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SYSTEMATIC REVIEW

Efficacy and Safety of Intermittent Theta Burst Stimulation and High-Frequency Repetitive Transcranial Magnetic Stimulation for Major Depressive Disorder: A Systematic Meta-Analysis

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Abstract

Aims/Background High-frequency repetitive transcranial magnetic stimulation (HF-rTMS) and intermittent theta burst stimulation (iTBS) are emerging neuromodulation techniques for major depressive disorder (MDD). However, clinical trials directly comparing their efficacy are limited. This meta-analysis aimed to evaluate the antidepressant effects and safety profiles of iTBS versus HF-rTMS for MDD.

Methods A systematic literature search was conducted in major databases to identify randomized controlled trials (RCTs) comparing iTBS and HF-rTMS for MDD. The primary outcome measures were response rate, remission rate, and common side effects. Meta-analysis was performed using fixed-effects and random-effects models. Publication bias was assessed.

Results Seven RCTs were included in the meta-analysis. No significant differences were found in response rate (odds ratio (OR) 0.97, 95% confidence interval (95% CI) 0.81 to 1.16, $p = 0.75$) or remission rate (OR 1.06, 95% CI 0.85 to 1.31, $p = 0.62$) between iTBS and HF-rTMS. Both active stimulations showed significantly higher response rates than sham treatment. The odds of response were 4–5 times greater for iTBS versus sham (OR 4.84, 95% CI 2.66 to 8.80, $p < 0.001$) and 3–4 times greater for HF-rTMS versus sham (OR 3.85, 95% CI 2.08 to 7.13, $p < 0.001$). No differences in common side effects such as headache were observed between iTBS and HF-rTMS.

Conclusion iTBS and HF-rTMS have comparable efficacy and safety profiles in treating MDD based on current evidence. Both neuromodulation techniques are superior to sham stimulation. iTBS could be considered an alternative to HF-rTMS, with the advantage of shorter daily treatment duration. Further large RCTs with long-term follow-up are warranted to confirm these findings.

Key words: intermittent theta burst stimulation; high-frequency repetitive transcranial magnetic stimulation; major depressive disorder

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Introduction

Major depressive disorder (MDD), a highly prevalent mental illness affecting more than 300 million people globally, is characterized by persistent low mood, anhedonia, fatigue, and suicidal thoughts, and severely impairs psychosocial functioning and quality of life. Antidepressant medications and psychotherapy remain

the first-line treatments, but 30–40% of patients fail to respond adequately (Battle, 2013). Repetitive transcranial magnetic stimulation (rTMS) has emerged as an effective and safe neuromodulation therapy for MDD over the past three decades. High-frequency repetitive transcranial magnetic stimulation (HF-rTMS) applied to the left dorsolateral prefrontal cortex (DLPFC) can normalize dysfunctional neural circuits implicated in depression, leading to robust antidepressant effects demonstrated in multiple sham-controlled trials (Berlim et al, 2014; Rush et al, 2006). However, the standard HF-rTMS protocol, requiring daily sessions over 3–6 weeks, may burden patients and reduce treatment compliance, thereby limiting its clinical utility.

Theta burst stimulation (TBS), a patterned form of rTMS, has drawn increasing research attention recently since it can achieve antidepressant effects comparable to HF-rTMS but with much shorter session duration. Intermittent TBS (iTBS) involves delivering 2 s bursts of high-frequency magnetic pulses (3 pulses at 50 Hz) repeated every 10 s over 190 s (Lefaucheur et al, 2020). Anodal iTBS is hypothesized to potentiate synaptic plasticity in superficial cortical regions via long-term potentiation effects (Huang et al, 2005). Meta-analyses have confirmed the superior efficacy of iTBS over sham stimulation for acute MDD treatment, but direct comparisons between iTBS and standard HF-rTMS remain limited. Thus, key questions remain regarding individual differences, treatment parameter optimization, and safety concerns. Some randomized controlled trials (RCTs) testing iTBS and HF-rTMS have yielded mixed results, particularly with respect to differences in efficacy, with some showing that iTBS is superior to HF-rTMS in the treatment of depression, while other studies have reached the opposite conclusion (Hyde et al, 2022; Ferrarelli and Phillips, 2022; Vaithianathan et al, 2022). Although earlier studies favored HF-rTMS, recent RCTs have shown comparable efficacy. HF-rTMS was approved by the US Food and Drug Administration (FDA) in 2008 and is covered by many public and private insurers in the USA and other countries. And based on a large non-inferiority trial, in which iTBS was shown to have the same level of clinical efficacy as standard high-frequency 10 Hz rTMS, the FDA approved the iTBS program for the treatment of MDD in 2018 (Shenasa et al, 2023).

iTBS is similar to HF-rTMS in that both can induce an increase in cortical excitability and both have comparable efficacy, but they differ in treatment duration and protocol (Lan et al, 2023). iTBS is characterized by a much shorter duration of treatment, which can be more cost-effective, and has potential advantages in terms of patient convenience and improved treatment adherence. In addition, several studies have shown that iTBS has a greater stimulatory effect compared to HF-rTMS, with acceptable inter-individual variability (Di Lazzaro et al, 2011; Mao et al, 2022).

In this study, we conducted a systematic review and meta-analysis, comparing the clinical efficacy and safety profiles of iTBS versus HF-rTMS and sham stimulation for MDD. The findings provide empirical evidence on the comparative antidepressant effects between the two major rTMS modalities. The results of the meta-analysis will help establish standardized iTBS protocols for MDD and guide clinical practice.

Methods

Literature Search Strategy

The systematic review followed PRISMA guidelines and a PRISMA check list which is provided as a supplementary material (**PRISMA Checklist**). A systematic literature search was conducted in PubMed, EMBASE, Web of Science, Cochrane Library, PsycINFO, and ClinicalTrials.gov from inception to November 2023. The search terms included "theta burst stimulation", "intermittent theta burst stimulation", "iTBS", "theta burst TMS", "high frequency repetitive transcranial magnetic stimulation", "HF-rTMS", "rTMS", "transcranial magnetic stimulation", "TMS", "major depressive disorder", "MDD", "depression", and "randomized controlled trial". Different combinations of these terms were used to retrieve the potential studies. Reference lists of relevant reviews and included studies were hand-searched for additional studies. The literature search was limited to English language publications.

