



Original Article

Electroencephalographic connectivity predicts clinical response to repetitive transcranial magnetic stimulation in patients with insomnia disorder



Xue Shi ^a, Yi Guo ^{a, b}, Lin Zhu ^a, Wei Wu ^c, Brenton Hordacre ^d, Xiaolin Su ^a, Qian Wang ^a, Xiaoxia Chen ^a, Xiaoyong Lan ^a, Ge Dang ^{a, *}

^a Department of Neurology, Shenzhen People's Hospital, The Second Clinical Medical College, Jinan University, The First Affiliated Hospital, Southern University of Science and Technology, Shenzhen, 518020, Guangdong, China

^b Shenzhen Bay Laboratory, Shenzhen, 518020, Guangdong, China

^c School of Automation Science and Engineering, South China University of Technology, Guangzhou, 510641, China

^d Innovation, Implementation and Clinical Translation (IIMPACT) in Health, Allied Health and Human Performance, University of South Australia, Australia

ARTICLE INFO

Article history:

Received 20 July 2021

Received in revised form

10 September 2021

Accepted 12 October 2021

Available online 25 October 2021

Keywords:

Repetitive transcranial magnetic stimulation
Electroencephalography
Functional connectivity
Power envelope connectivity
Insomnia disorder

ABSTRACT

Background: Accumulating evidence suggests that low frequency repetitive transcranial magnetic stimulation (rTMS), which generally decreases cortical excitability and remodels plastic connectivity, improves sleep quality in patients with insomnia disorder. However, the effects of rTMS vary substantially across individuals and treatment is sometimes unsatisfactory, calling for biomarkers for predicting clinical outcomes.

Objective: This study aimed to investigate whether functional connectivity of the target network in electroencephalography is associated with the clinical response to low frequency rTMS in patients with insomnia disorder.

Methods: Twenty-five patients with insomnia disorder were subjected to 10 sessions of treatment with 1 Hz rTMS over the right dorsolateral prefrontal cortex. Resting-state electroencephalography was collected before rTMS. Pittsburgh Sleep Quality Index, Hamilton Depression Rating Scale, Hamilton Anxiety Rating Scale, and Mini-Mental State Exam were performed before and after rTMS treatment, with a follow-up after one month. Electroencephalographic connectivity was measured by the power envelope connectivity at the source level. Partial least squares regression identified models of connectivity that maximally accounted for the rTMS response.

Results: Scores of Pittsburgh Sleep Quality Index, Hamilton Depression Rating Scale, and Hamilton Anxiety Rating Scale were decreased after rTMS and one-month later. Baseline weaker connectivity of a network in the beta and alpha bands between a brain region approximating the stimulated right dorsolateral prefrontal cortex and areas located in the frontal, insular, and limbic cortices was associated with a greater change in Pittsburgh Sleep Quality Index and Hamilton Depression Rating Scale following rTMS.

Conclusions: Low frequency rTMS could improve sleep quality and depressive moods in patients with insomnia disorder. Moreover, electroencephalographic functional connectivity would potentially be a robust biomarker for predicting the therapeutic effects.

© 2021 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

* Corresponding author. Department of Neurology, Shenzhen People's Hospital, The Second Clinical Medical College, Jinan University, The First Affiliated Hospital, Southern University of Science and Technology, Shenzhen, 518020, Guangdong, China.

E-mail address: dqg220@163.com (G. Dang).

Abbreviations

DLPFC	dorsolateral prefrontal cortex
HAMA	Hamilton Anxiety Scale
HAMA _{21change}	relative change of HAMA from Exam 1 to Exam 2
HAMA _{31change}	relative change of HAMA from Exam 1 to Exam 3
HAMD	Hamilton Depression Rating Scale
HAMD _{21change}	relative change of HAMD from Exam 1 to Exam 2
HAMD _{31change}	relative change of HAMD from Exam 1 to Exam 3
ID	insomnia disorder
MMSE	Mini-Mental State Exam
PEC	power envelope connectivity
PLS	partial least squares
PSQI	Pittsburgh Sleep Quality Index
PSQI _{21change}	relative change of PSQI from Exam 1 to Exam 2
PSQI _{31change}	relative change of PSQI from Exam 1 to Exam 3
RAMFG	right anterior division of middle frontal gyrus
ROI	regions of interest
RMT	resting motor threshold
rsEEG	resting-state electroencephalography
rTMS	repetitive transcranial magnetic stimulation
TMS	transcranial magnetic stimulation

