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*Review Article*

# Repetitive transcranial magnetic stimulation on primary insomnia electrophysiology detected by polysomnography: a systematic review and meta-analysis

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**Abstract:** Objective: This systematic review was performed to examine the efficacy of repetitive transcranial magnetic stimulation (rTMS) on the electrophysiology results of patients with primary insomnia based on prior polysomnography research. Methods: We performed a comprehensive literature search for randomized clinical trials evaluating the efficacy of rTMS by polysomnography addressing primary insomnia, and performed meta-analyses according to Cochrane guidelines. Results: We found that rTMS significantly improved the sleep architecture of primary insomnia patients. The pooled effect size of latency to onset of persistent sleep (LPS) was -6.90 (95% confidence interval (CI): -11.66, 2.15), of wakefulness after persistent sleep onset (WASO) -30.48 (95% CI: -43.13, -17.82), of number of awakenings (NA) -1.23 (95% CI: -1.84, -0.61), of non-rapid eye movement sleep-1 (NREM-1) -1.40 (95% CI: -2.43, -0.37), of total sleep time (TST) 35.19 (95% CI: 19.83, 50.55), of sleep efficiency (SE) 7.74% (95% CI: 3.87%, 11.70%), of NREM-3 2.49 (95% CI: 1.53, 3.45), and of rapid eye movement (REM) 1.33 (95% CI: 0.75, 1.91). In contrast, there was no significant effect on NREM-2 -0.47 (95% CI: -1.30, 0.36). Conclusion: The rTMS may be an effective technique to improve sleep architecture in the treatment of primary insomnia. However, the typical effect was uncertain due to heterogeneity. It may be valuable for further research to explore a more acceptable methodology, such as adequate blinding and allocation of concealment so as to provide more objective evidence.

**Keywords:** Primary insomnia, repetitive transcranial magnetic stimulation, polysomnography, meta-analysis

## Introduction

Primary insomnia, one of the most common types of sleep disorders [1], refers to difficulties in falling asleep, in sleep maintenance, or in early awakening, accompanied by fatigue, inattention, emotional instability, and other daytime social function impairment lasting for more than 3 months. Repetitive transcranial magnetic stimulation (rTMS) technology has the advantages of being non-invasive, simple, and has subjective effectiveness (the evaluation of Pittsburgh Sleep Quality Index for example), and is more and more used in the treatment of insomnia [2-7]. However, there are many controversies about the objective efficacy of rTMS. Massimini, et al. [4] showed that rTMS may be used as a physical means to induce slow waves and improve sleep. However, Zhang, et al. [6] found that rTMS had no effects on latency to onset of persistent sleep (LPS), wakefulness after persistent sleep onset (WASO), and total sleep time (TST) through sleep diaries and actigraphs; while Jiang, et al. [5] found that the effect of rTMS on non-rapid eye movement sleep (NREM)-3 sleep was primarily due to a placebo effect. It is therefore not clear what the effects of rTMS on primary insomnia are at each stage of sleep. Considering that polysomnography (PSG) is currently the most reliable examination technology to verify sleep architecture, we performed a systematic literature review and meta-analysis to further elucidate the objective clinical effect of rTMS on polysomnography monitoring of primary insomnia patients.

## Methods

This meta-analysis protocol has been registered at PROSPERO website and the number is CRD4202020569.

*Search strategy*

We systematically searched the electronic databases PubMed, EMBASE, Cochrane Library, Chinese Biomedical Literature Database, China National Knowledge Infrastructure, WANFANG Database, and the Chinese Scientific Journal Database, from inception to September 1, 2020, according to the Preferred Reporting Items for Systematic Review and Meta-Analysis statement [8]. The search terms entered were "primary insomnia" or "chronic insomnia" or "Sleep Initiation and Maintenance Disorders" or "nonorganic insomnia" or "insomnia" and "transcranial magnetic stimulation" or "repetitive transcranial magnetic stimulation" or "TMS" or "rTMS" and "randomized controlled trial" OR "randomized" OR "placebo". According to different databases, retrieval modes were able to combine keywords with free words to perform comprehensive searches. We also manually searched for ongoing trial registers in the trial registry websites Chinese Clinical Trial Registry and ClinicalTrials.gov to ensure the comprehensiveness of the search without restrictions on country, publication status, or year of publication.

*Inclusion criteria*

We used the PICO [9] (P = Patients, I = Intervention, C = Comparison, O = Outcomes) method to define the major components of this systematic review.

P: Adults above 18 years of age with primary insomnia were diagnosed by standard criteria such as International Classification of Diseases, Tenth Edition (ICD-10) [10], Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [11] or Fifth Edition (DSM-V) [12], International Classification of Sleep Disorders, Third Edition (ICSD-III) [13], or Chinese Classification and Diagnostic Criteria of Mental Disorders, Third Edition (CCMD-III) [14].

I: Intervention applied in the experimental group was rTMS alone or in combination with other therapies. The intensity of stimulation, frequency, target area, localisation method, dose, and duration were not limited [9].

C: Comparison with sham rTMS, or absence of rTMS.

O: Polysomnography: sleep parameters such as TST, SE%, LPS, WASO, NA, NREM-1, NREM-2, NREM-3, REM, or percentage of TST spent in each sleep stage (NREM-1, NREM-2, NREM-3, and REM).