Inclusion and Exclusion Criteria

Studies were included if they met the following criteria: (1) Comparing iTBS with HF-rTMS or sham stimulation; (2) Involving patients diagnosed with MDD based on standard criteria such as DSM-IV/V or ICD-10; (3) Reporting iTBS and HF-rTMS administered to the left DLPFC; (4) Reporting response rate and/or remission rate as outcome measures. Studies were excluded if they (1) Were non-RCTs or cohort studies; (2) Enrolled patients with other psychiatric disorders; (3) Did not report sufficient data on response or remission rate.

Data Extraction

Two reviewers independently extracted data from the included studies using a predefined data extraction form. The extracted information included: first author, year of publication, country, study design, sample size, patient characteristics, iTBS and HF-rTMS protocols, depression rating scales, definition of response and remission, number of responders and remitters in each group, and adverse events. Any discrepancies were resolved by discussion and consensus.

Quality Assessment

The methodological quality and risk of bias of the included studies were assessed using the Cochrane Collaboration's tool for assessing risk of bias (Huang et al, 2023). This tool evaluates seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Each domain was judged as low, unclear, or high risk of bias.

Statistical Analysis

Statistical analysis was performed using R software 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria) with the meta packages. Dichotomous data on response rate, remission rate, and adverse events were analyzed by calculating the odds ratio (OR) and 95% confidence interval (CI). The heterogeneity across

studies was assessed using the I^2 statistic and the Q test. I^2 values of 25–50% represent low heterogeneity, 50–75% medium heterogeneity, and >75% high heterogeneity. If I^2 was <50%, a fixed-effects model was applied. Otherwise, a random-effects model was used. Publication bias was evaluated through funnel plots, the Begg's test, and the Egger's test (Egger et al, 1997). Potential publication bias was identified statistically if both the Begg's and Egger's tests had *p*-values less than 0.05.

Results

Search Strategy

The meta-analysis followed a systematic and rigorous process to identify and select the relevant studies for the research question. The meta-analysis searched three major databases (PubMed, EMBASE, and Web of Science) and other sources to retrieve the potential studies. The meta-analysis applied the predefined inclusion and exclusion criteria to screen the records and assess the full-text articles for eligibility. The meta-analysis also removed the duplicates and the studies that did not provide sufficient data. The meta-analysis included a total of 7 studies in the meta-analysis. The flow diagram of the study selection process is shown in Fig. 1.

Characteristics of Included Studies

In a comprehensive meta-analysis encompassing various global studies on the effectiveness of rTMS and iTBS in treating depression, a diverse set of findings was observed across different countries and regions. In Canada, a RCT by Blumberger et al (2018), indicated that iTBS and high-frequency 10 Hz rTMS were comparably effective in alleviating depressive symptoms over a 4-week period with 20 sessions. This study highlighted iTBS's advantage of shorter treatment sessions without compromising clinical outcomes. In France, Bulteau et al (2022) conducted a prospective cohort study which also spanned 4 weeks with 20 sessions. The study concluded that iTBS and 10 Hz rTMS showed similar efficacy in treating treatment-resistant unipolar depression, resulting in notable decreases in depression scores and improvements in quality of life over 6 months. From Australia, two RCTs presented varied insights. Chen et al (2021) found that, compared to rTMS, accelerated bilateral TBS (low or high intensity) was effective and well-tolerated in treating treatment-resistant depression (TRD), with no significant differences in treatment response across the three groups. Meanwhile, Fitzgerald et al (2020) reported no significant differences in symptom alleviation, response rates, or adverse effects between intensive TBS and standard rTMS over 21 sessions in 4 weeks.

In Taiwan, China, two RCTs by Li et al (2020) provided distinct findings. The 2020 study (Li et al, 2020), conducted over 2 weeks with 10 sessions, revealed that prolonged intermittent TBS (piTBS) monotherapy was highly effective in treating recurrent depression, showing significant benefits over sham stimulation. However, MRI-guided coil positioning did not enhance antidepressant effects. The study (Prasser et al, 2015), with 20 sessions over 2 weeks, found that piTBS was viable for MDD, but extending treatment duration did not produce accelerated an-