1. Introduction

Insomnia disorder (ID) is the most common sleep disorder characterized by difficulties in falling asleep, maintaining sleep, and waking in the early morning [1]. It not only leads to dissatisfying daytime function, but also may serve as an indicator for mental disorders such as depression, anxiety, and dementia, as well as physical problems such as cardiovascular disease and diabetes [2]. Management of insomnia is vital for the prevention and amelioration of these conditions [3]. Cognitive behavioral therapy for insomnia is the initial treatment for ID. However, this therapy is time-consuming and costly, and the lack of specialty trained practitioners hinders its implementation in clinical practice [4]. Hypnotic agents, including benzodiazepine receptor agonist drugs, have been widely used as a first-line pharmacological treatment for ID in clinical practice. However, their side effects, such as increased risk of falls, cognitive impairment, and potential dependence, are unfavorable [5]. Approximately 40% of patients with ID do not achieve sustained remission with the treatment of cognitive behavioral therapy and benzodiazepine-receptor agonists [4]. Therefore, new treatments for ID are needed.

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation method, be easy to operate and have relatively few side effects, that can transiently modulate excitability/plasticity of neuronal networks and may persist in time [6]. It has been shown to improve sleep quality in several sleep disorders such as ID, restless legs syndrome, obstructive sleep apnea syndrome, and narcolepsy [7]. In subjects with ID, various rTMS strategies have been studied and low frequency (LF) rTMS over the right dorsolateral prefrontal cortex (DLPFC) showed therapeutic benefits by reducing cortical hyperexcitability [6,8]. However, the behavioral and physiological aftereffects of rTMS vary substantially across individuals [9]. Identifying biological predictors of rTMS outcomes would be beneficial for selecting an appropriate therapeutic approach and reduce unnecessary financial and time investments [10]. In restless legs syndrome, rTMS has disclosed clinical, electrophysiological, and neuroplastic markers of response, along with translational neurochemical implications [11].

Considering the potential for treating ID by rTMS and the subsequent possibility of clinical translation, it is necessary to identify robust predictive biomarkers of rTMS outcomes in these patients.

Multiple electrophysiological characteristics have been investigated for predicting therapeutic effects of rTMS. Several specific TMS variables, such as the balancing of resting motor threshold (RMT) and intracortical facilitation between the two hemispheres, have been used as both neuroplastic indexes and neuropsychological outcome measures to rTMS treatment [12]. Resting state electroencephalography (rsEEG) is effective for capturing brain electrophysiological activity, and emerging studies have shown its ability to identify rTMS treatment-predictive heterogeneity [13,14]. For instance, variability in treatment-emergent changes of rsEEG alpha spectral correlation was related to differences in rTMS treatment outcomes in patients with major depressive disorder [15,16]. Although electrophysiological connectivity predicting rTMS outcomes in major depressive disorder has been widely investigated, this is yet to be elucidated in ID. ID is a functional brain disorder with abnormal network connections and anomalous cortical plasticity [17–19]. Hence, it is rational to use rsEEG functional connectivity to predict rTMS outcomes in patients with ID.

In this study, we explored the association between baseline rsEEG functional connectivity and consequent neuropsychological performance after rTMS interventions in patients with ID. Functional connectivity was measured by the power envelope connectivity (PEC), a reliable connectivity measure reflecting the large-scale cortical correlation [20]. We hypothesized that electroencephalographic connectivity may serve as neural network biomarker of rTMS outcomes for insomniacs.

