in treating depressive symptoms and GPSs. **Methods**: We conducted a comprehensive search of multiple databases and performed a meta-analysis to evaluate the efficacy of NIBS in treating depressive symptoms and GPSs in schizophrenia. The effect sizes of NIBS for depression symptoms and GPSs were estimated using standard mean differences (SMDs) with 95% confidence intervals (CIs). Subgroup analyses were employed to examine potential influencing factors on the pooled SMD of NIBS for GPSs. **Results**: Our search yielded 35 randomized controlled trials involving 1715 individuals diagnosed with schizophrenia. The protocol of this systematic review was registered with INPLASY (protocol ID: INPLASY202320082). Neither repetitive transcranial magnetic stimulation (rTMS) nor transcranial direct current stimulation (tDCS) demonstrated significant improvements in depressive symptoms compared to sham controls. NIBS exhibited a small-to-moderate effect size for GPSs, with a pooled SMD of –0.2956 (95% CI: –0.459 to –0.132) and a heterogeneity (I^2) of 58.9% (95% CI: 41.5% to 71.1%; $p < 0.01$) based on a random-effects model. Subgroup analyses of different types of NIBS, different frequencies of rTMS, and different stimulation sites of rTMS revealed no significant differences. Only sex had a significant influence on the effect size of NIBS for general psychopathology symptoms ($p < 0.05$). However, rTMS might be superior to tDCS, and high-frequency rTMS outperformed low-frequency rTMS in treating GPSs. **Conclusions**: We found a small-to-moderate effect size of NIBS in alleviating GPSs in patients with schizophrenia. Both rTMS and tDCS were more effective than sham stimulation in reducing GPSs in schizophrenia. The frequency used was associated with rTMS efficacy for GPSs.

Keywords: noninvasive brain stimulation; SMD; depressive symptoms; general psychopathology symptoms; schizophrenia; meta-analysis

1. Introduction

Schizophrenia is a chronic, recurrent, and highly disabling mental illness [1]. Currently, the first-line treatment for schizophrenia is antipsychotic medication [2]. While these medications effectively address positive symptoms, their efficacy in treating negative and other symptoms of schizophrenia remains limited [3]. Additionally, the adverse effects of antipsychotics may lead to reduced treatment compliance among some patients with schizophrenia [4]. As a result, nonpharmacological interventions, such as noninvasive brain stimulation (NIBS), have emerged as innovative and crucial approaches in the treatment of schizophrenia [5]. NIBS technologies, particularly repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), have been extensively researched [6,7].

rTMS induces an electric field in a discrete area of the brain by applying a repetitively pulsed magnetic field over the scalp. This electric field modulates neuronal activity in the area where rTMS is applied. tDCS involves the application of a weak electrical current through two or more electrodes placed on the scalp to stimulate underlying brain tissue. The biological mechanisms underlying the effects of rTMS and tDCS on neuropsychiatric disorders are very complicated and remain unclear. However, the concept of neuroplasticity has been emphasized most often [8]. There is evidence that rTMS produces long-lasting neuroplastic changes and beneficial clinical effects across a variety of neuropsychiatric disorders [9], while tDCS can stimulate neuroplasticity by modulating changes in neuronal membrane potential and increasing cortex excitability [10]. Neuroplasticity refers to the capacity of the brain to change and reorganize itself in response to internal and/or external in-

fluences [11]. In summary, the rationale behind rTMS or tDCS therapy is to modulate cortical excitability, increase neural plasticity, and ultimately improve functional outcomes.

Several meta-analyses have evaluated the benefits of NIBS on the negative symptoms of schizophrenia [12,13]. Numerous studies have also investigated the effects of NIBS on positive symptoms [14–16]. However, current research data indicate that limited attention has been given to the treatment of general psychopathology symptoms (GPSs) in schizophrenia. General psychopathology symptoms, as measured separately from the Positive and Negative Syndrome Scale (PANSS), provide a separate but parallel measure of the severity of schizophrenic illness [17]. These symptoms encompass a wide range of conditions, including somatic concerns, anxiety, feelings of guilt, depression, motor retardation, poor attention, disturbance of volition, poor impulse control, and active social avoidance; all of which contribute to functional outcomes.

Existing evidence suggests that depression in schizophrenia is linked to a reduced quality of life and an increased risk of suicide [18,19]. Anxiety in schizophrenia has also been correlated with adverse outcomes, including heightened suicide risk, sleep disturbances, reduced quality of life, increased depression, and neuropsychological impairments [20,21]. Recent reviews have demonstrated that psychiatric symptoms (psychotic symptoms and GPSs) negatively impact the quality of life in patients with schizophrenia [22]. A previous study found no correlation between suicide attempts and PANSS positive and negative scores, while PANSS general psychopathology scores were associated with suicide attempts [23]. The presence of GPSs is likely to affect patients' functional outcomes and quality of life [24,25]. Therefore, GPSs intervention is also critical for the clinical treatment of schizophrenia. However, current NIBS technology primarily targets the main positive and negative symptoms [26,27], with few intervention studies focusing on GPSs. Treatment of GPSs in schizophrenia is an essential yet often overlooked aspect of schizophrenia management.

Some studies of NIBS interventions for negative symptoms also report changes in GPSs. For example, Zheng *et al.* [28] found that 10 Hz rTMS could improve both negative symptoms and general psychopathology symptoms. Gomes's research emphasized the therapeutic effects of tDCS for treating negative symptoms in schizophrenia, noting a significant reduction in general PANSS scores from baseline to post-tDCS compared to the sham control group [29]. Another study on rTMS for treatment of auditory hallucinations did not observe significant improvements in general psychopathological symptoms [30]. However, these are individual studies, and no meta-analysis has specifically focused on the effects of NIBS on GPSs.

Furthermore, we discovered that different targets and intervention techniques can yield varying results. Ray *et al.* (2015) [31] utilized 1 Hz rTMS to stimulate the left temporal-parietal cortex (TPC) and observed no significant improvement in total PANSS scores or general psychopathological scores. Similarly, Bais *et al.* (2014) [30] applied 1 Hz rTMS to the left or bilateral temporoparietal junction area and found no notable improvement in general psychopathological symptoms. In contrast, Li *et al.* (2020) [32] employed 10 Hz rTMS to stimulate the left dorsolateral prefrontal cortex (DLPFC) and reported significant improvements in both total PANSS scores and general psychopathological scores compared to the control group. Moreover, Lisoni *et al.* (2022) [33] observed significant improvements in the PANSS general psychopathology subscales following active tDCS in comparison to sham tDCS. These findings suggest that the effectiveness of NIBS interventions on GPSs may be influenced by several factors. Identifying factors that impact NIBS technology in GPSs intervention could prove valuable in designing specialized intervention techniques for GPSs in the future.

This meta-analysis aimed to examine the effectiveness of NIBS in treating General Psychopathology Scale symptoms in schizophrenia and to identify potential moderators influencing the effectiveness of NIBS treatment on GPSs in schizophrenia. We hypothesize that NIBS exerts a mild-to-moderate effect size on GPSs in schizophrenia, and factors such as varying intervention techniques, targets, and other variables may influence the intervention's efficacy.