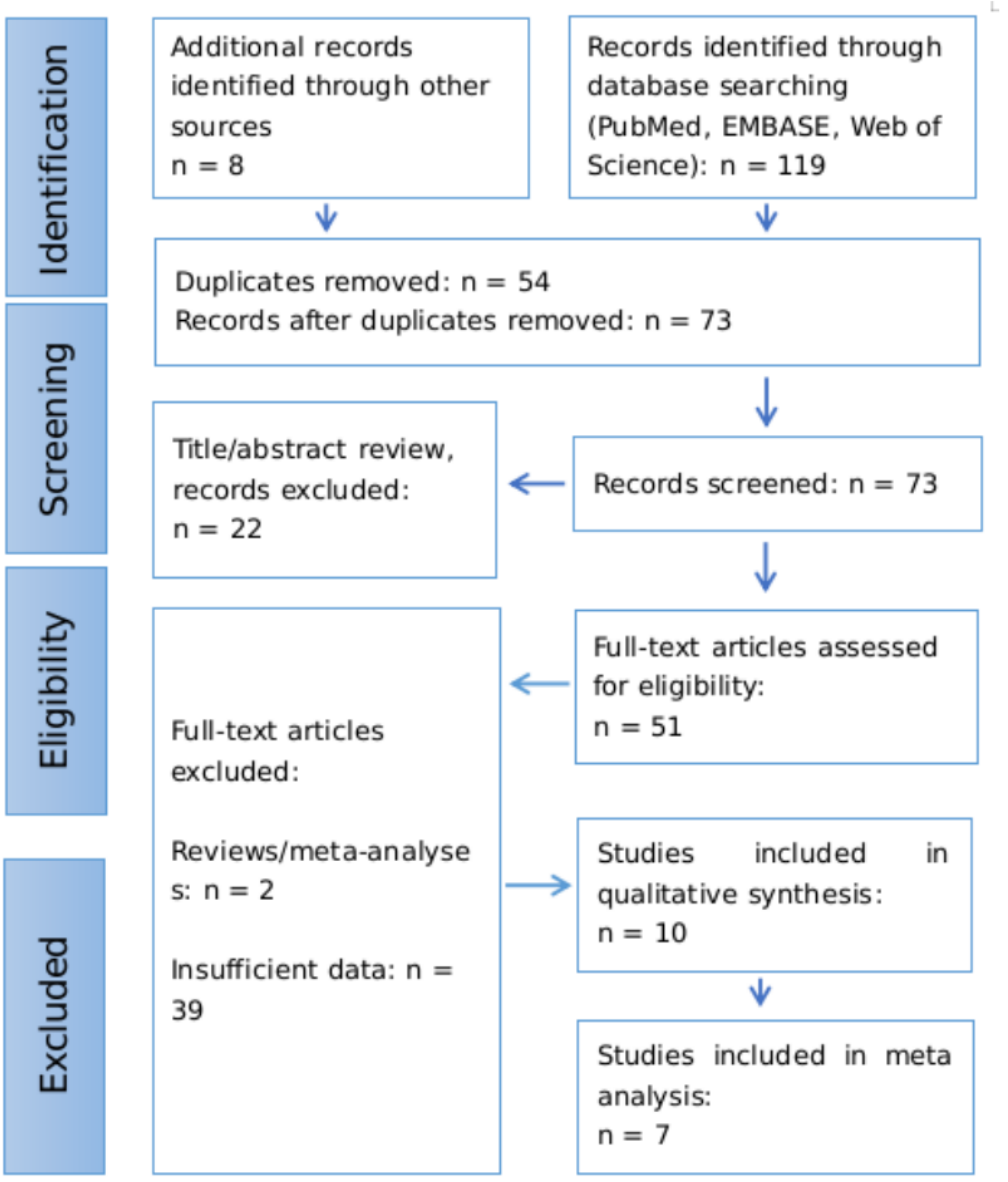

Fig. 1. Flow diagram of study selection process.

tidepressant effects. Interestingly, a substantial placebo effect was observed but did not intensify with prolonged stimulation. Lastly, in Germany, Prasser et al (2015) carried out a RCT over 3 weeks with 15 sessions. The study indicated that bilateral TBS as an adjunctive therapy did not significantly benefit major depression compared to sham treatment (Li et al, 2023). However, a trend towards a higher responder rate was observed in the TBS group by the end of the follow-up period, suggesting a potential for further efficacy assessments. Overall, these international studies collectively suggest that both iTBS and rTMS are promising in the treatment of depression, with variations in their effectiveness, treatment duration, and patient response. The characteristics of the included studies are summarized in Table 1. Specific parametric information is provided in the **Supplementary Table 1**.

Table 1. Summary of the studies selected.

Study	Country/Region	Study design	RCT number	Age, years		Scale for depression	Duration
				iTBS group	rTMS (Standard) group		
Blumberger et al (2018)	Canada	RCT	NCT01887782	41.6 (10.8)	43.2 (12.2)	HRSD-17	20 sessions for 4 weeks
Bulteau et al (2022)	France	Prospective cohort study	N/A	56.1 (10.9)	48.5 (14.7)	MADRS	20 sessions for 4 weeks
Chen et al (2021)	Australia	RCT	N/A	48.18 (14.14) [Low intensity] | 49.14 (15.77) [High intensity]	48.67 (16.06)	QIDS-C16	20 sessions for 4 weeks
Fitzgerald et al (2020)	Australia	RCT	ACTRN12616000443493	44.0 (12.2)	44.7 (12.2)	MADRS	21 sessions for 4 weeks
Li et al (2020)	Taiwan, China	RCT	UMIN000020892	47.16 (14.2)	47.16 (13.8)	HDRS-17	10 sessions for 2 weeks
Prasser et al (2015)	Germany	RCT	NCT01240083	48.2 (10.9)	50.4 (9.9)	HAMD	15 sessions for 3 weeks
Li et al (2023)	Taiwan, China	RCT	UMIN000044951	37.0 (3.1)	37.8 (2.7)	HDRS-17	20 sessions for 2 weeks

RCT, randomized controlled trial; iTBS, intermittent theta burst stimulation; rTMS, repetitive transcranial magnetic stimulation; N/A, not applicable; HRSD-17, Hamilton Rating Scale for Depression-17 items; QIDS-C16, Quick Inventory of Depressive Symptomatology-Clinician Administered, 16-item version; MADRS, Montgomery-Asberg Depression Rating Scale; HAMD, Hamilton Depression Scale.

Comparison of Response Rate between iTBS and HF-rTMS

The meta-analysis included 15 datasets of 7 studies. The overall response rate was 40.0% in the iTBS group and 40.2% in the HF-rTMS group. The meta-analysis showed that there was no significant difference between iTBS and HF-rTMS in terms of the response rate. The common-effect model yielded an OR of 0.97 (95% CI: 0.81, 1.16), with a *p*-value of 0.75. The random-effects model yielded an OR of 0.97 (95% CI: 0.83, 1.14), with a *p*-value of 0.71. The meta-analysis also showed that the heterogeneity among the studies was very low, indicating that the effect sizes were consistent across the studies. The tau^2 was 0 (95% CI: 0.00, 0.14), the tau was 0 (95% CI: 0.00, 0.37), the I^2 was 0% (95% CI: 0.0, 53.6), the H was 1.00 (95% CI: 1.00, 1.47), and the Q statistic was 9.31 ($p = 0.81$). This suggested that the fixed-effects model was more suitable than the random-effects model, as it assumed that all studies had a common effect size and gave more weight to the larger studies (Fig. 2).

Assessment of Publication Bias Using the Funnel Plot and Begg's Test for Response Rate

The funnel plot and the Begg's test were used to assess the publication bias of the included studies. The results of the funnel plot and the Begg's test are shown in Fig. 2B,C, respectively. The funnel plot showed that the studies were mainly scattered in the lower and middle part of the inverted funnel, and there was no obvious asymmetry. The Begg's test showed that the rank correlation between the effect size and the standard error was not significant (z = 0.99, *p*-value = 0.32). These results suggested that there was no evidence of publication bias in the meta-analysis.

Assessment of Influence and Heterogeneity of Response Rate Using the Baujat Plot and Galbraith Plot

The Baujat plot and the Galbraith plot were used to assess the influence and heterogeneity of the included studies. The results of the Baujat plot and the Galbraith plot are shown in Fig. 3A,B, respectively. The Baujat plot showed that most of the studies were located in the lower left quadrant, indicating that they had a low influence and a low heterogeneity. However, one study, Chen et al (2021) (High intensity), was located in the upper right quadrant, indicating that it had a large influence and a high heterogeneity. This study used a higher intensity of iTBS than the other studies, which may explain its different effect size and heterogeneity. The Galbraith plot showed that all the studies were located within the two parallel lines, indicating that they were consistent with the overall effect size. This suggested that there was no significant outlier or source of heterogeneity in the meta-analysis.