Other eligible criteria: Articles were included if they were published in English or Chinese, and were randomized controlled trials (RCTs).

*Exclusion criteria*

Articles were excluded if (1) they were duplicate studies; (2) the studies were case reports, review articles, or animal experiments; (3) outcomes were not PSG parameters; (4) or it was impossible to obtain valid data.

*Data extraction and quality assessment*

Authors YZ and YF independently searched and collected literature conforming to the inclusion criteria from the databases. **Figure 1** shows the flow chart of the study selection process. Inconsistency was discussed with the third author, JL. We then extracted the following data independently: author, publication year, sample size, age of participants, diagnostic criteria, disorder duration, interventions, comparison, treatment duration, "first night" effect management, and outcomes. YZ and YF independently assessed the quality of the included studies based on guidance in the Cochrane Handbook for Systematic Reviews of Interventions [15] from seven aspects including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Each aspect was scored as having low, unclear, or high risk of bias.

*Data analysis and synthesis*

We used Stata 15.1 and Cochrane Review Manager V.5.3 programs in the meta-analysis. Mean differences (MD) or standardized mean differences (SMD) as well as 95% confidence

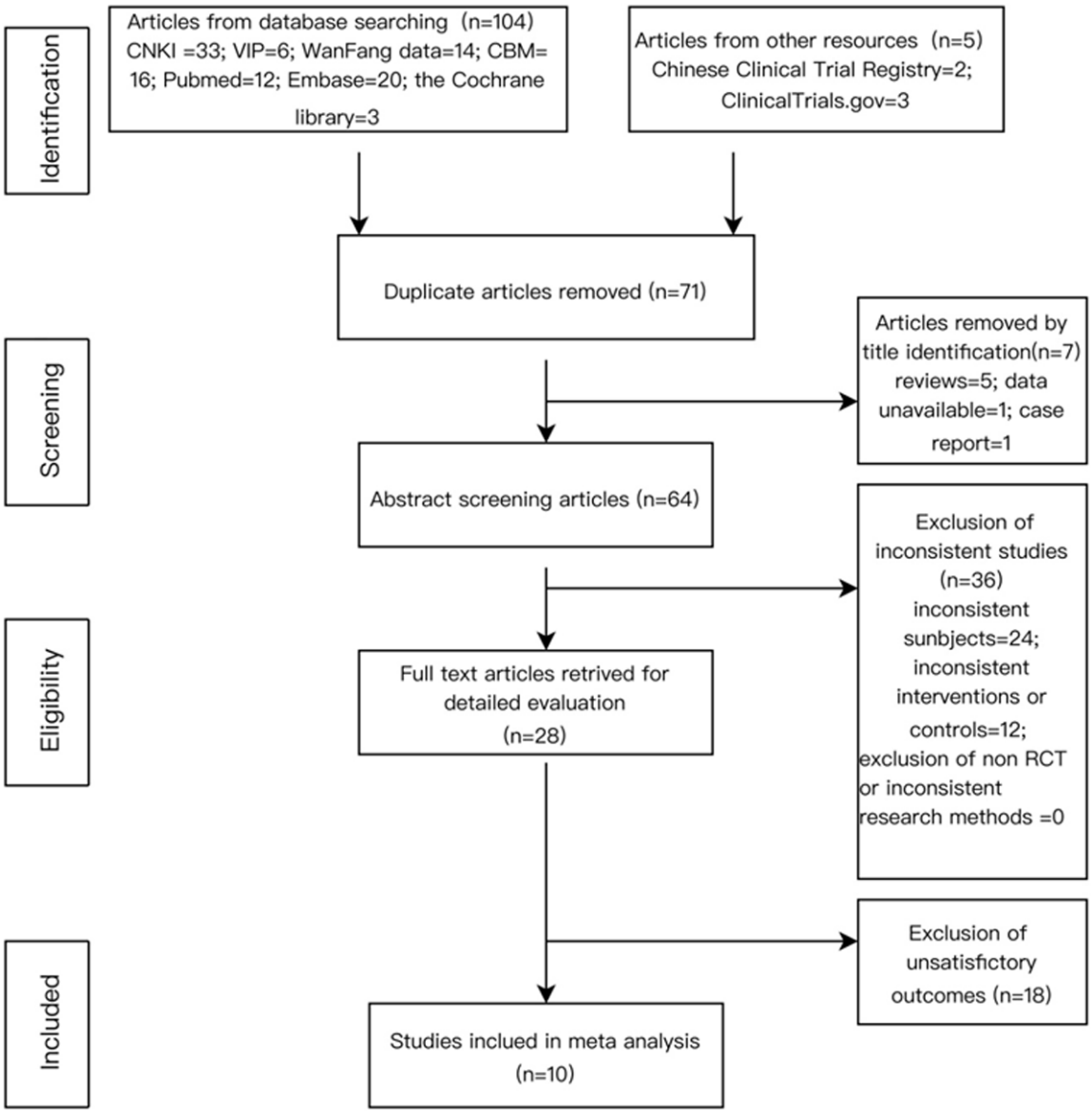


**Figure 1.** PRISMA flow diagram. Abbreviation: RCT: randomized controlled trial.

intervals (CIs) were computed for continuous data. We considered $P<0.05$ as statistically significant, and we used the $I^2$ and Cochran-Q test to assess heterogeneity between studies [16]. When $P>0.1$ or $I^2<50\%$, we used a fixed-effects model, while effects at $P<0.1$ or $I^2\geq50\%$ were modelled using random effects. If $P\leq0.1$, we considered statistical heterogeneity, and subgroup and sensitivity analyses were conducted on the following factors: diagnostic criteria, age groups, disorder duration, treatment duration, differences in basic treatment, and whether the studies managed the "first night" effect. Due to changes in the sleep environment during the PSG examination, connecting electrodes and wires to the head, tying the thoracoabdominal belt and/or pasting the oronasal airflow tube, may have caused discomfort and affected the results of sleep monitoring, in what is called the first night effect. The results of the meta-analysis were visualized as forest plots. Publication bias was assessed using a funnel plot [17] when a parameter reported ≥10 studies in the meta-analysis, and was then examined using both Begg's and Egger's tests [17, 18].

**Table 1.** Characteristics of the included studies

| Study and location | Sample (E/C) | Age (years) | | Gender (M/F) | Criteria | Disorder duration (E/C) | Interventions | Comparison | Treatment duration | "First night" effect management | Outcomes |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | E | C | | | | | | | | |