2. Methods

2.1. Participants

This study was approved by the ethics committee of Shenzhen People's Hospital and was conducted in accordance with the Declaration of Helsinki guidelines (chictr.org.cn identifier ChiCTR1900026904). Eligible patients with ID were recruited at the outpatient Department of Neurology of our hospital between March 2020 to March 2021. Consent forms were signed by all patients before participating in this study. The inclusion criteria were as follows: (1) met the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition for diagnosis of ID; (2) Pittsburgh Sleep Quality Index (PSQI) score >7; (3) aged 18–70 years old; (4) self-reported right handedness; (5) Chinese speaking, reading, and writing. The exclusion criteria included patients: (1) taking any insomnia drug in the four weeks prior to enrollment; (2) other sleep disorders (eg, sleep-related movement disorders, hypersomnia, or parasomnia); (3) significant psychiatric history (eg, bipolar disorder, schizophrenia, major depression disorder, generalized anxiety disorder); (4) neurological disorders (eg, stroke, Parkinson's disease, multiple sclerosis); (5) serious physical illnesses (eg, heart failure, kidney failure, or cancer); (6) history of alcohol or drug abuse; (7) Mini-Mental Status Exam (MMSE) score <24; or (8) any contraindication to TMS (eg, metallic implants, pregnancy, and a history of seizures) [21]. Consuming energy drinks, caffeinated beverages, or tea was not allowed [22] during the study period.

2.2. Transcranial magnetic stimulation

TMS was applied by a figure-of-eight magnetic coil (Coil B658, external wing diameter 90 mm) connected to a MagPro 100 magnetic stimulator (MagVenture, Denmark). RMT was defined as the minimum stimulus intensity producing a motor evoked potential

exceeding 50 μV in a minimum of five out of ten trials in the relaxed left abductor pollicis brevis [23]. During rTMS treatment, the coil was placed over the F4 electrode site (10–10 EEG system) for delivering the stimulations to the right DLPFC. It was held tangentially to the scalp with the handle pointing posterolaterally at an angle of 45° from the midline. Pulses at 100% intensity of the resting motor threshold were administered at 1 Hz (10 s trains, 1 s intertrain interval, 1360 pulses/session, total stimulation time 25 min). Patients received daily treatment, 5 days a week, over a 2-week course. Any discomfort during rTMS or adverse events during stimulation and follow-up were recorded.

2.3. Neuropsychological assessment

The neuropsychological assessments were evaluated by a trained neurologist at three time points: the day before rTMS (Exam 1), the day of the last rTMS session (Exam 2), and one month after the last rTMS session (Exam 3). The primary clinical outcome was the PSQI, and the secondary measures included the Hamilton Depression Rating Scale (HAM-D), the Hamilton Anxiety Scale (HAM-A), and the Mini-Mental State Exam (MMSE).

2.4. EEG recording and preprocessing

EEG was recorded on the day before first rTMS session. Patients were asked to sit in a comfortable chair and to relax during recording but avoid falling asleep. Sixty-four channels of EEG signals (electrodes in standard 10–10 positions) were recorded in eyes-closed condition for 8 min using a BrainAmp DC amplifier (Brain-Products, GmbH). The contact impedances were kept below 10 k Ω by applying conductive gel. The reference electrode for EEG recording was FCz channel, while the ground was mounted AFz. Signals were initially sampled at 5000 Hz.

Preprocessing analysis was performed in MATLAB using the EEGLAB toolbox [24]. The preprocessing steps are as follows: (1) the EEG signals were visually inspected, and the typical artifact segments were removed manually; (2) the signals were down-sampled to 250 Hz; (3) the signals were notch filtered to remove the 50 Hz A.C. line noise artifact; (4) the signals were bandpass filtered between 1 and 45 Hz by using finite impulse response filter; (5) the bad channels were rejected and were then interpolated via spherical spline interpolation; (6) the signals were then epoched into 2 s segments; (7) other contamination including eye movement, or muscle and heart noise were removed using an independent component approach; (8) the signals were re-referenced to the common average; and then (8) the signals were filtered into five frequency ranges: delta (1–3 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (13–30 Hz), and gamma (31–45 Hz).