2. Materials and Methods

2.1 Information Sources and Search Strategy

We conducted a search of five databases, including PubMed, Web of Science, PsycINFO, Google Scholar, and the China National Knowledge Infrastructure (CNKI). Only studies published between January 1, 1999, and December 1, 2022, were included in our search. The following search terms were used: "transcranial magnetic stimulation", "TMS", "transcranial direct current stimulation", "tDCS", "brain stimulation", "schizophrenia", "psychotic disorder", "psychosis", "general symptom", "general psychopathology", "positive and negative syndrome scale", "PANSS", "randomized controlled trial", and "RCT". Additionally, we reviewed the references of the retrieved articles to identify any other relevant studies and searched for corresponding terms in Chinese in CNKI.

2.2 Inclusion and Exclusion Criteria

In this study, the following inclusion and exclusion criteria were employed:

Inclusion Criteria:

(1) Utilization of a randomized sham-controlled study design.

(2) Diagnosis of schizophrenia in patients according to standardized criteria, such as the Diagnostic and Statisti-

cal Manual of Mental Disorders (DSM), International Statistical Classification of Diseases and Related Health Problems (ICD), or Chinese Classification of Mental Disorders (CCMD).

(3) Implementation of rTMS or tDCS interventions.

(4) Employment of the PANSS to evaluate general psychopathology symptoms as outcome measures.

(5) Maintenance of consistent psychotropic medication dosages before and throughout the intervention.

(6) Articles written in English or Chinese.

Exclusion Criteria:

(1) Participants exhibited significant positive or negative symptoms.

(2) Patients demonstrated additional psychotic symptoms.

(3) General psychopathology symptom scores were not reported.

(4) Articles consisted of duplicate records or contained overlapping samples.

(5) Articles were case reports, editorials, commentaries, or review papers.

(6) The study lacked a control group, or essential information for the control group was missing (e.g., symptom presence or age data).

(7) Participants were under the age of 18.

2.3 Quality Assessment of the Included Studies

The quality of each study was evaluated using the modified Jadad scale [34]. The assessment criteria included randomization, blinding strategy, withdrawals/dropouts, inclusion/exclusion criteria, adverse effects, and statistical analysis. Two authors independently assessed each trial, and any discrepancies were resolved through discussion to reach a consensus. All the studies incorporated in this analysis had Jadad scores of 5 or higher.

2.4 Data Extraction

We extracted the following information from the included studies: first author's name, year of publication, demographic, and clinical characteristics (sample size, male and female distribution, mean age), study location, diagnostic criteria, outcome measurements, participant groups, and the number of rTMS or tDCS sessions. These data were extracted independently by two authors, and any discrepancies were discussed with a third author to reach a consensus.

The Global Psychopathology Scale scores were measured independently from the positive and negative symptoms assessed by the PANSS. These scores offer a distinct yet complementary evaluation of the severity of schizophrenia, which is useful for interpreting syndrome scores [17]. The GPSs covers a range of symptoms, including somatic concerns, anxiety, feelings of guilt, depression, motor retardation, poor attention, disturbance of volition, poor impulse control, and active social avoidance, all of which are critical to functional outcomes.

2.5 Effect Measures

The standardized mean difference (SMD) for each study was calculated, along with the pooled SMD. A SMD between 0.2 and 0.5 indicated mild-to-moderate efficacy of NIBS, while SMD values between 0.5 and 0.8 suggested moderate-to-large efficacy [35]. The I^2 statistic was computed to assess the heterogeneity in effect size for the meta-analysis.

The choice of a computational model for meta-analysis depends on whether studies are expected to share a common effect size, as well as the objectives of the analysis [36]. A fixed-effect meta-analysis estimates a single effect, assumed to be common across all studies, while a random-effects meta-analysis estimates the mean of a distribution of effects. In this review, various types of NIBS studies collected from the published literature were incorporated into the meta-analysis, potentially leading to differences in effect size among the studies. Consequently, the random-effects model was a more suitable choice for this meta-analysis.

2.6 Statistical Analysis

Pre- and post-PANSS-G (General Psychopathology Scale of PANSS) differences (mean and standard deviation values) were extracted from the studies. All analyses were conducted in R (version 3.5.3, The website: https://www.r-project.org) using the "meta" and "metafor" packages, with a p value < 0.05 considered statistically significant. A random-effects model was employed to assess the efficacy of NIBS for GPSs. The I^2 statistic and forest plots were utilized to determine the heterogeneity of the effectiveness of noninvasive brain stimulation in treating GPSs.

First, the Jadad scale was applied to evaluate the quality of the included studies. Studies with Jadad scale scores below 4 were excluded. Second, publication bias for the included studies was assessed using Egger's test and illustrated with a funnel plot. Third, a sensitivity analysis identified studies contributing to high heterogeneity. Studies were excluded when the change in heterogeneity associated with a particular study exceeded 5%. Fourth, the pooled effect size was calculated based on the SMD. Fifth, subgroup analysis explored the heterogeneity in the effect sizes of NIBS for depressive symptoms and GPSs. These two methods (including the subgroup analysis and sensitivity analysis) also helped identify potential influencing factors of the efficacy of NIBS for treating GPSs.

3. Results

3.1 Study Selection

The flow diagram in Fig. 1 illustrates the search and selection process results. This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [37] and the protocol of this systematic review was regis-