| Shen and Wang [25], China | 46/39 | 40.6±9.2 | 41.4±8.9 | 42/56 | ICD-10 | 7.4±5.6/8.1±6.2 (months) | rTMS | sham rTMS | Four weeks, 20 times | Yes | TST, SE, LPS, WASO, REM, NREM-1, NREM-2, NREM-3 |
| Liang, et al. [28], China | 24/24 | 24.71±7.52 | 23.89±6.85 | 41/7 | CCMD-III | 4.68±3.26/ 4.24±2.81 (months) | rTMS+Alprazolam+ Psycho-therapy+ Relaxation training | sham rTMS+Alprazolam +Psychotherapy+Relaxation training | Three weeks, 15 times | No | TST, SE, LPS, NA, REM, NREM-1, NREM-2, NREM-3 |
| Yu, et al. [23], China | 37/38 | 67.59± 3.05 | 66.07±3.81 | 29/46 | DSM-IV | 9.34±4.49/ 9.42±4.58 (months) | rTMS+Zolpidem | sham rTMS+Zolpidem | Four weeks, 20 times | Yes | TST, SE, LPS, WASO, REM, NREM-1, NREM-2, NREM-3 |
| Yu, et al. [27], China | 27/28 | 44.6±9.1 | 46.1±7.8 | 17/38 | DSM-IV | 9.1±4.3/9.3±4.7 (months) | rTMS+Zolpidem | sham rTMS+Zolpidem | Four weeks, 20 times | Yes | TST, SE, LPS, WASO, REM, NREM-1, NREM-2, NREM-3 |
| Xie, et al. [26], China | 77/76 | 34.58±12.13 | 36.28±12.36 | 45/115* | ICSD-III | 9.84±1.33/ 9.75±1.30 (months) | rTMS+Zolpidem | sham rTMS+Zolpidem | Four weeks, 20 times | No | TST, SE, LPS, WASO, REM, NREM-1, NREM-2, NREM-3 |
| Anniwan, et al. [19], China | 30/30 | 48.30±6.07 | 48.75±6.16 | 29/31 | ICD-10 | 5.34±0.16/ 7.43±0.11 (years) | rTMS | sham rTMS | Two weeks, 14 times | Yes | TST, SE, LPS, NA, WASO, REM, NREM-1, NREM-2, NREM-3 |
| Chen, et al. [24], China | 42/42 | 40.6±9.2 | 41.4±8.9 | 49/35 | CCMD-III | 11.3±3.7/10.9±3.8 (months) | rTMS+Zolpidem | Zolpidem | Two weeks, 14 times | No | TST, SE, LPS, NA, WASO, REM, NREM-1, NREM-2, NREM-3 |
| Li, et al. [22], China | 60/60 | 43.56±21.1 | 41.57±22.95 | 51/69 | ICSD-III | 15.98±5.66/ 16.02±5.64 (years) | rTMS+Lorazepam | sham rTMS+Lorazepam | Four weeks, 20 times | Yes | TST, SE, LPS, NA, WASO |
| Yao, et al. [20], China | 50/50 | 56.3±5.1 | 56.3±5.1 | 43/57 | DSM-IV | 11.4±5.6/12.1±6.2 (months) | rTMS+CBTI | CBTI | Four weeks, 20 times | Yes | TST, SE, LPS |
| Liu, et al. [21], China | 30/30 | 41.3±8.6 | 40.2±7.9 | 28/32 | DSM-V | ≥6 (months) | rTMS+benzodiazepines drugs | sham rTMS+benzodiazepines drugs | Four weeks, 28 times | No | LPS, NA, WASO |

Abbreviations: C: control group, CCMD-III: Chinese Classification and Diagnostic Criteria of Mental Disorders, Third Edition, DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, DSM-V: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, E: experimental group, F: female, ICD-10: International Classification of Diseases, Tenth Edition, ICSD-III: International Classification of Sleep Disorders, Third Edition, LPS: latency to onset of persistent sleep, M: male, NA: number of awakening, NREM: non-rapid eye movement sleep, REM: rapid eye movement, rTMS: repetitive transcranial magnetic stimulation, SE: sleep efficiency, TST: total sleep time, WASO: wakefulness after persistent sleep onset.
* Including 7 patients lost to follow-up.

