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ORIGINAL ARTICLE

Effect of low-frequency repetitive transcranial magnetic stimulation as adjunctive treatment for insomnia patients under hypnotics: A randomized, double-blind, sham-controlled study

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Abstract

Background: Pharmacotherapy of insomnia is prescribed often but may be complicated by drug dependence. Cognitive-behavioral therapy for insomnia is effective, but requires time to take effect. Repetitive transcranial magnetic stimulation (rTMS) is effective for depression but of uncertain benefit for insomnia. We studied low-frequency rTMS of the left dorsal medial prefrontal cortex (DMPFC) as an adjunctive therapy of insomnia.

Methods: We recruited 60 patients with insomnia, of whom 49 completed the study. We applied 1 Hz rTMS to the DMPFC in the experimental group (n = 36) and sham coil for the placebo group (n = 13). Outcome measures included objective polysomnography (PSG) and subjective Pittsburgh Sleep Quality Index (PSQI). All participants were requested to continue prescribed pharmacotherapy.

Results: After 10 sessions of low-frequency DMPFC-rTMS, the experimental group demonstrated a reduction of duration of wake after sleep onset (WASO) from 75.4 (±53.3) to 51.2 (±75.1) min (p = 0.011). Sleep efficiency (SE) increased from 74.6% (±15.6) to 80.8% (±13.8) (p = 0.004). The sham group experienced improved SE from 79.4% (±30.7) to 88.9% (±5.6) (p = 0.039). After controlling for baseline PSG parameters and hypnotic dosage, the sham group exhibited better effects of sleep onset latency and SE than the rTMS group but no difference on PSQI.

Conclusion: Although the effects of rTMS and sham coil on insomnia were similar (which implied significant placebo effect), low-frequency DMPFC-rTMS might offer a safe, non-invasive, and useful adjunctive therapy of insomnia by reducing WASO. The DMPFC may represent a new target for future rTMS insomnia studies.

Keywords: Adjunctive treatment; Dorsal medial prefrontal cortex; Insomnia; Low-frequency stimulation; Transcranial magnetic stimulation

1. INTRODUCTION

Insomnia is the most common sleep symptom in industrialized countries, affecting roughly one-third of all adults, and causing significant daytime dysfunction in approximately 5% to 10% of the adult population.[1] As a syndrome, insomnia poses substantial public health risks related to daytime fatigue, functional impairment, reduced quality of life, increased healthcare utilization and costs, and disability.[2,3]

Insomnia is associated with the severe comorbidity of major depressive disorder (MDD) (DSM-IV TR).[4,5] The relationships between sleep disorders and depression are bidirectional,[6,7] and might share a common neurologic basis.[8] The addition of cognitive behavioral therapy for insomnia (CBT-I) is effective for treating patients with comorbid MDD who are receiving standard antidepressants.[9] Improvement of insomnia may benefit MDD and vice versa. Whether insomnia is a prodromal symptom, a residual feature, or a complication of depression or its treatment, clinicians must recognize and treat sleep disturbances because of the attendant risks of incident, progressive, or relapsing depression.[10]

Despite its high prevalence and consequent morbidity, chronic insomnia is treated in less than 15% of affected individuals.[11] Current treatments include pharmacotherapy and behavioral therapy.[12,13] CBT-I is effective both as a single modality and as an adjunct when combined with pharmacotherapy but requires time to take effect and places demands on limited

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staffing resources.[14] CBT-I is recommended as the first-line treatment for chronic insomnia in adults of any age.[15] Furthermore, pharmacotherapy can be offered if CBT-I is not available or ineffective.[16] However, pharmacotherapy is still the most commonly used treatment modality.[17,18] Although short-term (≤4 weeks) hypnotic pharmacotherapy may be indicated for acute insomnia, evidence regarding its long-term efficacy is lacking.[18,19] In addition, individuals with insomnia often consume disproportionate quantities of hypnotic medications for prolonged durations despite being at greater risk for residual daytime somnolence.[11,19,20] Most patients who are fearful of taking hypnotics and becoming drug-dependent seek behavioral treatment of chronic insomnia. Therefore, new treatment modalities are urgently needed.

High-frequency repetitive transcranial magnetic stimulation (rTMS) is a noninvasive intervention that modulates brain activity and thereby offers an alternative nonpharmacological treatment. Application of high-frequency rTMS to the left dorsal lateral prefrontal cortex (DLPFC) can treat depression effectively.[21,22] The convergent results of lesion, neuroimaging, stimulation, and connectivity studies identify multiple anatomic sites within the prefrontal cortex as potential therapeutic targets of rTMS.[23] Our team also performed rTMS studies for decades and observed that prolonged intermittent theta burst stimulation monotherapy targeting the left DLPFC is an effective treatment of recurrent depression.[24] Following the DLPFC, the dorsal medial prefrontal cortex (DMPFC) has received the most attention as it serves as a hyperconnected hub between distinct neural networks involved in depression.[25] DMPFC-rTMS is safe, tolerable, and effective to benefit patients with treatment-refractory depression,[26,27] obsessive-compulsive disorder,[28] posttraumatic stress disorder,[29] eating disorders,[30] and tinnitus.[31]