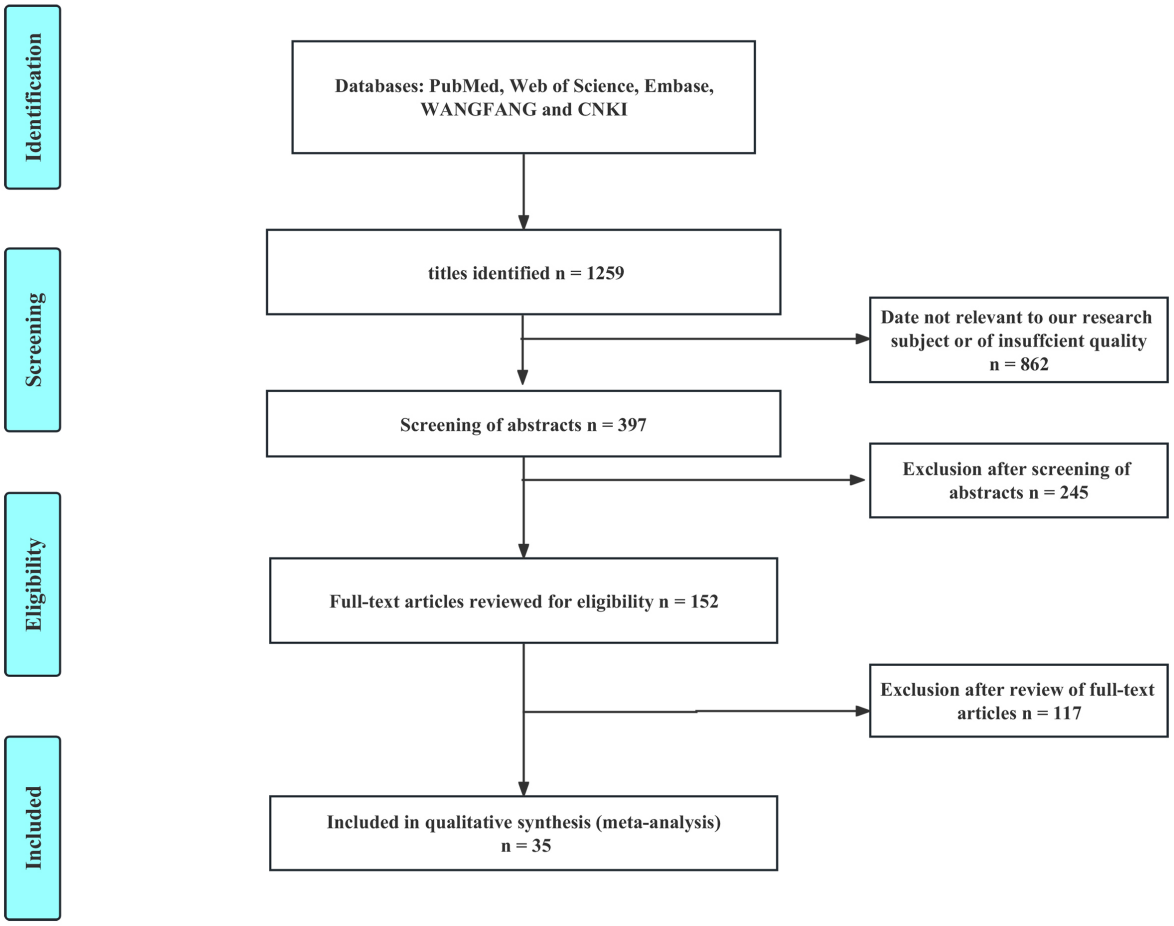

Fig. 1. Flowchart of the identification of included studies.

tered with INPLASY (protocol ID: INPLASY202320082). Ultimately, 35 studies were identified and incorporated into the meta-analysis. For a detailed view of the study identification process, please refer to Fig. 1. PRISMA checklist is shown in **Supplementary Material-PRISMA checklist**.

3.2 Characteristics of the Included Studies

We have compiled all the extracted data in Table 1 (Ref. [28–33,38–66]). Out of the 35 studies, 12 were conducted in East Asia, 10 in Europe, 5 in South Asia, 4 in North America, 3 in South America, and 1 in Western Asia. The intervention methods featured in these studies consisted of 25 rTMS studies and 10 tDCS studies. For more information, please refer to Table 1.

3.3 Quality Assessment of Included Studies

The quality assessment scores for the included studies based on the Jadad scale all exceeded 5. Details regarding the individual Jadad scale items for each study can be found in **Supplementary Table 1**.

3.4 Publication Bias of the Included Studies

The included studies were assessed for publication bias. A funnel plot was employed to visually represent potential publication bias. Additionally, Egger's test was conducted to determine the presence of any publication bias. The resulting p value of 0.20 suggests that no publication bias was detected (refer to **Supplementary Fig. 1**).

3.5 Effect Size of NIBS for Depressive Symptoms

We determined the effect size of NIBS for depressive symptoms using the SMD. The pooled SMD and confidence interval (CI) for NIBS in relation to depressive symptoms was –0.0249 (95% CI: –0.2447 to –0.1950). We observed a heterogeneity (I^2) of 56.2% (95% CI: 28.7% to 73.1%; $p > 0.05$) based on a random-effects model. These findings suggest that NIBS did not lead to significant improvements in depressive symptoms compared to sham stimulation. For further information, please refer to Fig. 2.

3.6 Effect Size of NIBS for General Psychopathology Symptoms

We also evaluated the effect size of NIBS on GPSs by calculating the SMD. The pooled SMD and CI for NIBS in addressing GPSs was –0.296 (95% CI: –0.459 to –0.132), with a heterogeneity (I^2) of 58.9% (95% CI: 41.5% to 71.1%; $p < 0.01$) based on a random-effects model. These

Table 1. The included studies.

No.	First author	Year	Age (Years)	Area	Male/Female	Diagnosis criteria	Sample size	Comparison group	Outcome measurements	Sessions	Stimulation site
1	Lisoni [33]	2022	tDCS: 40.96 ± 13.37 Sham: 44.44 ± 10.97	Italy	39/11	DSM-V	50	Sham	PANSS, CGI, SUMD, BACS	15 sessions	anode: left DLPFC; cathode: right orbitofrontal region
2	Du [40]	2022	rTMS: 45.9 ± 10.0 Sham: 45.1 ± 10.4	Mainland China	20/21	ICD-10	41	Sham	SANS, PANSS, PRM	20 sessions	left DLPFC
3	Gupta [41]	2021	rTMS: 29.70 ± 9.05 Sham: 31.26 ± 7.78	India	39/0	N/A	39	Sham	PANSS, PGI-MS	10 sessions	left temporo-parietal cortex
4	Wen [42]	2021	rTMS: 41.4 ± 7.5 Sham: 38.8 ± 9.1	Mainland China	25/20	DSM-IV	45	Sham	PANSS, RBANS, SCWT, UKU	20 sessions	left DLPFC
5	Dharani [43]	2021	tDCS: 39.14 ± 3.76 Sham: 33.85 ± 6.81	India	12/2	ICD-10	14	Sham	SANS, PANSS, CGI-S	10 sessions	anode: left DLPFC
6	Valiengo [44]	2020	tDCS: 34.6 ± 8.4 Sham: 35.9 ± 10.1	Brazil	80/20	DSM-IV	100	Sham	PANSS, CDSS, AHRS, GAF, SANS	10 sessions	anode: left prefrontal cortex; cathode: left temporoparietal junction
7	Guan [45]	2020	rTMS: 51.9 ± 10.1 Sham: 56.0 ± 7.3	Mainland China	41/0	DSM-IV	41	Sham	PANSS, RBANS	40 sessions	left DLPFC
8	Kumar [46]	2020	rTMS: 32.4 ± 9.20 Sham: 30.8 ± 9.34	India	57/43	ICD-10	100	Sham	PANSS, SANS, CGI-S, CDSS	20 sessions	left DLPFC
9	Li [32]	2020	rTMS: 23.9 ± 5.7 Risperidone: 24.0 ± 5.3	Mainland China	47/50	DSM-IV	97	Sham	MCCB, PANSS	10 sessions	left DLPFC
10	Xiu [47]	2020	10 Hz rTMS: 50.7 ± 9.0 20 Hz rTMS: 52.0 ± 10.1 Sham: 54.7 ± 6.4	Mainland China	97/0	DSM-IV	97	Sham	RBANS, PANSS	40 sessions	left DLPFC
11	Zhuo [48]	2019	rTMS: 28.97 ± 7.40 Sham: 30.63 ± 8.25	Mainland China	41/19	DSM-IV	60	Sham	SANS, PANSS, MCCB, CGI	20 sessions	left DLPFC
12	Gomes [29]	2018	tDCS: 39.17 ± 9.34 Sham: 33.75 ± 12.08	Brazil	17/7	DSM-IV	24	Sham	PANSS, CDSS, GAF, MATRICS	10 sessions	anode: left prefrontal cortex; cathode: contralateral area
13	Jeon [49]	2018	tDCS: 40.00 ± 9.41 Sham: 39.86 ± 12.42	Korea	25/27	DSM-V	52	Sham	PANSS, CGI, CDSS, MCCB, WCST	10 sessions	anode: left DLPFC; cathode: right DLPFC

Table 1. Continued.