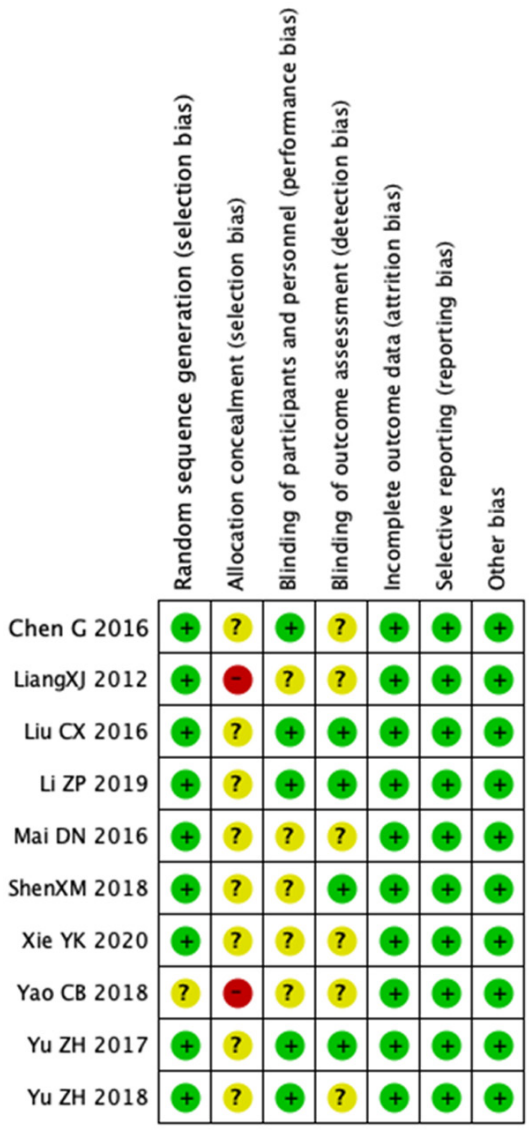


**Figure 2.** Risk of bias across each study [19-28].

## Results

*Characteristics of studies included*

We identified 10 studies [19-28] meeting the inclusion and exclusion criteria. A total of 840 primary insomnia patients were included. Among the 10 studies, 9 involved 18-60 year old patients, and in only 1 study [23] included patients with a mean age above 65 years. ICD-10 was taken as the diagnostic criteria for the two studies [19, 25], DSM-IV for three studies [21, 23, 27], DSM-V in one study [20], CCMD-III for two studies [24, 28], and ICSD-III for two studies [22, 26]. Among the 10 studies, we found that disorder duration in two studies [19, 22] was greater than 5 years, while that of other eight studies was about 1 year in duration. Eight studies [19, 21-23, 25, 26, 28] used sham rTMS as their control group, and the other two studies [20, 24] did not include rTMS in their control groups. Among the 10 studies, seven [21-24, 26-28] used hypnotics in the basic treatments, including benzodiazepines [21, 22, 28] and non-benzodiazepines [23, 24, 26, 27]. Two studies' [19, 24] had intervention periods that lasted two weeks, one [28] lasted 3 weeks, and seven [20-23, 25-27] lasted 4 weeks. Six [19, 20, 22, 23, 25, 27] studies referred to the management of the "first night" effect during polysomnography, while the other four did not refer to it. LPS was reported in all studies, TST and SE% were reported in nine studies [19, 20, 22-28], WASO was reported in eight studies [19, 21-27], and NA was reported in five studies [19, 21, 22, 24, 28]. Seven studies [19, 23-28] reported complete sleep stages, in which three studies [19, 24, 28] reported in the form of percentage of total sleep time, and four [23, 25-27] reported in the form of minutes. **Table 1** shows a summary of these characteristics.

*Assessing risk of bias in included studies*

Two authors (YZ and YF) assessed the risk of bias in the 10 selected studies using Review Manager 15.3. Inconsistency was discussed with the third author (JL). Nine studies [19, 21-28] that reported adequate methods of random sequence generation were rated as having a low risk of bias, and one [20] reported that it was a randomized controlled study, but did not clarify about its methods of random sequence generation, so it was assessed as having unclear risk. Two studies [20, 28] that reported no allocation concealment were rated as having a high risk of bias, while the other eight [19, 21-27] did not mention it and so were assessed as having unclear risk. Among the 10 RCTs, five [21-24, 27] described blinding of participants and personnel, four [21, 22, 25, 27] described blinding of outcome assessments, while the others were unclear. Each RCT completely reported the main outcome data: four studies [23, 25-27] reported follow-up, including dropouts and the reasons for dropout, and so were designated with low risk of attrition bias. None were found containing bias for selective reporting. **Figure 2** shows the risk of bias.