Because the pathogenesis of insomnia involves genetic, environmental, behavioral, and physiological factors that culminate in hyperarousal,[13] low-frequency inhibitory rTMS should decrease hyperarousal in insomnia patients. Both sleep impairment and MDD/anxiety disorder exhibit brain circuit dysfunction that features a hyper-engaged default mode network and a hyperactive negative affective network.[8] rTMS is thought to suppress the excitabilities of the motor and visual cortices that are expressed as increases of motor or phosphene thresholds, respectively.[32,33] Consequently, rTMS, a brain-modulating therapy, might offer a suitable treatment option.

The first study of rTMS for the treatment of insomnia applied high-frequency (5Hz) TMS to the left motor cortex. Increased local slow wave activities were recorded by high-definition electroencephalography (EEG). However, no significant differences in the architecture of slow-wave sleep recorded by polysomnography (PSG) were noted between treated subjects and sham controls.[34] Most subsequent study protocols have used low-frequency rTMS to inhibit the right DLPFC,[35] which is also the conventional rTMS target for MDD. Another study disclosed increased rostral anterior cingulate cortex (rACC) volume, which might result from heightened regional activity in chronic primary insomnia.[36] A substudy correlated left rACC volume with sleep onset latency (SOL) by diary, and wake after sleep onset (WASO) and sleep efficiency (SE) by actigraphy.[36] DMPFC and ACC were hypothesized to function as an emotional processing circuit.[37,38] Therefore, we chose the left DMPFC as our target region because it is accessible by low-frequency rTMS and might indirectly suppress the adjacent left ACC, and might subsequently benefit patients with insomnia. Previous rTMS insomnia studies performed in China that targeted the DLPFC improved Pittsburgh Sleep Quality Index (PSQI) total scores.[35] However, only four study designs included sham rTMS controls combined with pharmacotherapy and only three adopted PSG measurements. Notably, these studies yielded inconsistent results. The most recent TMS-EEG study applied low-frequency rTMS to the right posterior parietal cortex that improved sleep ratings such as PSQI, but did not adopt PSG as an outcome measure.[39]

We applied low-frequency inhibitory rTMS on the left DMPFC of patients with primary insomnia to evaluate its potential role as an adjunct to pharmacotherapy. We aimed to use low-frequency rTMS to suppress both the DMPFC and the adjacent ACC by inhibiting the DMPFC, the brain region that lies within both networks. The primary aim was to evaluate wake after sleep onset (WASO). The secondary aim was to identify changes in self-reported sleep quality (ISI and PSQI) and other objective PSG findings such as (SOL), sleep efficiency (SE), and slow wave sleep (stage N3). To our knowledge, this is the first study of DMPFC-rTMS for the treatment of primary insomnia.

2. METHODS

2.1. Participants and study design

We recruited participants with primary insomnia who met DSM-5 diagnostic criteria with either difficulty initiating or maintaining sleep, or experiencing early morning awakening; and consequent daytime distress or dysfunction that were not attributable to other medical or psychiatric disorders. Participants were enrolled at our outpatient clinic from 2013 to 2020. This study was performed in accordance with the Declaration of Helsinki and was approved by the Taipei Veterans General Hospital Institutional Review Board. In addition, the study was approved by Ministry of Health and Welfare, Taiwan as a new medical technique and device trial (1036062953). Informed consent was provided by all participants.

Inclusion criteria were Insomnia Severity Index (ISI)[40,41] total score ≥10 and PSQI[42] total score ≥5 and dissatisfaction with sleep condition under medical treatment for ≥6 months. Candidates were interviewed individually by a board-certificated psychiatrist and took the 17-item Hamilton Depression Rating Scale[43] to rule out MDD (total score ≤ 7). Bipolar disorder, posttraumatic stress disorder, obsessive-compulsive disorder, and substance use disorder were excluded by using the Structured Clinical Interview for DSM-IV Axis-I Disorders.[44] Eligible participants received PSG with pre- and poststudy questionnaires to evaluate subjective sleep parameters and to exclude other sleep disorders, such as obstructive sleep apnea syndrome and periodic limb movement disorder (Fig. 1).

Participants were randomized by our research coordinator via a random number table to receive either rTMS adjunctive treatment (experimental group) or sham coil treatment (sham group) by a 2:1 ratio for 10 sessions. Treatment procedures were performed by our registered rTMS technologist so that both the participants and physician rater were blinded. Furthermore, the registered polysomnographic technologist was also blinded to the grouping of the subjects. All participants were requested to continue their previously prescribed hypnotic pharmacotherapy. Post-rTMS PSG was performed to compare pre- and post-rTMS sleep parameters.