No.	First author	Year	Age (Years)	Area	Male/Female	Diagnosis criteria	Sample size	Comparison group	Outcome measurements	Sessions	Stimulation site
14	Mellin [50]	2018	tDCS: 29.57 ± 10.97 Sham: 38.86 ± 10.01 tACS: 47 ± 9.72	United States	N/A	DSM-IV	14	Sham	AHRS, PANSS, BACS	10 sessions	anode: left DLPFC
15	Lindenmayer [39]	2019	tDCS: N/A Sham: N/A	New York	24/4	DSM-V	28	Sham	PANSS, MCCB, AHRS, CGI-S	40 sessions	anode: frontal cortex on the left side; cathode: left auditory cortex
16	Hasan [51]	2017	rTMS: 33.88 ± 8.88 Sham: 36.00 ± 9.86	Germany	60/13	N/A	73	Sham	PANSS, CGI, GAF, MADRS, MRI	15 sessions	left DLPFC
17	Garg [52]	2016	rTMS: 32.40 ± 8.44 Sham: 30.75 ± 7.90	India	33/7	ICD-10	40	Sham	PANSS, CDSS	10 sessions	the vermal part of cerebellum
18	Fröhlich [53]	2016	tDCS: 43.38 ± 12.64 Sham: 40.00 ± 10.74	USA	22/4	DSM-IV	26	Sham	AHRS, PANSS	5 sessions	anode: left DLPFC; cathode: left temporo-parietal junction
19	Huang [54]	2016	rTMS: 40.58 ± 3.01 Sham: 39.39 ± 3.03	Mainland China	37/0	DSM-IV	37	Sham	PANSS, WCST, MADRS	21 sessions	left DLPFC
20	Dlabac-de Lange [38]	2015	rTMS: 41.8 ± 11.6 Sham: 32.3 ± 9.7	The Netherlands	26/6	DSM-IV	32	Sham	SANS, PANSS, MADRS, WHOQOL-BREF, BIS	30 sessions	the bilatera-l DLPFC
21	Mondino [55]	2016	tDCS: 36.7 ± 9.7 Sham: 37.3 ± 9.7	France	15/8	DSM-IV	23	Sham	PANSS, AHRS, fMRI	10 sessions	anode: left DLPFC; cathode: left temporo-parietal junction
22	Gan [56]	2015	rTMS: 28 ± 9 Sham: 29 ± 9	Mainland China	44/23	DSM-IV	67	Sham	PANSS, TESS, VAS	20 sessions	left DLPFC
23	Quan [57]	2015	rTMS: 46.87 ± 7.87 Sham: 46.87 ± 9.07	Mainland China	72/45	DSM-IV	117	Sham	PANSS, SANS, CGI, UKU	N/A	left DLPFC
24	Ray [31]	2015	rTMS: 31.35 ± 7.13 Sham: 29.30 ± 8.71	India	N/A	ICD-10	40	Sham	AHRS, PANSS, CGI	10 sessions	left temporo-parietal region
25	Smith [58]	2015	tDCS: 46.76 ± 11.06 Sham: 44.88 ± 9.19	United States	22/8	DSM-IV	30	Sham	MCCB, PANSS	5 sessions	anode: left DLPFC; cathode: the contralateral supraorbital ridge
26	Bais [30]	2014	Left rTMS: 37.2 ± 14.9 Bilateral TMS: 33.9 ± 9.2 Sham: 37.3 ± 11.6	The Netherlands	27/20	DSM-IV	47	Sham	PANSS, AHRS	12 sessions	left temporo-parietal junction area

Table 1. Continued.

No.	First author	Year	Age (Years)	Area	Male/Female	Diagnosis criteria	Sample size	Comparison group	Outcome measurements	Sessions	Stimulation site
27	Prikryl [59]	2014	rTMS: 30.40 ± 6.56 Sham: 34.58 ± 10.66	Czech Republic	35/0	ICD-10	35	Sham	PANSS, MADRS, CDSS	21 sessions	left DLPFC
28	Zhao [60]	2014	10 Hz rTMS: 48.0 ± 12.2 20 Hz rTMS: 49.1 ± 10.6 Sham: 46.7 ± 13.1	Mainland China	33/36	DSM-IV	69	Sham	PANSS, SANS, TESS	10 sessions	left DLPFC
29	Prikryl [61]	2012	rTMS: 30.47 ± 9.19 Sham: 34.55 ± 10.57	Czech Republic	30/0	ICD-10	30	Sham	PANSS, VFT, fMRI	15 sessions	left DLPFC
30	Zheng [28]	2012	10 Hz rTMS: 56.5 ± 7.4 20 Hz rTMS: 56.8 ± 5.4 Sham: 55.6 ± 5.8	Mainland China	45/0	CCMD-3	45	Sham	PANSS, VSWM, VFT	5 sessions	left DLPFC
31	Prikryl [62]	2007	rTMS: 31.36 ± 8.43 Sham: 36.46 ± 10.74	Czech Republic	22/0	ICD-10	22	Sham	PANSS, SANS, SAPS, MADRS, CDSS	15 sessions	left DLPFC
32	Rosa [63]	2007	rTMS: 29.83 ± 8.40 Sham: 33.00 ± 12.08	Brazil	6/5	DSM-IV	11	Sham	PANSS, CGI, AHRS, VAS	10 sessions	the left temporo-parietal cortex
33	Saba [64]	2006	rTMS: 30.7 ± 7.95 Sham: 30.6 ± 8.0	France	13/3	DSM-IV	16	Sham	PANSS, CGI	10 sessions	the left temporo-parietal cortex
34	Holi [65]	2004	rTMS: 38.5 ± 10.2 Sham: 34.8 ± 9.8	Finland	19/3	DSM-IV	22	Sham	PANSS, MMSE, SCL-90	10 sessions	left DLPFC
35	Klein [66]	1999	rTMS: 30.2 ± 10.0 Sham: 29.5 ± 9.3	Israel	11/20	DSM-IV	31	Sham	CGI, PANSS, BPRS, HDRS	10 sessions	the right prefrontal area

Abbreviations: AHRS, Auditory Hallucinations Rating Scale; CDSS, Calgary Depression Scale for Schizophrenia; GAF, Global Assessment of Functioning; NA, not applicable; PANSS, Positive and Negative Syndrome Scale; SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms; tDCS, transcranial direct current stimulation; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; WHOQOL-BREF, World Health Organization Quality of Life-BREF; BIS, Birchwood Insight Scale; PRM, pattern recognition memory; VAS, visual analog scale; BACS, Brief Assessment of Cognition in Schizophrenia; UKU, Udvalg for Kliniske Under sogelser; VFT, verbal fluency task; VSWM, visual spatial working memory; PGI-MS, Postgraduate Institute Memory Scale; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th. Edition; DSM-V, Diagnostic and Statistical Manual of Mental Disorders, 5th edition; WCST, Wisconsin Card Sorting Test; rTMS, repetitive transcranial magnetic stimulation; CGI, Clinical global impression; CGI-S, Clinical global impression-Severity scale; SUMD, Scale to Assess Unawareness of Mental Disorder; DLPFC, dorsolateral prefrontal cortex; MATRICS, Measurement and Treatment Research to Improve Cognition in Schizophrenia; SCWT, Stroop Color and Word Test; BPRS, Brief Psychiatric Rating Scale; SCL-90, Symptom Checklist-90; MMSE, Mini-mental State Examination; TESS, Treatment Emergent Symptom Scale; MCCB, MATRICS Consensus Cognitive Battery; MRI, Magnetic resonance imaging; fMRI, functional magnetic resonance imaging; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; ICD-10, The International Statistical Classification of Diseases and Related Health Problems 10th Revision; CCMD, Chinese Classification and Diagnostic Criteria of Mental Disorders.