2.5. EEG source connectivity analysis

Source localization was performed using the Brainstorm toolbox [25]. The FreeSurfer average brain template was used and a symmetric boundary element method was used to compute the head model with OpenMEG [26]. To compute the inverse operator, the following analysis strategy was defined: (1) using unconstrained orientations with all three current components at each location, (2) a depth weighting algorithm was used to compensate for any bias affecting the superficial sources calculation, and (3) the regularization parameter was set to 0.33 minimizing numerical instability to reduce the sensitivity of the minimum-norm estimates to noise and to effectively obtain a spatially smoothed solution. Rotating dipoles at 3003 vertices were generated on the cortical surface.

EEG functional connectivity based on the PECs between orthogonalized spontaneous signals was calculated among 31

regions of interest (ROIs) in the Montreal Neurological Institute space which was derived from an independent parcellation of resting-state functional magnetic resonance imaging (fMRI) connectivity using an independent component analysis from 38 healthy subjects applied in a prior study [27]. For details estimating the PECs between orthogonalized signals were described previously, see Ref. [28]. Briefly, the analytical signal of each vertex in the source space was separately and iteratively orthogonalized with respect to all other vertices. Power envelopes were then calculated from each of the orthogonalized analytical time series, and the natural logarithm of these envelopes was obtained to render them more normal. Pearson's correlation coefficient between the log-transformed power envelopes was obtained for each pair of vertices. For each pair of ROIs, the Fisher Z transforms of the Pearson correlations of each pair of vertices within each ROI were averaged to determine the connectivity of that specific pair of ROIs. PEC was calculated at each frequency.

2.6. Partial least squares regression

Partial least squares (PLS) regression analysis is a suitable way for evaluating brain activity–behavior relationships in neuroimaging studies [29]. The N-way Toolbox was used to perform the PLS analyses in this study [30]. The PEC at each frequency band was taken as separate independent variables. The dependent variable consisted of the relative change of PSQI from Exam 1 to Exam 2 (PSQI_{21change}) and relative change of PSQI from Exam 1 to Exam 3 (PSQI_{31change}). First, data were mean-centered, after which they underwent a direct orthogonal signal correction to remove the largest independent measures orthogonal to the behavior score to ensure more efficient PLS models with fewer components. Right anterior division of middle frontal gyrus (RAMFG), which is approximating the stimulated right DLPFC, was chosen as the seed ROI in this study. The connectivity between the RAMFG and brain regions strongly related to behavioral status was identified by setting an arbitrary threshold for each model [31]. A threshold of 0.75 relative to the absolute value of the maximal correlation coefficient which is more conservative than similar previous studies [32,33] was set in this study. Cross-validation using a leave-one-out and predict approach was performed, where data from one subject were iteratively removed, and the removed subject's behavioral data were predicted from the PEC data using the PLS model generated from the remaining n-1 subjects. Once PLS models were generated, the mean connectivity values of the network between the RAMFG and the identified regions were determined and correlated against the dependent variable. Multiple linear regression was used with age and gender as additional nuisance covariates if there was a correlation between the bivariate. Moreover, the mean connectivity for the identified network was correlated to the relative change of HAM-D and HAM-A from Exam 1 to Exam 2 (HAM-D_{21change}, HAM-A_{21change}), and the relative change of HAM-D and HAM-A from Exam 1 to Exam 3 (HAM-D_{31change}, HAM-A_{31change}).

2.7. Statistical analysis

Statistical analyses of clinical data were conducted using SPSS 11.0 (Chicago, IL, USA) and MATLAB. Normality was checked using the Shapiro–Wilk test. Normally distributed data were presented as mean \pm standard deviation, while non-normally distributed data were presented as medians and interquartile ranges. Nonparametric statistics were used when necessary. The statistical differences of neuropsychological assessments at three different time points were analyzed using one-way repeated measures analysis of variance (Bonferroni correction was used for the post-hoc test). Relative changes of PSQI, HAM-D, and HAM-A were calculated;

hence, higher percentages of these changes represent better improvement in sleep quality and depressive or anxious symptoms separately. The correlation analysis between the clinical characteristics, baseline, and the relative change in neurological scores, and that between the mean connectivity value of the identified network and the dependent variables following PLS analysis were performed by Pearson's correlation or Spearman's rank-order correlation.