2.2. Sleep assessment

Whole-night PSG recording (Embla N7000 RemLogic PSG software) was performed at the Sleep Lab at the Department of Psychiatry, Taipei Veterans General Hospital. PSG included EEG monitoring (Fp1, Fp2, C3, C4, T3, T4, O1, O2), electrooculography, chin and leg electromyography, electrocardiography, and monitoring of body position and respiration. Respiratory monitoring evaluated air flow by using a nasal cannula-pressure transducer and mouth thermistor, thoracic and abdominal bands, a neck microphone, and finger pulse oximetry. Subjects

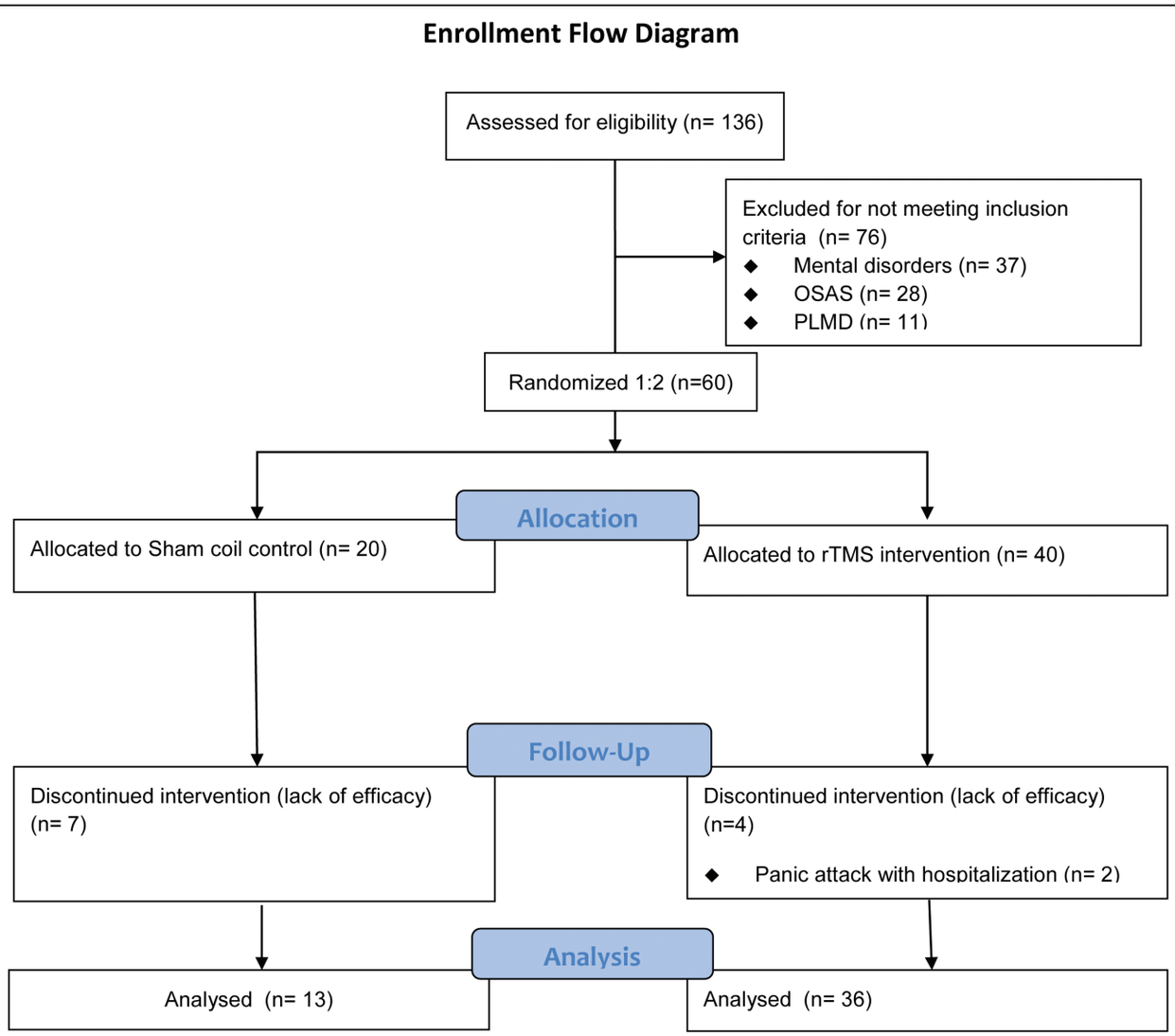

Fig. 1 Enrollment flow diagram. OSAS = obstructive sleep apnea syndrome; PLMD = periodic limb.

were videotaped during PSG. An experienced, registered PSG technologist scored all sleep recordings. Scoring of sleep stages (Rapid eye movement stage [REM]; Non-REM stages N1, N2, N3), every stage onset since PSG recording (Onset), every stage period sum up times during the entire PSG recording (Time), and every stage time/total sleep time ratio (Ratio%), EEG arousals, respiratory events, and periodic leg movements was performed according to the American Academy of Sleep Medicine manual.[45] The ISI total score and PSQI total score with seven subcomponents of sleep symptoms based on the PSQI were analyzed. These included sleep efficiency (components 3 and 4: sleep duration and habitual sleep efficiency), perceived sleep quality (components 1, 2, and 6: subjective sleep quality, sleep latency, and use of sleep medication), and daily disturbances (components 5 and 7: sleep disturbances and daytime dysfunction).[46]