**Table 2.** Summary of pooled effects of rTMS on PSG parameters for primary insomnia

| Outcomes | Heterogeneity ($I^2$) | MD/SMD | 95% CI | Z | P |
|---|---|---|---|---|---|
| TST [19, 20, 22-28] | P<0.00001; $I^2$=80% | 35.19 | 19.83, 50.55 | 4.49 | <0.00001 |
| SE (%) [19, 20, 22-28] | P<0.00001; $I^2$=92% | 7.74 | 3.87, 11.70 | 3.83 | 0.0001 |
| LPS [19-28] | P<0.00001; $I^2$=95% | -6.90 | -11.66, 2.15 | 2.85 | 0.004 |
| NREM-1 [19, 23-28] | P<0.00001; $I^2$=96% | -1.40 | -2.43, -0.37 | 2.67 | 0.008 |
| NREM-2 [19, 23-28] | P<0.00001; $I^2$=95% | -0.47 | -1.30, 0.36 | 1.10 | 0.27 |
| NREM-3 [19, 23-28] | P<0.00001; $I^2$=94% | 2.49 | 1.53, 3.45 | 5.07 | <0.00001 |
| REM [19, 23-28] | P<0.00001; $I^2$=89% | 1.33 | 0.75, 1.91 | 4.48 | <0.00001 |
| NA [19, 21, 22, 24, 28] | P=0.35; $I^2$=10% | -1.23 | -1.84, -0.61 | 3.92 | <0.0001 |
| WASO [19, 21-27] | P<0.00001; $I^2$=92% | -30.48 | -43.13, -17.82 | 4.72 | <0.00001 |

Abbreviations: CI: confidence interval, LPS: latency to onset of persistent sleep, MD: mean differences, NA: number of awakening, NREM: non-rapid eye movement sleep, PSG: polysomnography, REM: rapid eye movement, rTMS: repetitive transcranial magnetic stimulation, SE: sleep efficiency, SMD: standardized mean differences, TST: total sleep time, WASO: wakefulness after persistent sleep onset.

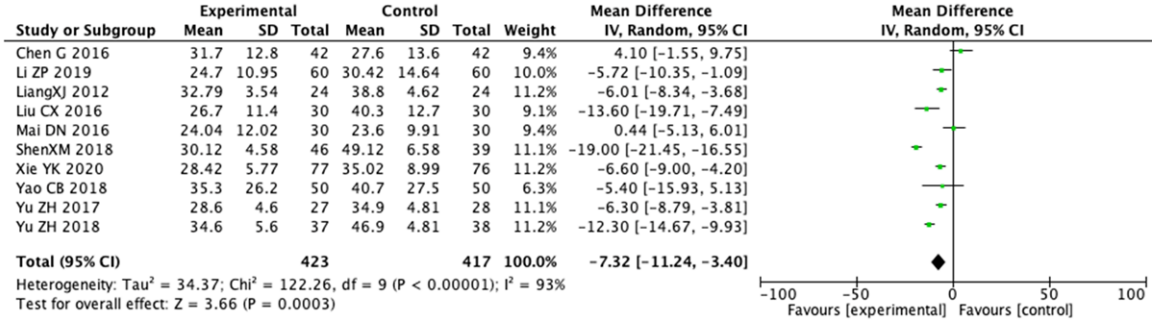


**Figure 3.** Pooled effect and heterogeneity of LPS [19-28]. Abbreviations: CI: confidence interval, IV: inverse variance, LPS: latency to onset of persistent sleep, SD: standard deviation.

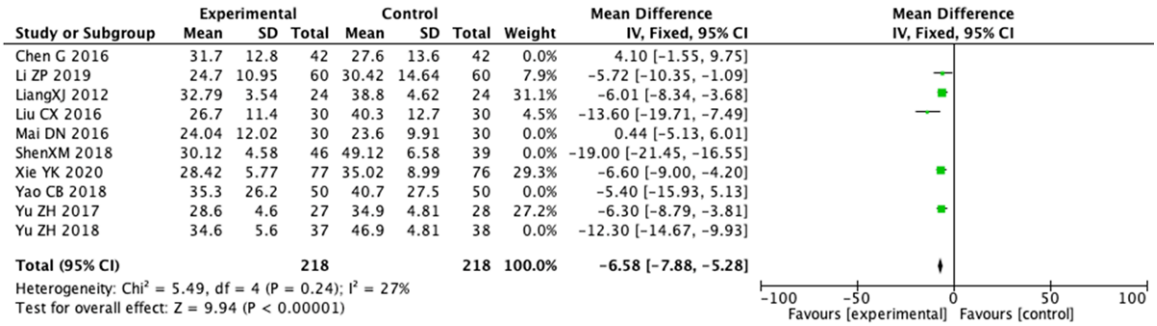


**Figure 4.** Heterogeneity effects of LPS disappeared after controlling for advanced age, short treatment duration, and no usage of hypnotics in basic treatment [19-28]. Abbreviations: CI: confidence interval, IV: inverse variance, LPS: latency to onset of persistent sleep, SD: standard deviation.

*Efficacy of rTMS*

For primary insomnia, rTMS was associated with reduced LPS, WASO, NA, and NREM-1, increasing TST, SE, NREM-3, and REM sleep. The efficacy of NREM-2 was not significant (95% CI: -1.30, 0.36; P=0.27, **Table 2**).