Comparison of Remission Rate between iTBS and HF-rTMS

The meta-analysis included 11 datasets of 7 studies. The remission rate was the primary outcome measure, and different scales were used to assess the remission status, such as Hamilton Rating Scale for Depression-17 items (HRSD-17), The Inventory of Depressive Symptomatology, 30-item version (IDS-30), Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR), Quick Inventory of

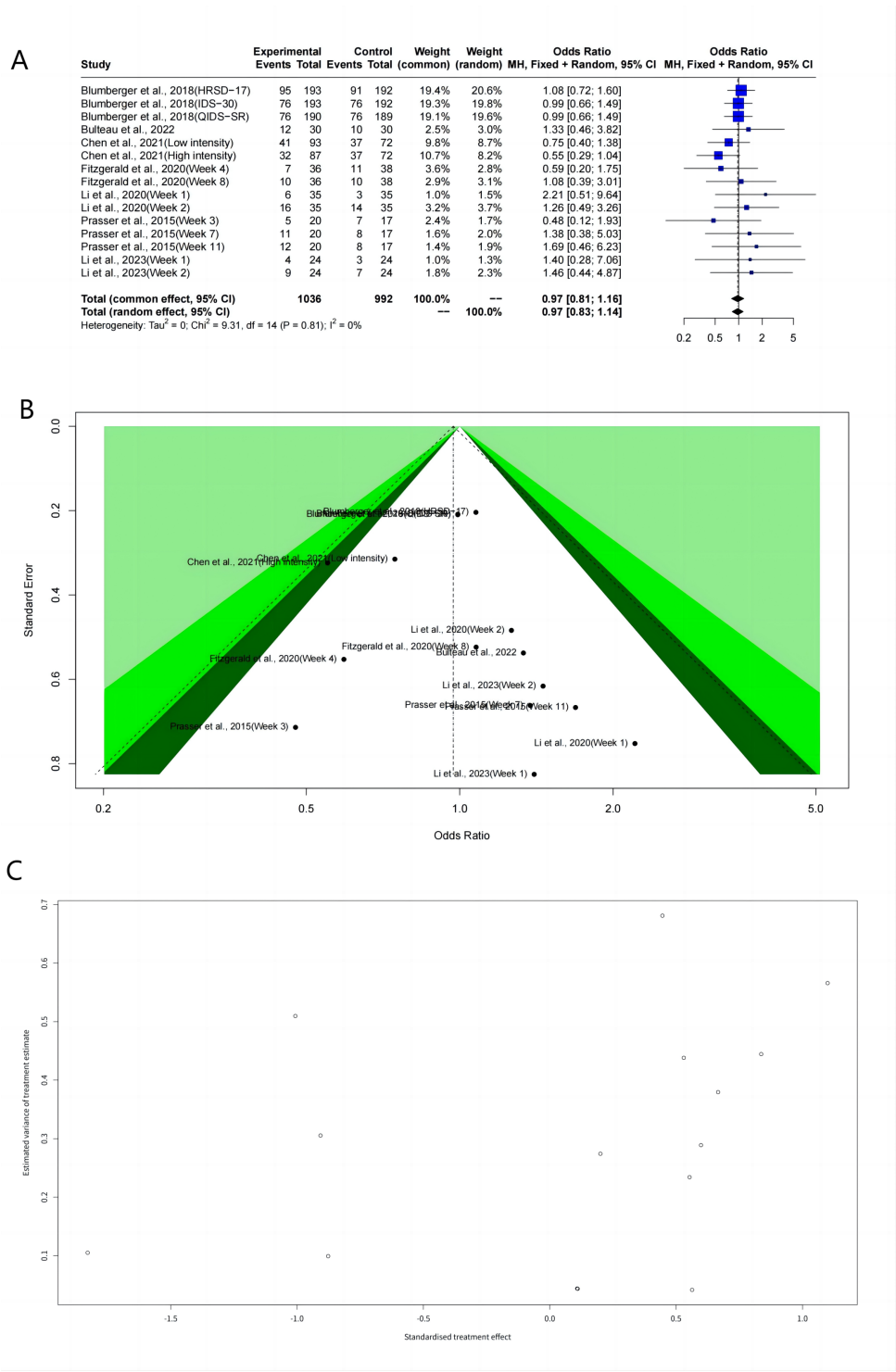

Fig. 2. The meta-analysis of response rate between iTBS and HF-rTMS including the Forest plot (A), funnel plot (B), and Begg's test (C). HF-rTMS, High-frequency repetitive transcranial magnetic stimulation.

Depressive Symptomatology-Clinician Administered, 16-item version (QIDS-C16) and Montgomery-Asberg Depression Rating Scale (MADRS). The meta-analysis showed that there was no significant difference between iTBS and HF-rTMS in terms of the remission rate. The fixed-effects model yielded an OR of 1.06 (95%