2.3. rTMS protocol

rTMS was delivered using the Magstim Rapid^2 stimulator with a figure-of-8 coil (Magstim Co., Ltd., Whitland, United Kingdom). All subjects in the study group received a two-week course of rTMS (five sessions/week) with stimulus frequency 1 Hz, stimulus intensity 80% motor threshold, stimulation number 30 pulses/string, string interval 2 seconds, total of 60 strings, total stimulation pulses 1800, and total stimulation time 30 minutes in each session.[47] Subjects in the sham control group received a sham treatment (parameters given as rTMS study group; 10 sessions) using a sham coil (Magstim Placebo Coil; Magstim Co., Ltd.). Neuro-navigation computer software with an infrared system (Brainsight, Rogue Research, Inc., Montreal, Quebec, Canada) was used to guide the coil to target the left DMPFC. We registered individual brain images, and then Talairach and Tournoux coordinate (X 0, Y+30, Z+30) was set to find the closest approximate scalp point.[26,48] One centimeter left from the scalp point at the coronal view was defined as the left DMPFC spot for stimulation. The coil was positioned at 90° relative to midline (coil handle was fixed by a bracket pointing to the left side) to target the DMPFC.[48,49]

2.4. Statistical analysis

Demographic and clinical characteristics were presented as the total number (n) and percentage (%) or the median and the interquartile range. Continuous and categorical variables were

analyzed through the Mann-Whitney U test and Fisher's exact test, respectively, to compare differences in demographic and clinical data between groups as appropriate. The differences of variables between baseline and after rTMS among groups were analyzed with the Wilcoxon signed-rank test. A two-tailed p value of <0.05 was considered significant. After adjusting for baseline measurements and defined daily dose (DDD) of hypnotic, ANCOVA was performed to compare PSG parameters and PSQI scores between the DMPFC and placebo groups. The effect size was calculated as Cohen's d for paired t-test. The criteria of Cohen's d are 0.2 (small effect), 0.5 (moderate effect) and 0.8 (large effect). The SPSS, Version 24 for Windows (IBM, Armonk, NY, USA) was used to perform all statistical analyses.

3. RESULTS

3.1. Demographic data

We identified 136 patients with symptoms of persistent and significant sleep disturbance. Of these, 76 were excluded for having mental disorders (n = 37), obstructive sleep apnea syndrome (n = 28), and periodic limb movement disorder (n = 11). Participants (n = 60) were randomized 2:1 to rTMS DMPFC (n = 40) and sham (n = 20) groups. Four and seven participants dropped out of the rTMS and sham groups, respectively, due to lack of efficacy, resulting in a final evaluable population of 36 participants in the rTMS group and 13 in the sham group. Two dropouts in the rTMS group developed panic attack and were hospitalized (Fig. 1). Baseline demographic (age, sex) and clinical (mood, anxiety, sleep related symptoms, and DDD) data did not differ between the two groups, although the rTMS group had higher ISI baseline total scores. PSG disclosed that the sham group had shorter SOL and stage N2 and N3 onset times than the rTMS group. Arousal, apnea/hypopnea, and periodic limb movement indexes were similar between the two groups (Table 1).

3.2. rTMS effects on PSG

The rTMS group exhibited significantly decreased WASO (effect size: 0.36) and increased SE (effect size: 0.42). The sham group showed increased SE (Table 2) (Fig. 2). Statistical powers of decreased WASO in the experimental group and sham groups were 0.67 and 0.70, respectively.

3.2.1. rTMS effects on PSG after controlling baseline data and DDD of hypnotics

After controlling for baseline PSG data and DDD of hypnotics, the sham group demonstrated longer TST, shorter SOL, and better SE than the study group (Table 3).

3.3. rTMS effects on PSQI and 7 subcomponents

The PSQI total score did not change significantly in either group. The rTMS group displayed significant improvement of subjective sleep quality, sleep duration and sleep disturbances. The sham group reported significant improvements of sleep latency, habitual sleep efficiency, sleep disturbances, and daytime dysfunction (Table 4).

3.3.1. rTMS effects on PSQI and 7 subcomponents after controlling baseline data and DDD of hypnotics

After controlling for baseline PSG data and DDD of hypnotics, there was no significant difference in PSQI total score and seven subcomponents between two groups (Table 5).