Sensitivity analysis revealed that the heterogeneity of different parameters may stem from many different factors. For example, the heterogeneity of LPS may be due to older patients, short treatment duration, and usage of hypnotics in basic treatment, from which elimination could remove heterogeneity (**Figures 3** and **4**).

**Table 3.** Subgroup analysis for disorder duration

| Outcomes | Heterogeneity ($I^2$) | MD/SMD | 95% CI | Z | P |
|---|---|---|---|---|---|
| More than 5 years | | | | | |
| TST [19, 22] | 0% | 17.83 | 4.60, 31.07 | 2.64 | 0.008 |
| SE (%) [19, 22] | 0% | 2.54 | 1.23, 3.84 | 3.81 | 0.0001 |
| LPS [19, 22] | 64% | -2.84 | -8.87, 3.18 | 0.93 | 0.35 |
| NA [19, 22] | 0% | -1.38 | -2.56, -0.20 | 2.29 | 0.02 |
| WASO [19, 22] | 0% | -8.86 | -16.75, -0.97 | 2.2 | 0.03 |
| One year more or less | | | | | |
| TST [20, 23-28] | 77% | 39.80 | 23.45, 56.15 | 4.77 | <0.00001 |
| SE (%) [20, 23-28] | 80% | 9.48 | 6.20, 12.76 | 5.67 | <0.00001 |
| LPS [20, 21, 23-28] | 94% | -8.43 | -12.79, -4.07 | 3.79 | 0.0002 |
| NA [21, 24, 28] | 51% | -1.05 | -2.14, 0.03 | 1.91 | 0.06 |
| WASO [21, 23-27] | 91% | -37.04 | -50.52, -23.55 | 5.38 | <0.00001 |

Abbreviations: CI: confidence interval, LPS: latency to onset of persistent sleep, MD: mean differences, NA: number of awakening, SE: sleep efficiency, SMD: standardized mean differences, TST: total sleep time, WASO: wakefulness after persistent sleep onset.

**Table 4.** Subgroup analysis for treatment duration

| Outcomes | Heterogeneity ($I^2$) | MD/SMD | 95% CI | Z | P |
|---|---|---|---|---|---|
| Short treatment duration (2-3 weeks, 14-15 times) | | | | | |
| TST [19, 24, 28] | 35% | 8.84 | -8.41, 26.08 | 1.00 | 0.32 |
| SE (%) [19, 24, 28] | 75% | 2.75 | -3.72, 9.23 | 0.83 | 0.40 |
| LPS [19, 24, 28] | 85% | -0.88 | -7.48, 5.71 | 0.26 | 0.79 |
| NA [19, 24, 28] | 41% | -0.94 | -1.77, -0.11 | 2.21 | 0.03 |
| WASO [19, 24] | 0% | -0.28 | -23.12, 22.55 | 0.02 | 0.98 |
| NREM-1 [19, 24, 28] | 60% | -0.54 | -2.70, 1.63 | 0.49 | 0.63 |
| NREM-2 [19, 24, 28] | 94% | -1.29 | -2.64, 0.06 | 2.95 | 0.06 |
| NREM-3 [19, 24, 28] | 92% | 5.55 | 1.86, 9.23 | 2.95 | 0.003 |
| REM [19, 24, 28] | 0% | 5.52 | 3.97, 7.07 | 6.98 | <0.00001 |
| Long treatment duration (4 weeks, 20-28 times) | | | | | |
| TST [20, 22, 23, 25-27] | 78% | 45.71 | 30.27, 61.16 | 5.80 | <0.00001 |
| SE (%) [20, 22, 23, 25-27] | 94% | 9.95 | 4.96, 14.94 | 3.91 | <0.0001 |
| LPS [20-23, 25-27] | 92% | -10.13 | -14.53, 5.74 | 4.52 | <0.00001 |
| NA [21, 22] | 0% | -1.57 | -2.47, -0.66 | 3.38 | 0.0007 |
| WASO [21-23, 25-27] | 94% | -35.95 | -49.57, -22.32 | 5.17 | <0.00001 |
| NREM-1 [23, 25-27] | 99% | -13.04 | -25.95, -0.12 | 1.98 | 0.05 |
| NREM-2 [23, 25-27] | 90% | 0.14 | -0.53, 0.82 | 0.41 | 0.68 |
| NREM-3 [23, 25-27] | 93% | 30.15 | 23.08, 37.22 | 8.36 | <0.00001 |
| REM [23, 25-27] | 0% | 27.10 | 24.45, 29.75 | 20.06 | <0.00001 |

Abbreviations: CI: confidence interval, LPS: latency to onset of persistent sleep, MD: mean differences, NA: number of awakening, NREM: non-rapid eye movement sleep, REM: rapid eye movement, SE: sleep efficiency, SMD: standardized mean differences, TST: total sleep time, WASO: wakefulness after persistent sleep onset.