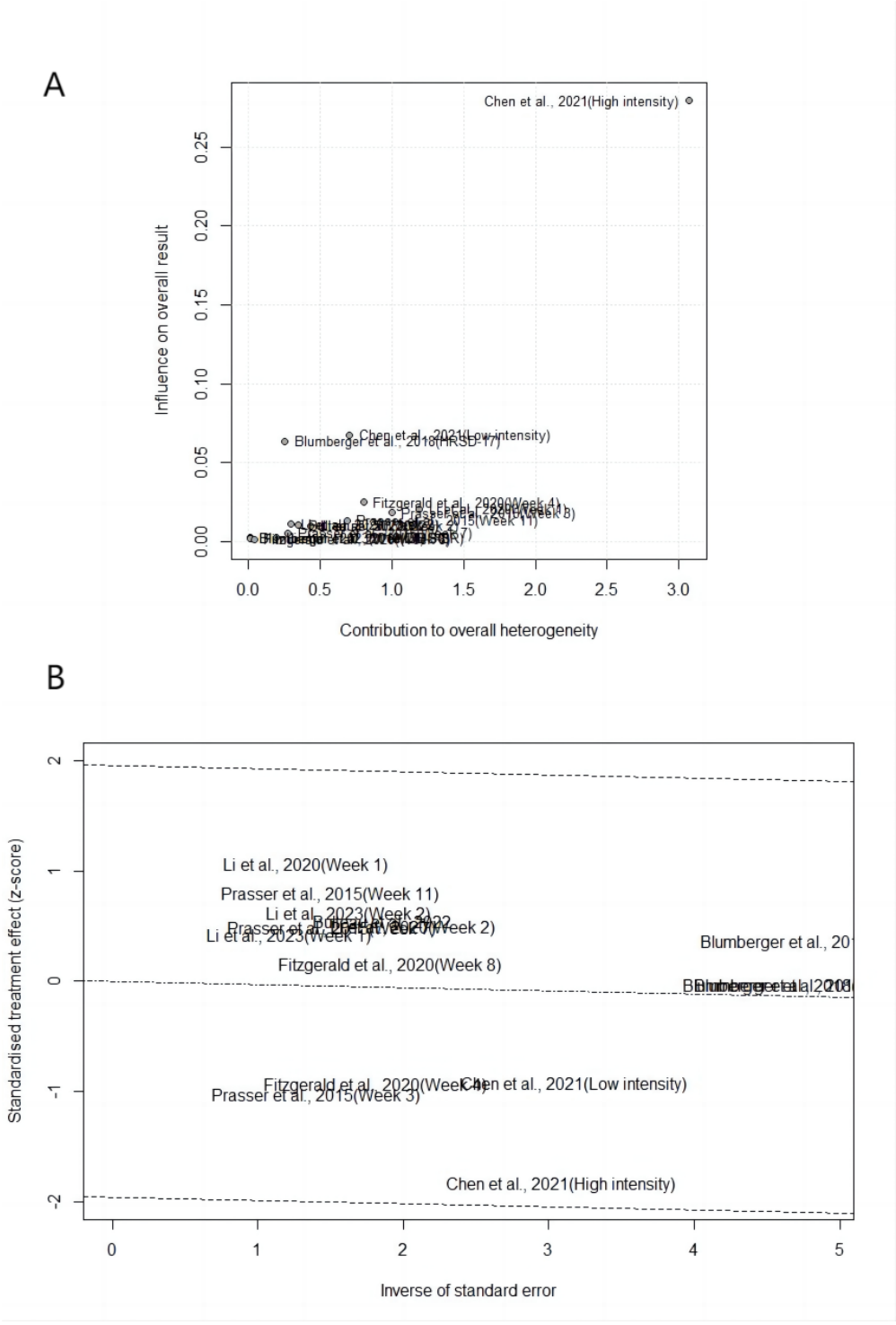

Fig. 3. Baujat plot (A) and Galbraith plot (B) of the meta-analysis of response rate between iTBS and HF-rTMS.

CI: 0.85, 1.31), with a *p*-value of 0.62. The random-effects model yielded an OR of 1.06 (95% CI: 0.82, 1.35), with a *p*-value of 0.63. This indicated that the odds of remission were similar in both groups, and neither iTBS nor HF-rTMS had a superior effect on MDD. The meta-analysis also showed that the heterogeneity among the studies was very low, indicating that the effect sizes were consistent across the

studies. The tau^2 was 0.0002 (95% CI: 0.00, 0.38), the tau was 0.16 (95% CI: 0.00, 0.61), the I^2 was 0% (95% CI: 0.0, 60.3), the H was 1.00 (95% CI: 1.00, 1.59), and the Q statistic was 10.02 (p = 0.44). This suggested that the fixed-effects model was more suitable than the random-effects model, as it assumed that all studies had a common effect size and gave more weight to the larger studies (Fig. 4A).

Assessment of Publication Bias Using Funnel Plot and Begg's Test for Remission Rate

The funnel plot and the Begg's test were used to assess the publication bias of the included studies. The funnel plot was basically in the shape of an inverted funnel, and the studies were mainly scattered in the lower and middle part of the plot. This indicated that there was no obvious asymmetry in the funnel plot, and the effect sizes were not influenced by the sample sizes or the standard errors of the studies. The Begg's test confirmed the absence of publication bias in the meta-analysis. The test result showed that the z-value was –0.70, and the p-value was 0.481. This indicated that the rank correlation between the effect size and the standard error was not significant, and there was no evidence of funnel plot asymmetry. The sample estimates showed that the Kendall's score was –9.00, and the standard error of the Kendall's score was 12.77 (Fig. 4B,C).

Assessment of Influence and Heterogeneity of Remission Rate Using Baujat Plot and Galbraith Plot

The Baujat plot and the Galbraith plot were used to assess the influence and heterogeneity of the included studies. The results of the Baujat plot and the Galbraith plot are shown in Fig. 5A,B, respectively. The Baujat plot showed that most of the studies were located in the lower left quadrant, indicating that they had a low influence and a low heterogeneity. However, two studies, Blumberger et al (2018) (QIDS-SR) and Chen et al (2021) (High intensity), were located in the upper right quadrant and the right side of the plot, respectively, indicating that they had a large influence and a high heterogeneity. These studies have different characteristics or methods from the other studies, which may explain their different effect sizes and heterogeneity. For example, Blumberger et al (2018) (QIDS-SR) used a different scale (QIDS-SR) than the other studies to assess the remission status, and Chen et al (2021) (High intensity) used a higher intensity of iTBS than the other studies. The Galbraith plot showed that all the studies were located within the two parallel lines, indicating that they were consistent with the overall effect size. This suggested that there was no significant outlier or source of heterogeneity in the meta-analysis. The Galbraith plot also showed the CI of the overall effect size, which was close to the null value of zero, indicating that there was no significant difference between iTBS and HF-rTMS in terms of the remission rate.

Comparison of Headache Rate between iTBS and HF-rTMS

The meta-analysis included 4 studies. The occurrence of headache was the primary outcome measure, as it was one of the most common adverse effects of both iTBS and HF-rTMS. The meta-analysis showed that there was no significant difference between iTBS and HF-rTMS in terms of the occurrence of headache.