4. DISCUSSION

We found that low-frequency DMPFC-rTMS may benefit patients with insomnia by decreasing WASO and increasing SE, albeit the effect sizes were moderate (0.36 and 0.42, respectively), which indicates relatively medium stability. Our finding of decreased WASO is consistent with previous sham-controlled rTMS studies that revealed reduced all time awake (WASO).[33] A meta-analysis of rTMS for insomnia also demonstrated reduced WASO and increased SE.[50] Interestingly, after we controlled baseline for PSG parameters and DDD, the sham group revealed longer TST, shorter SOL, and better SE than the rTMS group, which further demonstrated a relatively strong placebo effect. A highly significant placebo effect of sham rTMS for reducing insomnia was also demonstrated in a meta-analysis of rTMS insomnia studies, which is consistent with our finding.[50]

Table 1

Comparison of demographic and clinical characteristics for rTMS and sham control groups

Median, IQR	DMPFC (n = 36)	Placebo (sham) (n = 13)	p^a
Male, n (%)	10 (27.8)	1 (7.7)	0.246[b]
AGE, y/o	53.5 (18.5)	37.0 (21.0)	0.115
BMI	22.4 (4.5)	21.6 (2.9)	0.141
Mood and Anxiety rating scales			
HARS	14.5 (10.8)	14.0 (13.0)	0.915
YMRS	2 (2)	2 (2)	0.948
HAMD	6 (2.0)	5 (3.5)	0.426
BDI	10 (16.8)	15 (15.0)	0.906
DSSS	39 (24.5)	40 (24.5)	0.691
Subjective sleep rating scales			
PSQI	20 (10)	22 (12)	0.767
ISI	18 (5.0)	13 (5.5)	**<0.001**
ESS	4 (4)	3 (5)	0.650
DDD	2 (1.75)	1 (1.25)	0.528
PSG parameters			
TST	293.2 (59.8)	329 (146.3)	0.054
WASO	75.4 (53.3)	81.9 (85.8)	0.553
SOL	20.3 (18.8)	9 (18.2)	**0.029**
SE	74.6 (15.6)	79.4 (30.7)	0.167
N1			
Onset	20.3 (22.1)	9.5 (27. 8)	0.123
Time	22.8 (14.0)	20 (24.0)	0.854
Ratio%	8 (5.7)	6.4 (8.4)	0.767
N2			
Onset	23.5 (19.1)	11 (21.9)	**0.019**
Time	226.7 (71.3)	236.5 (122.3)	0.794
Ratio%	79 (11.6)	74.6 (26.9)	0.416
N3			
Onset	77.5 (64.8)	41.5 (50.6)	**0.040**
Time	0.5 (13.5)	3.5 (73.0)	0.237
Ratio%	0.3 (5.1)	1 (24.3)	0.276
REM			
Onset	120 (95.6)	112 (84.8)	0.667
Time	19.4 (25.6)	18 (32.3)	0.907
Ratio%	8.5 (8.0)	6.5 (7.6)	0.767
AI	0.1 (2.0)	1.7 (2.7)	0.371
AHI	1.2 (3.6)	2.5 (3.7)	0.915
PLMI	0 (1.5)	0 (0)	0.064

AHI = apnea hypopnea index; AI = arousal index; BDI = beck depression index; BMI = body mass index; DDD = defined daily dose of hypnotics; DMPFC = dorsal medial prefrontal cortex; DSSS = depression subscales for somatic symptoms; ESS = Epworth sleepiness scale; HAMD = Hamilton depression rating scales-17 items; HARS = Hamilton anxiety rating scale; IQR = interquartile range = Q3–Q1; ISI = insomnia severity index; N1 = stage N1; N2 = stage N2; N3 = stage N3; PLMI = periodic limb movement index; PSG = polysomnography; PSQI = Pittsburgh sleep quality index; REM = rapid eye movement; rTMS = repetitive transcranial magnetic stimulation; SE = sleep efficiency (min) ; SOL = sleep onset latency (min); TST = total sleep time; WASO = wake after sleep onset (min); YMRS = young mania rating scale.

[a]Mann-Whitney U test.

[b]Fisher's exact test.

Bold values indicates statistically significant of p<=0.05.

Table 2

Within group comparison of PSG parameters before and after rTMS for experimental and sham control groups