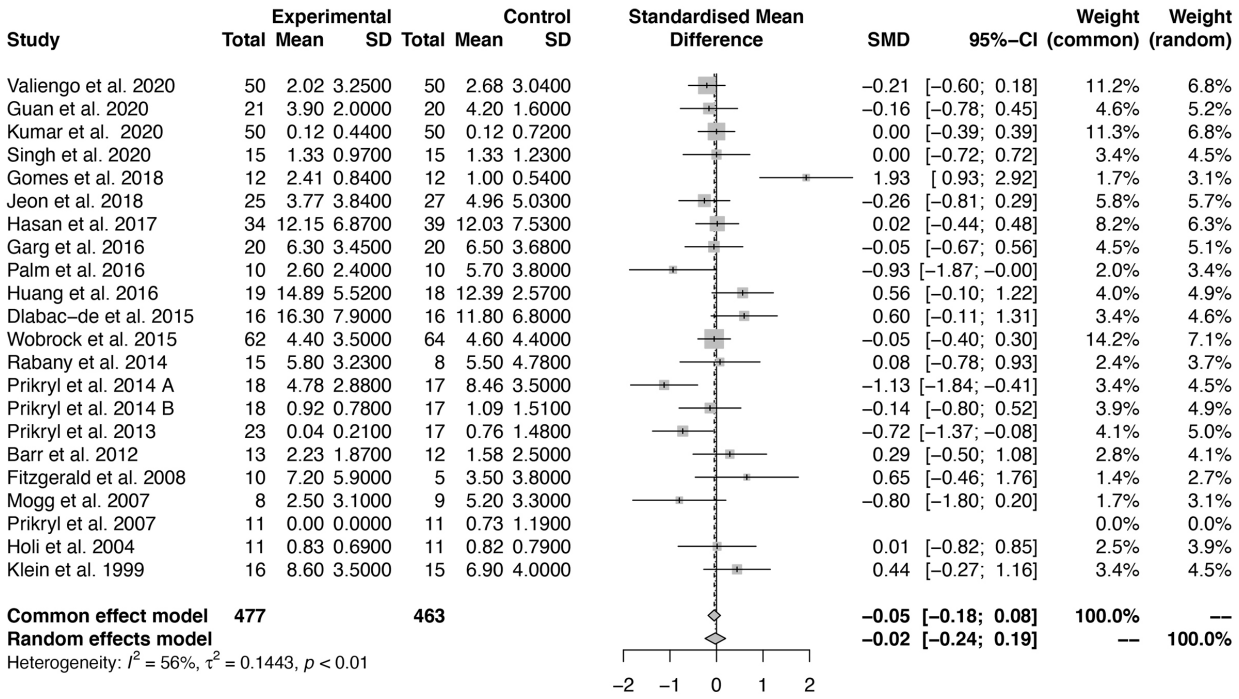

Fig. 2. Forest plot of the effect size of noninvasive brain stimulation (NIBS) for depressive symptoms. SMD, Standard mean difference; SD, Standard deviation; CI, Confidence interval.

findings suggest that NIBS, in comparison to the sham group, led to significant mild-to-moderate improvements in GPSs. For further information, please refer to Fig. 3.

3.7 Subgroup Analysis

3.7.1 Different Types of NIBS for Depressive Symptoms

The subgroup analysis showed no significant difference (p = 0.824) in improvement of depressive symptoms between the rTMS and tDCS groups (rTMS: SMD = –0.032, 95% CI: –0.224 to 0.161; tDCS: SMD = 0.099, 95% CI: –1.040 to 1.239). These findings suggest that neither rTMS nor tDCS contributed to the improvement of depressive symptoms. For further information, please refer to **Supplementary Fig. 2**.

3.7.2 Different Types of NIBS for GPSs

We conducted a subgroup analysis of the pooled SMD of NIBS for GPSs to compare the effects of rTMS and tDCS. The heterogeneity test revealed significant differences between the studies (I^2 = 58.9%, p < 0.01). Although the subgroup analysis showed no significant difference in GPSs improvement between the rTMS and tDCS groups (p = 0.177), a small-to-moderate effect size favoring rTMS for general psychopathology symptoms was observed when compared to the tDCS groups (rTMS: SMD = –0.343, 95% CI: –0.544~–0.142; tDCS: SMD = –0.144, 95% CI: –0.352~0.065). These results suggest that rTMS is effective in ameliorating GPSs, whereas tDCS is not. For further information, please refer to Fig. 4.

3.7.3 Different Frequency of rTMS for GPSs

Moderate heterogeneity was observed among the 25 included rTMS RCTs (I^2 = 64.8%, p < 0.01). Subgroup analysis revealed no significant difference in the improvement of GPSs between high- and low-frequency rTMS stimulation (p = 0.995). However, a small-to-moderate effect size was identified for high-frequency rTMS in improving GPSs in comparison to the low-frequency group (high frequency: SMD = –0.326, 95% CI: –0.562~–0.090; low frequency: SMD = –0.324, 95% CI: –0.783~0.135). These findings indicate that high-frequency rTMS is effective in improving GPSs, while low-frequency rTMS is not. For further information, please refer to Fig. 5.

3.7.4 Different Stimulation Sites of rTMS for GPSs

A subgroup analysis was performed to examine the pooled SMD of various rTMS treatment stimulation sites for GPSs. The heterogeneity test revealed significant disparities between studies (I^2 = 59.1%, p < 0.01). However, the subgroup analysis indicated that differences in stimulation sites did not significantly impact GPSs (p > 0.05). For further information, please refer to **Supplementary Fig. 3**.

3.8 Meta-Regression Analysis

For other associated continuous variables (including mean age, sex, and the number of sessions) that might have potential influences on the effect size of NIBS for GPSs, a meta-regression analysis was used to identify whether these associated continuous variables could significantly predict the effect size of NIBS for GPSs.