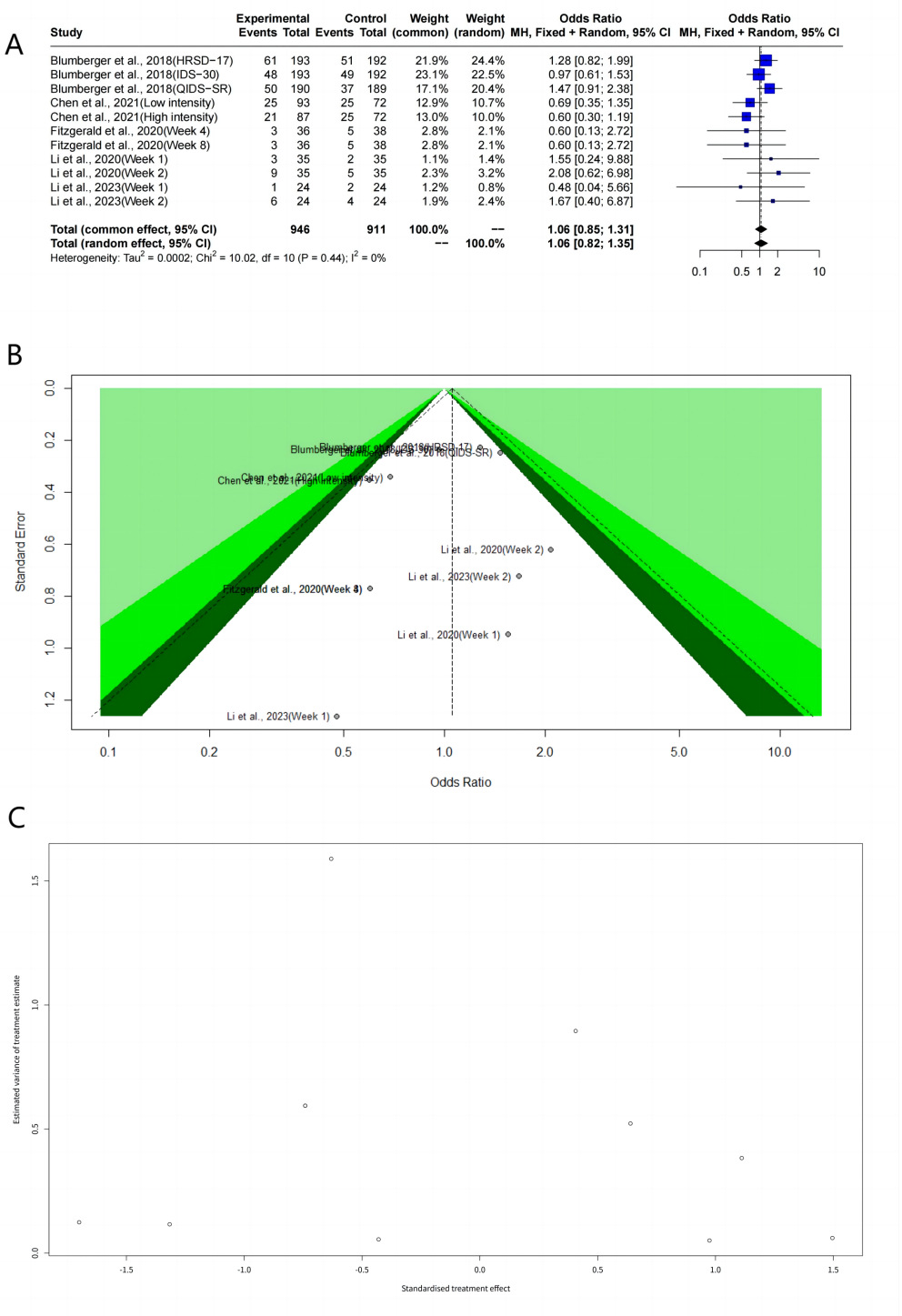

Fig. 4. The meta-analysis of remission rate between iTBS and HF-rTMS including the Forest plot (A), funnel plot (B), and Begg's test (C).

The fixed-effects model yielded an OR of 1.19 (95% CI: 0.84, 1.70), with a *p*-value of 0.33. The random-effects model yielded an OR of 1.32 (95% CI: 0.51, 3.38), with a *p*-value of 0.42. This indicated that the odds of headache were similar in both groups, and neither iTBS nor HF-rTMS had a higher risk of causing headache