	DMPFC (n = 36)			Placebo (Sham) (n = 13)		
Median, IQR	**Baseline**	**Posttreatment**	***p*[a]**	**Baseline**	**Posttreatment**	***p*[a]**
TST	293.2 (59.8)	306.3 (66.9)	0.132	329 (146.3)	351.8 (64)	0.388
WASO	75.4 (53.3)	51.2 (75.1)	**0.011**	81.9 (85.8)	32 (24.3)	0.146
SOL	20.3 (18.8)	18.8 (17.5)	0.311	9 (18.2)	8.5 (11.3)	>0.999
SE	74.6 (15.6)	80.8 (13.8)	**0.004**	79.4 (30.7)	88.9 (5.6)	**0.039**
N1						
Onset	20.3 (22.1)	18.8 (18.4)	0.500	9.5 (27.8)	8.5 (14.8)	>0.999
Time	22.8 (14.0)	29.5 (28.0)	**0.029**	20 (24.0)	36 (40.0)	0.388
Ratio	8 (5.7)	11.3 (9.7)	0.405	6.4 (8.4)	9.1 (11.5)	0.388
N2						
Onset	23.5 (19.1)	22.3 (20.1)	0.311	11 (21.9)	11 (10.3)	>0.999
Time	226.7 (71.3)	223.3 (77.5)	>0.999	236.5 (122.3)	246.8 (99.7)	>0.999
Ratio	79 (11.6)	76.2 (14.5)	0.132	74.6 (26.9)	72.9 (24.3)	0.146
N3						
Onset	77.5 (64.8)	47 (65.9)	0.629	41.5 (50.6)	29 (41.5)	0.688
Time	0.5 (13.5)	1.5 (23.0)	0.845	3.5 (73.0)	2.5 (63.8)	>0.999
Ratio	0.3 (5.1)	0.5 (6.9)	>0.999	1 (24.3)	0.7 (21.3)	0.453
REM						
Onset	120 (95.6)	129 (63.8)	>0.999	112 (84.8)	104.5 (98.0)	0.388
Time	19.4 (25.6)	26.8 (31.0)	0.175	18 (32.3)	37.5 (30.1)	0.146
Ratio	8.5 (8.0)	8.5 (8.6)	0.405	6.5 (7.6)	10.7 (7.9)	0.146
AI	0.1 (2.0)	0 (1.2)	0.845	1.7 (2.7)	0.4 (3.2)	>0.999
AHI	1.2 (3.6)	1.5 (4.8)	0.110	2.5 (3.7)	0.9 (4.2)	>0.999
PLMI	0 (1.5)	0 (1.0)	0.581	0 (0)	0 (0)	>0.999

AHI = apnea hypopnea index; AI = arousal index; DMPFC = dorsal medial prefrontal cortex; IQR = interquartile range = Q3–Q1; N1 = stage N1; N2 = stage N2; N3 = stage N3; PLMI = periodic limb movement index; PSG = polysomnography; REM = rapid eye movement; rTMS = repetitive transcranial magnetic stimulation; SE = sleep efficiency; SOL = sleep onset latency (min); TST = total sleep time (min); WASO = wake after sleep onset (min).

[a]Analyzed by the Wilcoxon signed-rank test.

Bold values indicates statistically significant of $p<=0.05$.

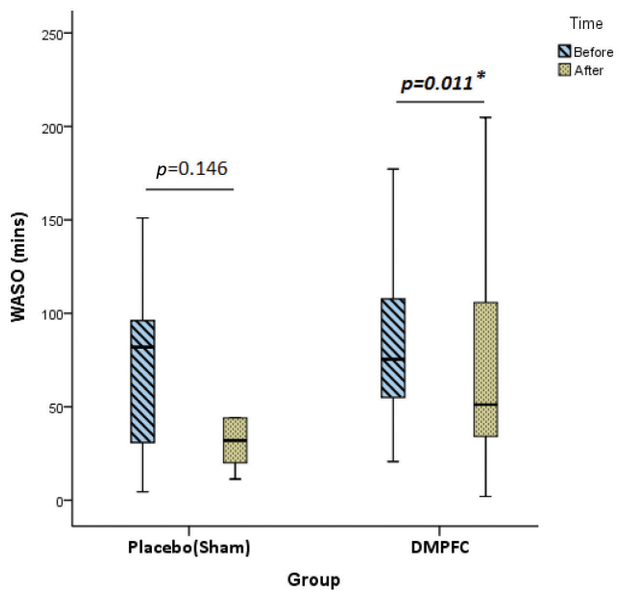

Fig. 2 WASO reduction before and after rTMS treatment. rTMS = repetitive transcranial magnetic stimulation; WASO = wake after sleep onset.

The underlying mechanisms of rTMS for treating primary insomnia remain unclear. Patients with primary insomnia may have hyperarousability of cortical and subcortical areas.[51] Another study of 15 patients with primary insomnia correlated WASO with increased glucose metabolism in brain regions such as the pontine tegmentum and thalamocortical networks including the ACC,[52] suggesting that increased WASO and lighter sleep are related to heightened arousal system activity as well as high-order cognitive processes during sleep. In addition, the ACC and DMPFC, which may be linked as an emotional processing circuit,[37,38] exhibit reduced gray matter in patients with MDD.[53] Our rTMS protocol used 1 Hz low-frequency stimulation that is thought to inhibit DMPFC activity. In contrast to previous rTMS studies targeting the DLPFC,[50] we targeted the DMPFC for direct inhibition and for indirect suppression the adjacent ACC, to thereby decrease WASO and increase SE. A meta-analysis revealed that the effect size of active rTMS for improving symptoms of insomnia seemingly increased with the prolongation of treatment duration within 30 days.[50] We question whether a modification of our protocol to increase DMPFC rTMS from 10 to 20 sessions would further decrease WASO or lengthen the rTMS effect.