Depending on the data permitted, subgroup analyses were computed from disorder duration (more than 5 years as a group & other studies as a group for the disorder duration were one year more or less), treatment duration (2-3 weeks, 14-15 times & 4 weeks, 20-28 times), "first night" effect management (non-management of "first night" effect & management "first night" effect) and hypnotics application in basic treatment (non-hypnotics in basic treatment & combination of hypnotics). Two studies [19, 22] reported patients with disorder duration longer than 5 years, while others reported one year more or less. The result revealed rTMS had no effect on LPS (MD: -2.84, 95% CI: -8.87, 3.18, P=0.35, **Table 3**) in the long disorder duration

**Table 5.** Subgroup analysis for "first night" effect

| Outcomes | Heterogeneity ($I^2$) | MD/SMD | 95% CI | Z | P |
|---|---|---|---|---|---|
| Subgroup of non management of "first night" effect | | | | | |
| TST [24, 26, 28] | 88% | 19.2 | -20.21, 58.61 | 0.95 | 0.34 |
| SE (%) [24, 26, 28] | 90% | 6.34 | -1.51, 14.37 | 1.59 | 0.11 |
| LPS [21, 24, 26, 28] | 84% | -5.56 | -9.96, -1.17 | 2.48 | 0.01 |
| NA [21, 24, 28] | 51% | -1.05 | -2.41, 0.03 | 1.91 | 0.06 |
| WASO [21, 24, 26] | 92% | -22.80 | −38.27, -7.32 | 2.89 | 0.004 |
| NREM-1 [24, 26, 28] | 96% | -0.87 | -2.25, 0.51 | 1.24 | 0.22 |
| NREM-2 [24, 26, 28] | 97% | -0.31 | -1.98, 1.36 | 0.37 | 0.72 |
| NREM-3 [24, 26, 28] | 96% | 1.97 | 0.36, 3.58 | 2.4 | 0.02 |
| REM [24, 26, 28] | 96% | 1.51 | 0.11, 2.92 | 2.11 | 0.04 |
| Subgroup of management of "first night" effect | | | | | |
| TST [19, 20, 22, 23, 25, 27] | 78% | 41.74 | 24.25, 59.22 | 4.68 | <0.00001 |
| SE (%) [19, 20, 22, 23, 25, 27] | 93% | 8.33 | 3.30, 13.36 | 3.25 | 0.001 |
| LPS [19, 20, 22, 23, 25, 27] | 94% | -8.47 | -14.08, -2.87 | 2.96 | 0.003 |
| NA [19, 22] | 0% | -1.38 | -2.56, -0.20 | 2.29 | 0.02 |
| WASO [19, 22, 23, 25, 27] | 94% | -35.86 | -62.39, -9.33 | 2.65 | 0.008 |
| NREM-1 [19, 23, 25, 27] | 97% | -1.85 | -3.64, -0.06 | 2.02 | 0.04 |
| NREM-2 [19, 23, 25, 27] | 93% | -0.59 | -1.58, 0.40 | 1.17 | 0.24 |
| NREM-3 [19, 23, 25, 27] | 99% | 24.91 | 8.45, 41.38 | 2.97 | 0.003 |
| REM [19, 23, 25, 27] | 0% | 1.18 | 0.92, 1.44 | 8.98 | <0.00001 |

Abbreviations: CI: confidence interval, LPS: latency to onset of persistent sleep, MD: mean differences, NA: number of awakening, NREM: non-rapid eye movement sleep, REM: rapid eye movement, SE: sleep efficiency, SMD: standardized mean differences, TST: total sleep time, WASO: wakefulness after persistent sleep onset.

**Table 6.** Subgroup analysis for hypnotics

| Outcomes | Heterogeneity ($I^2$) | MD/SMD | 95% CI | Z | P |
|---|---|---|---|---|---|
| Subgroup of no hypnotics applied in basic treatment | | | | | |
| TST [19, 20, 25] | 0% | 40.75 | 26.18, 55.32 | 5.48 | <0.00001 |
| SE (%) [19, 20, 25] | 79% | 8.56 | 2.33, 14.79 | 2.69 | 0.007 |
| LPS [19, 20, 25] | 95% | -8.24 | -22.83, 6.34 | 1.11 | 0.27 |
| WASO [19, 25] | 93% | -43.35 | -117.95, 31.24 | 1.14 | 0.25 |
| NREM-1 [19, 25] | 99% | -3.01 | -9.11, 3.09 | 0.97 | 0.33 |
| NREM-2 [19, 25] | 98% | -0.79 | -3.26, 1.69 | 0.62 | 0.53 |
| NREM-3 [19, 25] | 96% | 3.01 | 0.53, 5.49 | 2.38 | 0.02 |
| REM [19, 25] | 0% | 1.11 | 0.76, 1.47 | 6.21 | <0.00001 |
| Subgroup of hypnotics applied in basic treatment | | | | | |
| TST [22-24, 26-28] | 87% | 33.49 | 12.43, 54.56 | 3.12 | 0.002 |
| SE (%) [22-24, 26-28] | 93% | 7.42 | 2.53, 12.32 | 2.97 | 0.003 |
| LPS [21-24, 26-28] | 85% | -6.81 | -9.88, -3.75 | 4.36 | <0.0001 |
| WASO [21-24, 26, 27] | 91% | -25.62 | -37.32, -13.92 | 4.29 | <0.0001 |
| NREM-1 [23, 24, 26-28] | 93% | -0.85 | -1.63, -0.06 | 2.11 | 0.03 |
| NREM-2 [23, 24, 26-28] | 95% | -0.35 | -1.32, 0.62 | 0.71 | 0.48 |
| NREM-3 [23, 24, 26-28] | 95% | 2.29 | 1.15, 3.42 | 3.95 | <0.0001 |
| REM [23, 24, 26-28] | 92% | 1.41 | 0.59, 2.23 | 3.36 | 0.0008 |