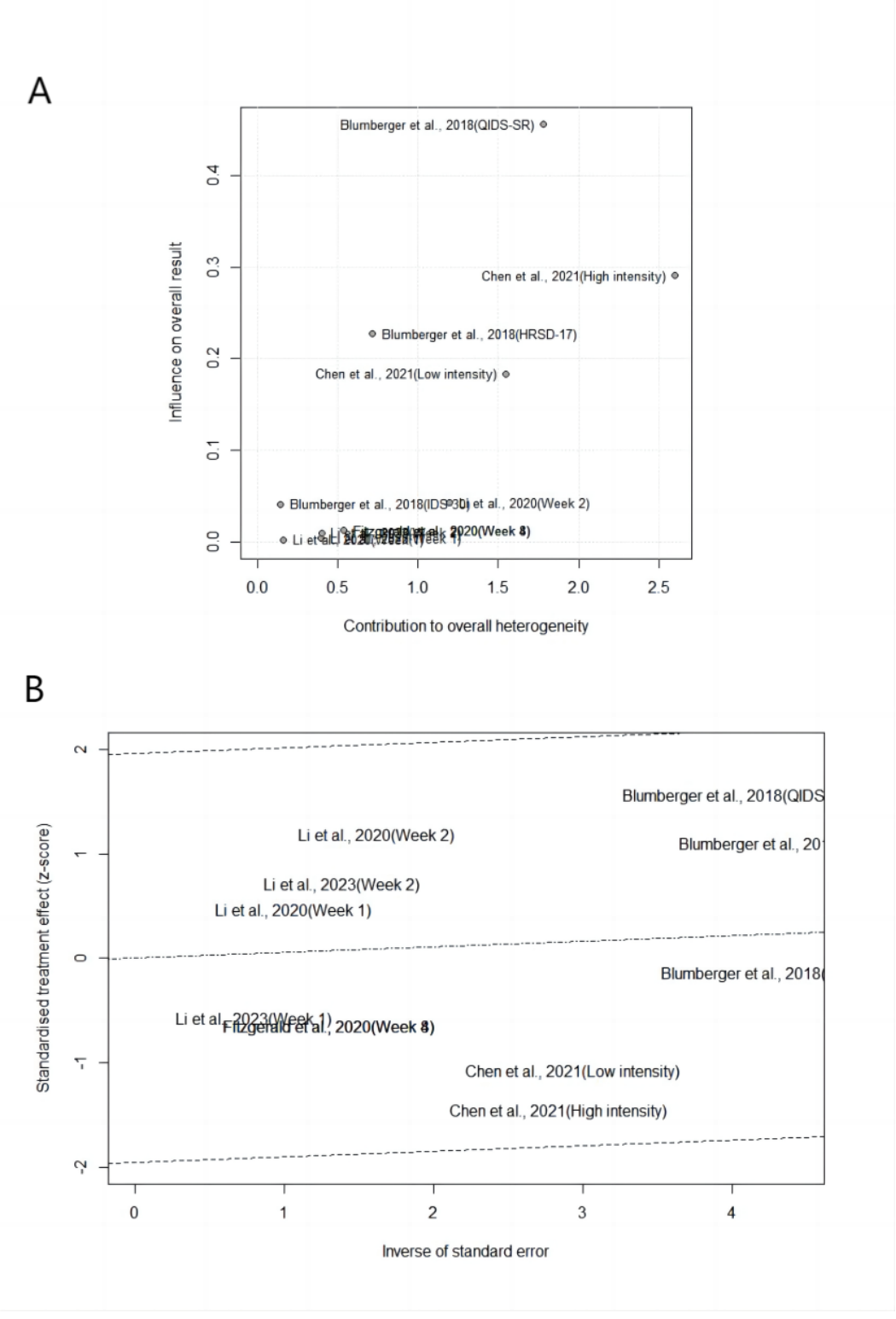

Fig. 5. Baujat plot (A) and Galbraith plot (B) of the meta-analysis of remission rate between iTBS and HF-rTMS.

in MDD patients. The meta-analysis also showed that the heterogeneity among the studies was low to moderate, indicating that the effect sizes were relatively consistent across the studies. The tau^2 was 0.1133 (95% CI: 0.00, 10.02), the tau

was 0.3366 (95% CI: 0.00, 3.17), the I^2 was 24% (95% CI: 0.0, 88.4), the H was 1.15 (95% CI: 1.00, 2.93), and the Q statistic was 3.95 ($p = 0.27$). This suggested that both the fixed-effects model and the random-effects model were suitable for the meta-analysis, as they gave similar results and CIs (Fig. 6).

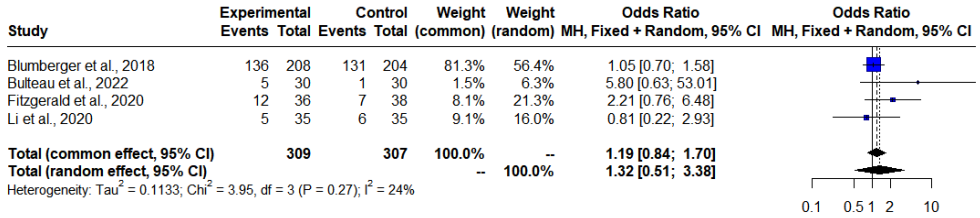

Fig. 6. Forest plot of the meta-analysis of headache rate between iTBS and HF-rTMS.

Comparison of Response Rate between iTBS and Sham Stimulation

The meta-analysis aimed to compare the efficacy and safety of iTBS and sham stimulation for MDD. The meta-analysis showed that iTBS was significantly more effective than sham in terms of the response rate. The fixed-effect model yielded an OR of 4.84 (95% CI: 2.66, 8.80), with a p-value of <0.001. The random-effects model yielded an OR of 4.21 (95% CI: 1.92, 9.23), with a p-value of <0.001. This indicated that the odds of response were about 5 times higher in the iTBS group than in the sham group, and iTBS had a superior effect on MDD. The meta-analysis also showed that the heterogeneity among the studies was very low, indicating that the effect sizes were consistent across the studies. The tau^2 was <0.0001 (95% CI: 0.00, 3.53), the tau was 0.00 (95% CI: 0.00, 1.88), the I^2 was 0% (95% CI: 0.0, 70.8), the H was 1.00 (95% CI: 1.00, 1.85), and the Q statistic was 5.99 ($p = 0.42$). This suggested that the fixed-effects model was more suitable than the random-effects model, as it assumed that all studies had a common effect size and gave more weight to the larger studies (Fig. 7).

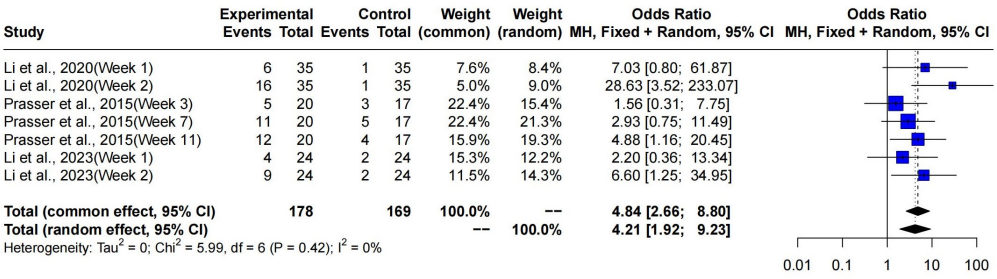

Fig. 7. Forest plot of the meta-analysis of response rate between iTBS and sham stimulation.

Comparison of Response Rate between rTMS and Sham Stimulation

The meta-analysis showed that rTMS was significantly more effective than sham in terms of the response rate. The fixed-effects model yielded an OR of 3.85 (95% CI: 2.08 7.13), with a *p*-value of <0.001. The random-effects model yielded an OR of 3.37 (95% CI: 1.70, 6.68), with a *p*-value of <0.001. This indicated that the odds of response were about 4 times higher in the rTMS group than in the sham group, and rTMS had a superior effect on MDD. The meta-analysis also showed that the heterogeneity among the studies was very low, indicating that the effect sizes were consistent across the studies. The tau^2 was 0 (95% CI: 0.00, 2.56), the tau was 0 (95% CI: 0.00, 1.60), the I^2 was 0.0% (95% CI: 0.0, 70.8), the H was 1.00 (95% CI: 1.00, 1.85), and the Q statistic was 4.36 ($p = 0.63$). This suggested that the fixed-effects model was more suitable than the random-effects model, as it assumed that all studies had a common effect size and gave more weight to the larger studies (Fig. 8).