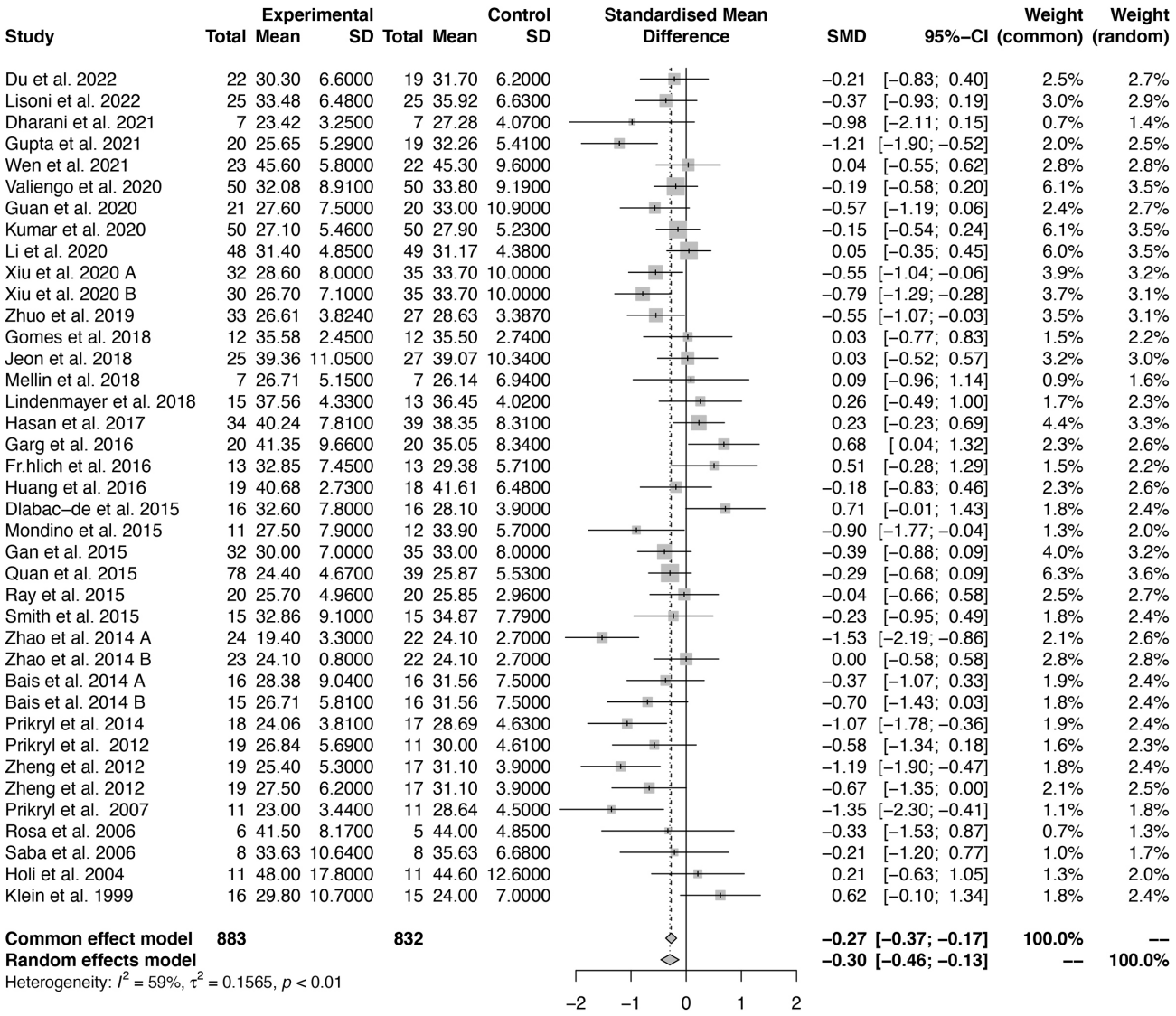

Fig. 3. Forest plot of the effect size of NIBS for general psychopathology symptoms (GPSs).

Only sex had a significant influence on the effect size of NIBS for general psychopathology symptoms ($p < 0.05$). We summarized the details of these meta-regression results in Table 2.

4. Discussion

To our knowledge, this meta-analysis is the most recent and largest study to directly investigate the potential efficacy of NIBS for both depressive and GPSs in schizophrenia. Our study produced several important findings. First, neither rTMS nor tDCS showed a significant improvement in the depressive symptoms associated with schizophrenia compared to the sham controls. However, the main finding of this meta-analysis is that NIBS was effective for GPSs in schizophrenia. The pooled SMD of NIBS for GPSs was small to moderate across 35 studies.

In our study, we found a small-to-moderate effect size of NIBS with rTMS or tDCS on GPSs in the treatment groups when compared to the controls. This finding is consistent with the results of a related meta-analysis conducted by Lee *et al.* (2022) [67], indicating that NIBS has potential therapeutic effects on GPSs in schizophrenia. Human magnetic resonance spectroscopy (MRS) studies showed that tDCS could modulate the concentration of gamma-aminobutyric acid (GABA), which is a neurotransmitter acting at inhibitory synapses in the brain [68]. rTMS and tDCS have been shown to increase GABA levels in the DLPFC [69,70]. Accordingly, we speculate that rTMS and tDCS may induce changes in neuroplasticity by modulating the concentration of GABA in stimulated brain regions, which ultimately leads to changes in pathological symptoms. The site of GPSs is related to the pathophysiology of the target symptom. The efficacy of NIBS on GPSs was an additional result of most clinical trials. This may be the reason why the effect of NIBS on GPSs is not strong, with only a small-to-moderate effect.

Table 2. Results of meta-regression analysis.

Moderators	tau^2	I^2	H^2	R^2	Test of moderators (p)
Mean age	0.134	58.02%	2.38	14.47%	0.059
Sex	0.144	60.14%	2.51	13.63%	0.048*
Number of sessions	0.176	63.43%	2.73	0.00%	0.840

tau^2, the estimated amount of residual heterogeneity; I^2, the residual heterogeneity; H^2, the unaccounted variability; R^2, the amount of heterogeneity accounted for; *, $p < 0.05$.