Most rTMS insomnia studies have chosen PSQI as a subjective outcome measure. Only a few studies have used PSG objective measurements due to limited accessibility, availability, and human resources. Compared to previous rTMS insomnia studies, which demonstrated significant decreases in PSQI total score and reduced scores of seven subscales,[33] our study revealed improved ISI but not PSQI total score in both groups. Previous studies associated rTMS with significant positive effects in PSQI subcomponents especially in elderly patients.[33] Consequently, our negative findings in PSQI might be related to the underrepresentation of elderly patients in our study populations. The PSQI is a self-rated questionnaire evaluating sleep quality over the preceding month and measures sleep-wake symptoms. However, the PSQI is unrelated to objective sleep measures such as actigraphy or PSG, which might explain why our findings

Table 3

Between group comparison of PSG parameters after controlling baseline data and DDD for rTMS and sham control groups

Median, IQR	DMPFC (n = 36)	Placebo (sham) (n = 13)	
	Two weeks later	Two weeks later	*p*[a]
TST	306.3 (66.9)	351.8 (64)	**0.049**
WASO	51.2 (75.1)	32 (24.3)	0.085
SOL	18.8 (17.5)	8.5 (11.3)	**0.030**
SE	80.8 (13.8)	88.9 (5.6)	**0.020**
N1			
Onset	18.8 (18.4)	8.5 (14.8)	0.673
Time	29.5 (28.0)	36 (40.0)	0.654
Ratio	11.3 (9.7)	9.1 (11.5)	0.326
N2			
Onset	22.3 (20.1)	11 (10.3)	**0.011**
Time	223.3 (77.5)	246.8 (99.7)	**0.035**
Ratio	76.2 (14.5)	72.9 (24.3)	0.939
N3			
Onset	47 (65.9)	29 (41.5)	0.356
Time	1.5 (23.0)	2.5 (63.8)	0.692
Ratio	0.5 (6.9)	0.7 (21.3)	0.524
REM			
Onset	129 (63.8)	104.5 (98.0)	0.990
Time	26.8 (31.0)	37.5 (30.1)	0.471
Ratio	8.5 (8.6)	10.7 (7.9)	0.604

DDD = defined daily dose of hypnotics; DMPFC = dorsal medial prefrontal cortex; IQR = interquartile range = Q3–Q1; N1 = stage N1; N2 = stage N2; N3 = stage N3; PLMI = periodic limb movement index; PSG = polysomnography; REM = rapid eye movement; rTMS = repetitive transcranial magnetic stimulation; SE = sleep efficiency; SOL = sleep onset latency (min); TST = total sleep time (min); WASO = wake after sleep onset (min).

[a]Analyzed by the two-way ANCOVA test.

Bold values indicates statistically significant of $p<=0.05$.

differed between PSG and PSQI.[54] Discrepant subjective ratings and objective measures have been noted in both healthy individuals and insomnia patients. A large sleep lab cohort study revealed that a most patients with sleep-wake disorders tended to overestimate their SOL and to underestimate WASO.[55] Objective, but not self-reported, measures are associated with prominent pathophysiological effects, such as an increased risk of hypertension.[56] A prior work revealed that subjective WASO was significantly greater than objective WASO and that subjective and objective measures of sleep-maintenance disturbances were positively correlated. Both subjective and objective WASO were correlated with regional cerebral metabolism in similar overall patterns.[52] The comparatively longer duration of self-reported WASO than PSG WASO might explain why PSG WASO improvement after rTMS treatment was not reflected in improving the self-rated PSQI total score. However, the diagnosis of insomnia disorder is based on a subjective report of sleep complaints, which might explain the high dropout rate in our study.

We also found improved ISI total scores and SE in both DMPFC rTMS and sham groups. The placebo effect in primary insomnia has long been discussed; a substantial therapeutic effect could be achieved by optimizing placebo mechanisms.[57] Simulated treatment induces psychological anticipation that may be positive or negative, and that enhances the production of endogenous substances to further achieve the psychological anticipatory effect.[58,59] The sham rTMS group might experience the aforementioned processes and anticipate the seemingly valuable sham coil to be effective to treat their insomnia. Anticipation produces endogenous substances acting on sleep-arousal systems and might further improve SE. Although WASO also improved in the sham group, statistical significance was not achieved, possibly due to small sample size. Despite the DDD of hypnotics which were used by both groups nightly and were not significantly different, the median DDD were 2 in the rTMS group and 1 in the sham group. The sham group might have used lower hypnotic dosages, and also had lower ISI baseline total scores than rTMS group. The seemly milder insomnia in the sham group might have facilitated prominent placebo effects. All 11 dropouts left the study due to lack of efficacy. We supposed that 13 remaining sham group participants might have experienced a prominent psychological anticipatory effect which improved their insomnia symptoms comparably to rTMS effects. Considering the high dropout rate in the sham group and that all dropouts reported lack of efficacy, we suggest that sham therapy might be inferior to rTMS, although a prominent placebo effect remained in this study. Although two dropouts in the DMPFC rTMS group experienced panic attacks and were subsequently hospitalized, no other side effects were observed. We conclude that rTMS is generally safe and well-tolerated.