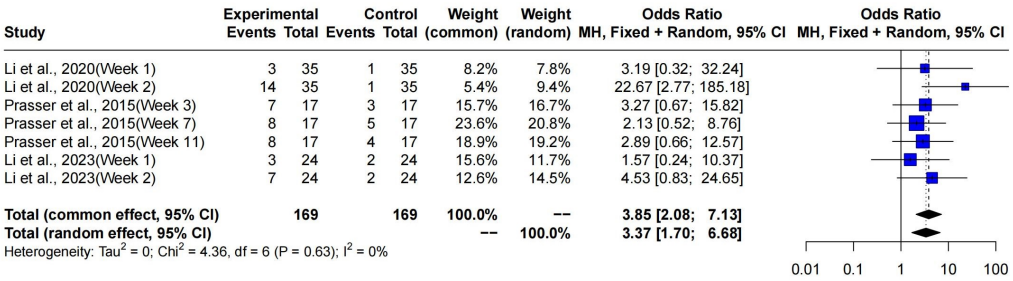

Fig. 8. Forest plot of the meta-analysis of response rate between rTMS and sham stimulation.

Discussion

This systematic review and meta-analysis of 7 RCTs aimed to compare the efficacy and safety profiles of iTBS versus HF-rTMS and sham stimulation for MDD. The main findings were: (1) No significant differences in response and remission rates were found between iTBS and HF-rTMS; (2) Both iTBS and HF-rTMS had significantly higher response rates than sham stimulation; (3) The rates of common adverse events such as headache were similar between active stimulation groups.

The meta-analysis revealed no significant differences in response and remission rates between iTBS and HF-rTMS, with odds ratios close to 1. These results align with those of recent sham-controlled RCTs directly comparing these treatment modalities (van't Wout-Frank et al, 2021). Our findings indicate that iTBS could achieve antidepressant outcomes comparable to the standard HF-rTMS protocol when applied to the left DLPFC at intensities of 80–120% resting motor threshold. iTBS offers practical benefits such as shorter daily treatment sessions that may improve tolerability and accessibility over HF-rTMS (Duarte et al, 2020; Liu et al, 2022).

The overall response rates were around 40% for both active stimulations in our analysis. This moderate efficacy could potentially be attributed to the hetero-

geneity of individual patient attributes, encompassing age, gender, illness severity, and past treatment regimens. These variances may engender disparities in the responsiveness of distinct patients to neuromodulation therapy, consequently impacting the overall efficacy of treatment (Lindsey et al, 2023; Pulopulos et al, 2019). Further optimizing iTBS protocols and identifying biomarkers to select ideal candidates may help improve clinical outcomes (Walther et al, 2024). The remission rates based on rating scale thresholds were generally lower than response rates, implying that many patients still had residual symptoms post-treatment. Longer follow-up periods could provide more insights into delayed and sustained effects of both rTMS modalities.

As expected, iTBS and HF-rTMS both demonstrated clear superiority over sham stimulation. The odds of treatment response were 4–5 times higher for active versus sham groups. This verifies the efficacy of left DLPFC rTMS for MDD and confirms that the effects extend from HF-rTMS to the novel iTBS modality. Consistent sham-controlled evidence builds confidence for the antidepressant properties specific to neuromodulation rather than placebo factors. Our findings corroborate recent meta-analyses showing robust effects of iTBS over sham TMS (Yu et al, 2020). No significant differences were found between iTBS and HF-rTMS for common adverse events such as headache, which occurred at comparable rates across groups. Both modalities have been established as safe treatment options for MDD in previous reviews (Chung et al, 2015; Kishi et al, 2023; Philip et al, 2022; Tsai et al, 2023). iTBS could have safety advantages over HF-rTMS due to the ultra-brief magnetic pulses and shorter protocols. Few studies directly compared safety outcomes between these stimulations. More comprehensive data collection on side effects would be informative. Overall, rTMS is considered well-tolerated especially under proper monitoring (Chou et al, 2021; Chu et al, 2023; De Risio et al, 2020; Moffa et al, 2022).

There are certain limitations to this meta-analysis. The small number of eligible RCTs and their variable intervention designs limited subgroup analyses. Many studies had modest sample sizes. Only English-language articles were included. Publication bias was not detected but could not be ruled out. There was predominantly short-term follow-up after acute treatment courses. Additionally, the sham coils used may not have been optimal for blinding. Finally, we were unable to examine neurocognitive effects, predictor variables, and cost-effectiveness. Future research should prioritize an examination of patients' quality of life to comprehensively evaluate the efficacy and significance of the interventions under study.

Conclusion

In conclusion, this meta-analysis found that iTBS and HF-rTMS have comparable efficacy and safety in the treatment of MDD. Both neuromodulation techniques are superior to sham stimulation. iTBS could be considered an alternative to HF-rTMS with the advantages of shorter session duration and likely better tolerability. iTBS has shown advantages in several ways, with the daily duration of iTBS treatment being significantly shorter, usually only 3 to 6 minutes, compared to 20 to

30 minutes for HF-rTMS. In addition, iTBS is better tolerated by patients, possibly due to the shorter duration of treatment and fewer side effects (Battle, 2013). Our findings provide evidence to support the use of iTBS protocols for MDD in clinical practice and research. Further large-scale RCTs directly comparing iTBS and HF-rTMS would help strengthen the conclusions. There remains opportunity for future studies to identify optimal responders, refine targeted stimulation parameters, and improve long-term remission rates.

Key Points

- This meta-analysis found no significant difference in efficacy between iTBS and HF-rTMS for treating major depressive disorder (MDD).
- Both iTBS and HF-rTMS were significantly more effective than sham treatment.
- The safety profiles of iTBS and HF-rTMS, including common side effects like headaches, were comparable.
- iTBS offers the advantage of shorter daily treatment duration compared to HF-rTMS.

Availability of Data and Materials

The corresponding author will provide the data that underpin the study's conclusions with a reasonable application.

Author Contributions

YS designed the study, and both authors conducted the study. LLF collected and analyzed the data. LLF participated in drafting the manuscript, and both authors contributed to the critical revision of the manuscript for important intellectual content. Both authors gave final approval for the version to be published. Both authors participated fully in the work, take public responsibility for appropriate portions of the content, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or completeness of any part of the work are appropriately investigated and resolved.

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://www.magonlinelibrary.com/doi/suppl/10.12968/hmed.2024.0157.

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