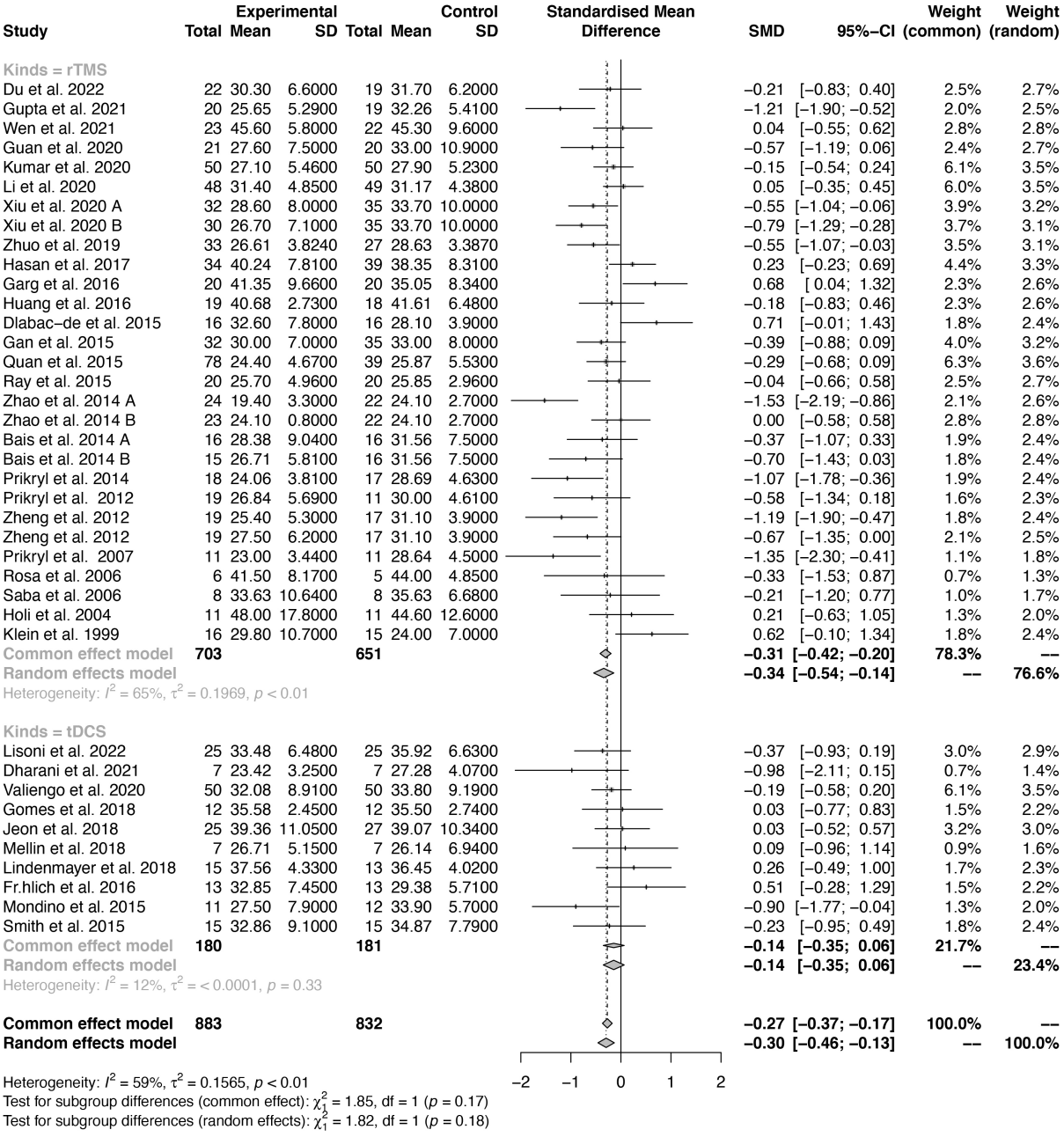

Fig. 4. Forest plot of different types of effect sizes of NIBS for GPSs.

Since rTMS and tDCS are distinct types of stimulation, further subgroup analysis was conducted in this study. The results indicated that while rTMS had a mild-to-moderate impact on improving GPSs, tDCS had no effect. These results suggest that rTMS may be more effective than tDCS in addressing GPSs in individuals with schizophrenia. Although evidence is currently stronger for rTMS than tDCS, this may be due to the limited number of studies conducted on tDCS. The divergent effects of rTMS and tDCS on symptom dimensions underscore the importance of in-

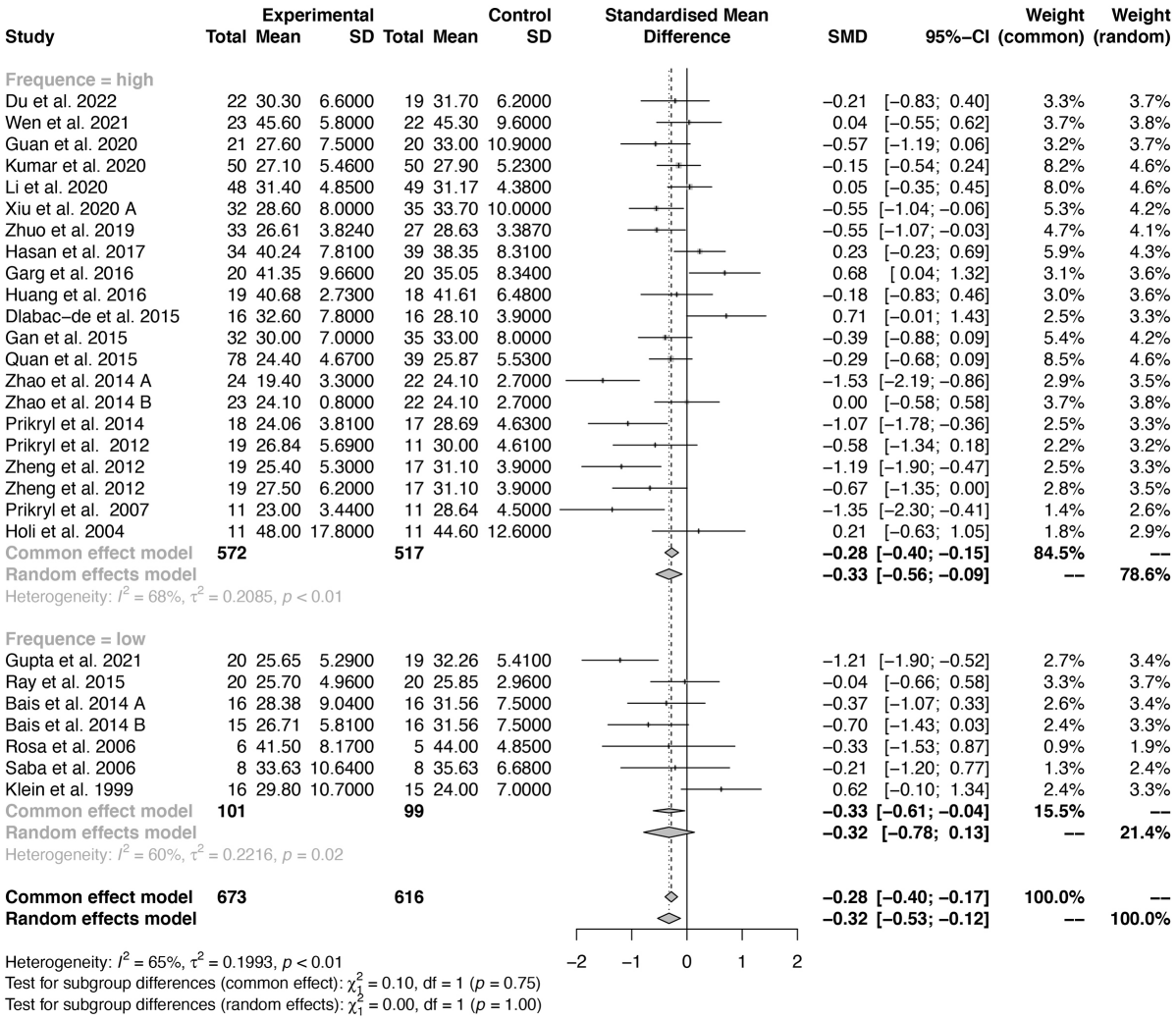

Fig. 5. Forest plot of different frequencies of rTMS for General Psychopathology Scale.

vestigating these treatments separately. Combining their analyses may obscure subtle differences between the two modalities that may have implications for disease characteristics and treatment mechanisms, as well as for guiding the selection of different neuroregulatory interventions for different symptom groups of schizophrenia. Details regarding the specific effects of rTMS and tDCS on symptom dimensions can be found in the study's report.