Abbreviations: CI: confidence interval, LPS: latency to onset of persistent sleep, MD: mean differences, NA: number of awakening, NREM: non-rapid eye movement sleep, REM: rapid eye movement, SE: sleep efficiency, SMD: standardized mean differences, TST: total sleep time, WASO: wakefulness after persistent sleep onset.

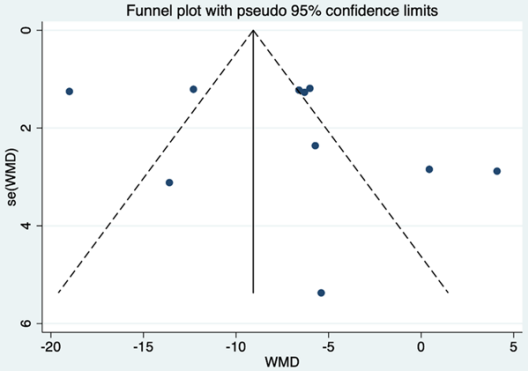


**Figure 5.** Funnel plot for publication bias. Abbreviation: WMD: weighted mean difference.

group. Among the 10 studies, three [19, 24, 28] reported 2-3 weeks of treatment, and the pooled effects revealed that rTMS has no effect on TST, SE, LPS, WASO, NREM-1 and NREM-2, but had an effect on NREM-3 and REM sleep (**Table 4**). This result suggests that 4 weeks of rTMS treatment could be better than 2-3 weeks. Four studies [21, 24, 26, 28] did not discuss management of the "first night" effect during polysomnography, and after pooling them, we found that rTMS had no effect on TST, SE, NA, and NREM-1 (**Table 5**). It suggested that polysomnograph's "first night" effect was prone to TST, SE, NA, and NREM-1 and might not affect NREM-3 and REM sleep. Three studies [19, 20, 25] did not apply hypnotics in basic treatment for either experimental group or control. We pooled this subgroup and found that rTMS has no effect on LPS and WASO (**Table 6**). Thus, the combination of both rTMS and hypnotics for primary insomnia may be a better therapy, especially for patients with difficulties in falling asleep or sleep maintenance.

*Addressing publication bias*

Publication bias was assessed by graphing funnel plots (**Figure 5**) and examining both Begg's and Egger's tests. Parameter LPS was tested as it was reported by 10 studies, while other outcome parameters were not tested as they were reported fewer [18]. The results revealed that there was no significant publication bias among the papers (Begg's test: Z = 0.18, P = 0.858; Egger's test: t = 1.01, P = 0.344).

## Discussion

In the current study, we found that rTMS improved patients' sleep architecture in the treatment of primary insomnia, and most effective with prolonged treatment to 4 weeks and simultaneously applied with hypnotics. We also observed that it was more effective for patients with a short duration course (1 year or less) compared with patients with long courses of the disorder. We also found that rTMS has an effect on NREM-1, in contrast to another review [29]. The reason for this may be due to the application of hypnotics, course of disorder, or treatment duration. The potential mechanisms of rTMS for primary insomnia may involve inhibiting the hyper-arousal of the cerebral cortex, affecting metabolism and hormone levels in the body, and stimulating hippocampal neurogenesis [2, 30, 31]. However, rTMS showed no effects on NREM-2, which could be valuable for further study. One limitation is that all studies included in the review were from China. We found some scholars from other countries used actigraphy as a tool to evaluate the objective effect of rTMS on sleep improvement. Among them, van Dijk, et al. [32] found that rTMS improved Parkinson's sleep fragmentation and sleep efficiency and reduced the average duration of neurological awakes. While more studies [6, 33, 34] found sleep variables assessed by actigraphy did not show significant changes after the treatment of rTMS. While most studies [5, 6, 33, 34] approved the subjective improvement effect of rTMS on sleep, such as Athens Insomnia Scale or Pittsburgh Sleep Quality Index. In addition to the placebo effect, another reason for this contradiction could possibly be that rTMS changed the sleep architecture, especially the changes of NREM-3 and REM sleep which were found as significant differences in each subgroup in this study. However, this kind of change can't be revealed by actigraphy. In addition, the papers reviewed in this study could have more risk of bias in terms of allocation concealment and blinding methods, making it necessary to conduct improved methodological clinical research in the future.

## Conclusion

rTMS may be effective in improving sleep architecture in the treatment of primary insomnia, as well as for sleep initiation disorder, sleep maintenance disorder, and early awakening. However, for more definitive assessments of clinical effects in the future, our subgroup analyses suggest that it may be reasonable to avoid studies that consider the PSG "first night

effect", select patients with a shorter course of disorder, extend the treatment duration longer than two weeks, and use rTMS in combination with hypnotics.

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## Disclosure of conflict of interest

None.

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