The present study has several limitations in. First, the sample size of the sham group was inadequate and the mean age of the sham group was younger than that of the DMPFC group, although the difference was not statistically significant. We experienced difficulty in enrolling patients who could complete our 10-session protocol, as evidenced by the 8-year time interval (2013-2020) required to recruit 60 participants. The mean age of the seven dropouts in the sham group was

Table 4

Within group comparison of PSQI total and 7 subcomponents before and after rTMS for experimental and sham control groups

	DMPFC (n = 36)			Placebo (Sham) (n = 13)		
Median, IQR	Baseline	Posttreatment	*p*[a]	Baseline	Posttreatment	*p*[a]
PSQI	20 (10)	19.5 (10.75)	0.573	22 (12)	19 (13)	0.129
PSQI1	2 (2)	1.5 (1)	**0.001**	2 (1)	1 (1)	0.078
PSQI2	3 (2)	3 (3.5)	**0.001**	4 (3)	3 (3)	**0.029**
PSQI3	2 (1)	1.5 (1)	**0.022**	2 (0.5)	1 (1)	0.057
PSQI4	1 (3)	1 (2.75)	**0.030**	1 (2)	0 (1.5)	**0.034**
PSQI5	8 (7)	7.5 (8.75)	**0.001**	10 (9.5)	9 (11)	**0.004**
PSQI6	3 (0)	3 (0)	0.250	3 (0.5)	3 (1.5)	0.500
PSQI7	2 (2.75)	2 (2)	0.150	2 (2)	1 (2)	**0.039**

DMPFC = dorsal medial prefrontal cortex; IQR = interquartile range = Q3–Q1; PSQI = Pittsburgh Sleep Quality Index; PSQI1 = subjective sleep quality; PSQI2 = sleep latency; PSQI3 = sleep duration; PSQI4 = habitual sleep efficiency; PSQI5 = sleep disturbances; PSQI6 = use of sleeping medications; PSQI7 = daytime dysfunction; rTMS = repetitive transcranial magnetic stimulation.

[a]Analyzed by the Wilcoxon signed-rank test.

Bold values indicates statistically significant of $p<=0.05$.

Table 5

Between group comparison of PSQI total and 7 subcomponents after controlling baseline data and DDD for rTMS and sham control groups

Median, IQR	DMPFC (n = 36)	Placebo (Sham) (n = 13)	
	Two weeks later	Two weeks later	*p*[a]
PSQI	19.5 (10.75)	19 (13)	0.107
PSQI1	1.5 (1)	1 (1)	0.361
PSQI2	3 (3.5)	3 (3)	0.999
PSQI3	1.5 (1)	1 (1)	0.898
PSQI4	1 (2.75)	0 (1.5)	0.052
PSQI5	7.5 (8.75)	9 (11)	0.305
PSQI6	3 (0)	3 (1.5)	0.146
PSQI7	2 (2)	1 (2)	0.073

DDD = defined daily dose of hypnotics; DMPFC = dorsal medial prefrontal cortex; IQR = interquartile range = Q3–Q1; PSQI = Pittsburgh sleep quality index; PSQI1 = subjective sleep quality; PSQI2 = sleep latency; PSQI3 = sleep duration; PSQI4 = habitual sleep efficiency; PSQI5 = sleep disturbances; PSQI6 = use of sleeping medications; PSQI7 = daytime dysfunction; rTMS = repetitive transcranial magnetic stimulation.

[a]Analyzed by the two way ANCOVA test.

49.3; consequently we speculate that older people might tolerate insomnia poorly and withdraw from the study due to lack of efficacy. Second, all participants were requested to continue hypnotic pharmacotherapy at their previously prescribed dosing schedule throughout the course of rTMS, which may have led to heterogeneity in participant composition, although DDD was not significantly different between two groups. We advocate the recruitment of drug-naive patients with new-onset insomnia for future studies to determine whether low-frequency DMPFC-rTMS is effective as a monotherapy rather than as an adjunctive treatment. Third, most of our subjects were female, although the male/female ratios were not statistically different between the two groups. Future enrollment of male subjects is mandatory to clarify gender differences. Finally, the underlying mechanisms of DMPFC-rTMS inhibition in the modulation of WASO and SE in patients with insomnia should be investigated further by large-scale sham-controlled neuroimaging studies.

In conclusion, a 2-week course of low-frequency DMPFC-rTMS as an adjunctive therapy for insomnia may offer a safe, noninvasive, nonpharmacological option that may improve WASO and SE. However, the placebo effect of sham rTMS was also prominent. To our knowledge, this is the first randomized, sham-controlled trial of this modality targeting the DMPFC. The DMPFC might represent a useful, plausible, and accessible new target for future studies of rTMS to treat patients with insomnia.

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