In a study utilizing functional magnetic resonance imaging (fMRI) to assess activation during a planning task, increased frontal activation was observed in patients with schizophrenia following stimulation of the DLPFC with rTMS [38]. Therefore, it is speculated that the improvement in GPSs may be related to activation of frontal lobe function in patients with schizophrenia. It is possible that rTMS can regulate neuronal activity and produce a potential therapeutic effect on GPSs.

tDCS has shown promise in alleviating both positive and negative symptoms in schizophrenia. However, its effect on functional outcomes is less clear than that of rTMS. No effect of tDCS on GPSs was observed in this study, which could be attributed to the short treatment duration and limited number of stimulus sessions used. Previous research has predominantly focused on 1–2 weeks of stimulation with 5–10 sessions, which is likely influenced by practical considerations surrounding subject compliance. However, some tDCS studies have reported significant positive effects with twice-daily stimulation [39,71], indicating that tDCS may only be effective with frequent applications. Despite the current lack of robust evidence to support its effectiveness, we are unable to advise against the use of tDCS for schizophrenia patients, as no reports have suggested that it worsens GPSs poststimulation. In 2022, a meta-analysis was carried out to specifically investigate the impact of tDCS treatment on GPSs. This review included only 8 relevant studies [67]. Notably, Lee *et al.* [67] reported a pooled SMD of 0.31 (0.05 to 0.57) for GPSs across the 8 studies, while our meta-analysis of 10 studies showed a pooled SMD of –0.1437 (–0.35 to 0.07). Lee *et al.* [67] also reported a significant reduction in General Psychopathology Scale scores from PANSS after active tDCS treatment compared to sham treatment and examined 5 trials that re-

ported having followed up with their patients. The conclusion drawn by Lee *et al*. [67] was that tDCS improved GPSs in the short term, but there was no evidence to suggest that the treatment worked in the long term. The inconsistency between our findings and Lee *et al*. [67] may be attributed to several factors. First, as Lee *et al*. [67] observed, GPSs encompass a broad range of symptoms, and individual differences in symptom profiles may influence the efficacy of tDCS. Second, our meta-analysis included two additional tDCS studies from 2021 and 2022 that were not included in the Lee *et al*. [67] analysis. To clarify the findings on the efficacy of tDCS in treating GPSs, further studies with larger sample sizes are needed.

In our meta-analysis, we did not impose restrictions on rTMS parameters during study selection, which resulted in the inclusion of studies utilizing different stimulus frequencies (ranging from 1 Hz to 20 Hz) and stimulus locations (including left DLPFC, bilateral DLPFC, and left TPC). Our subgroup analysis focusing on the different frequencies of rTMS treatment showed that high-frequency rTMS was effective in improving general psychopathology symptoms in schizophrenia, while low-frequency rTMS was not found to be effective. It should be noted that rTMS can be divided into high-frequency stimulation (5–20 Hz) and low-frequency stimulation ($\leq$1 Hz), with high frequencies increasing cortical excitability and low frequencies suppressing it [72].

Although the left DLPFC has been the most studied target region for NIBS in the treatment of negative symptoms due to its significant role in the pathophysiology of schizophrenia [73,74], our meta-analysis results indicate that NIBS has no significant effect on improving depressive symptoms in schizophrenia. There are several possible explanations for this finding. First, depressive symptoms in schizophrenia are different from other depressive disorders, and in schizophrenia patients, reductions in prefrontal cortex grey matter (GM) volume are associated with depressive symptoms and auditory verbal hallucinations (AVHs) [75]. GM damage is more severe in patients with first-episode schizophrenia who have depressive symptoms than in those who do not [76], indicating that depressive symptoms in schizophrenia may be a nonnegligible factor in treatment resistance. Schizophrenia patients with depressive symptoms do not respond as well to current medications and have a worse long-term prognosis than those without depressive symptoms [77]. Therefore, we speculate that schizophrenia patients with depressive symptoms are less sensitive to NIBS.

Second, depression is not a negative symptom but a common confound for negative symptoms of schizophrenia due to their overlapping conditions. Negative symptoms may mask depressive symptoms, making it difficult to distinguish them clinically. Third, the efficacy of NIBS for depression may be affected by the frequency of stimulation, duration of treatment, and other factors. For example, a previous RCT study applied bimodal tDCS with bi-anodal stimulation over the DLPFC on both sides and demonstrated that this mode could reduce negative and depressive symptoms in patients with schizophrenia [78]. This finding may indicate that improving depressive symptoms in schizophrenia requires a stronger electrical dosage as well as deeper brain stimulation. Fourth, the assessment tools used were not uniform. The Calgary Depression Scale for Schizophrenia (CDSS) is an ideal tool for the assessment of depressive symptoms in people with schizophrenia [79]. However, the CDSS has not been widely used, and some of the included studies adopted other scales for the assessment of depressive symptoms in patients with schizophrenia, for example, the PANSS-Depression score and Montgomery-Asberg Depression Rating Scale. Finally, it is worth noting that most of the research designs and target populations for NIBS do not involve GPSs. The studies we included mostly concerned NIBS treating positive or negative symptoms of schizophrenia, and there were few studies directly investigating GPSs or depressive symptoms of schizophrenia. Therefore, it cannot be ruled out that there is a floor effect with negative outcomes; that is, NIBS is ineffective for depressive symptoms in schizophrenia. Given the high prevalence of depressive symptoms in schizophrenia, there is an urgent need for an understanding of the underlying neural mechanisms to identify therapeutic targets for its effective treatment.

Our study focused on the effect of NIBS on the GPSs and depressive symptoms of schizophrenia. General psychopathology symptoms encompass a broad range of symptoms, and some of these symptoms overlap with negative symptoms of schizophrenia, such as anhedonia. This also suggests that anhedonia may be a more common symptom in people with schizophrenia. Our findings may indicate a direction for future large-scale randomized controlled trials. Future studies should also investigate the neural basis of GPSs in more detail, such as MRI or combined transcranial magnetic stimulation and electroencephalography (TMS-EEG) techniques, which may provide insights into its underlying mechanisms and clues for more targeted interventions.

For individuals with obvious GPSs rTMS therapy may be the preferred therapeutic technique. However, effective treatment involves considering numerous parameters, such as stimulus intensity, frequency of stimulus train, site of stimulation, and course of treatment. Further research is necessary to test and optimize these settings and explore the maintenance effect of rTMS after treatment. Given challenges in the treatment of schizophrenia patients with GPSs and depressive symptoms, it is essential to conduct in-depth neural mechanistic studies to identify targets for the development of effective therapies.

5. Limitations

While our study provides evidence supporting the efficiency of rTMS as an adjunctive treatment for GPSs in schizophrenia, it is important to acknowledge several limitations. First, the credibility of our results may be reduced due to the limited number of trials included and their small sample sizes. Second, the subgroup analysis was limited to only three related factors due to the lack of available data. Third, the potential therapeutic effect of concomitant antipsychotic medication cannot be entirely excluded, as no RCTs excluded them from their study design. Finally, the limited reporting of follow-up data a month or more after treatment prevents conclusions from being drawn about the duration of effects, which is a significant limitation. Despite these limitations, our study provides valuable insights into the use of rTMS as an adjunctive treatment for schizophrenia.

6. Conclusions

In conclusion, our meta-analysis demonstrates that rTMS is effective in treating GPSs in schizophrenia, while the efficacy of tDCS in addressing these symptoms requires further exploration. Psychiatrists should prioritize the management of GPSs during physical interventions, and rTMS may provide advantages in this regard. However, more conclusive evidence is needed to support this claim.

Availability of Data and Materials

The datasets generated and/or analysed in this study are publicly available. They can be obtained from the corresponding authors upon reasonable request.

Author Contributions

WQH, HW, NH, JBC, and XZZ were involved in the interpretation of results and manuscript preparation. FQL and YL were involved in the conceptualization and design of the study. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.jin2301007.

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