3. Results

A total of 25 patients participated in this study. They all completed rsEEG recording, rTMS treatment, and the neuropsychological assessments at Exam 1 and Exam 2. Four patients dropped out for the neuropsychological assessments at Exam 3. All patients tolerated rTMS well, and none reported adverse effects. The patients' age ranged from 22 to 69 (48.5 ± 11.6) years, with 16 females and 9 males, and RMT was $39.4 \pm 12.5\%$.

3.1. Effect of rTMS on clinical performance

Table 1 shows the neuropsychological scores at Exam 1, Exam 2 and 3. There was a significant difference among the three exams in PSQI [$F(2, 40) = 21.58, p < 0.001$], as well as in the HAMD [$F(2, 40) = 19.03, p < 0.001$] and HAMA [$F(2, 40) = 20.24, p < 0.001$]. A post hoc paired t-test showed the PSQI scores significantly declined after rTMS and one month later. Moreover, the HAMD and HAMA scores declined as well. No significant difference was found in MMSE (Table 1). Additionally, $PSQI_{21change}$ was positively correlated with $HAMD_{21change}$ ($p < 0.001, r = 0.649$) but not to $HAMA_{21change}$ ($p = 0.109$). $PSQI_{31change}$ was positively correlated with $HAMD_{31change}$ ($p = 0.007, r = 0.580$), but not with $HAMA_{31change}$ ($p = 0.112$). Age, gender, and RMT were not associated with the PSQI, HAMD, or HAMA at any time point and their changes from Exam 1 to Exam 2, or Exam 1 to Exam 3.

3.2. Baseline EEG connectivity and rTMS clinical response at Exam 2

PLS regression analyses were used to identify models of connectivity between RAMFG and the whole brain that maximally predicted $PSQI_{21change}$. Models were generated for delta, theta, alpha, beta, and gamma frequencies with the strongest relationship observed in beta frequency (fitted PLS model $R^2 = 0.80$), which also had a high predictive value (cross-validated $R^2 = 0.80$).

The beta PLS model identified a RAMFG-whole brain network that predicted $PSQI_{21change}$ to rTMS. The network involved the bilateral frontal cortex, bilateral insular cortex, and limbic cortex. All brain regions within the network are shown in Fig. 1. The mean connectivity strength of the network was negatively associated with $PSQI_{21change}$ ($r = -0.68, p < 0.001$; Fig. 1). Multiple linear regression showed that the mean connectivity in this network ($\beta = -0.629, t = -3.297, p = 0.003$) negatively predicts $PSQI_{21change}$.

Table 1
Neurological assessment scores of the day before rTMS (Exam 1), the day of the last rTMS session (Exam 2) and one month after the last rTMS session (Exam 3). * $p < 0.05$ (bonferroni corrected) compared with Exam1. ^a $p < 0.05$ (bonferroni corrected) compared with Exam2.

Variables	Exam 1	Exam 2	Exam 3
PSQI	15.10 ± 2.17	11.90 ± 4.25 *	9.86 ± 4.76 ^a
HAMD	12.43 ± 3.17	8.29 ± 4.30 *	7.14 ± 4.23 *
HAMA	13.29 ± 5.71	6.29 ± 3.84 *	6.00 ± 4.51 *
MMSE	29.29 ± 1.43	29.50 ± 1.06	29.86 ± 0.36

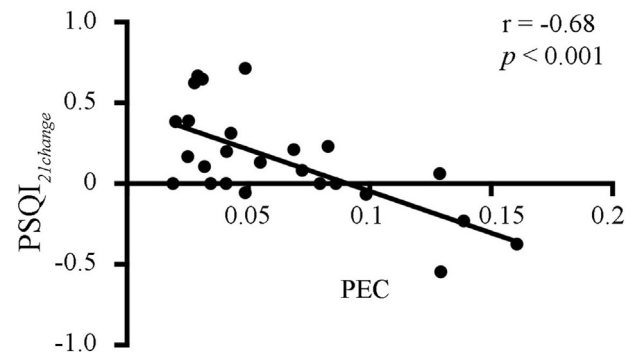
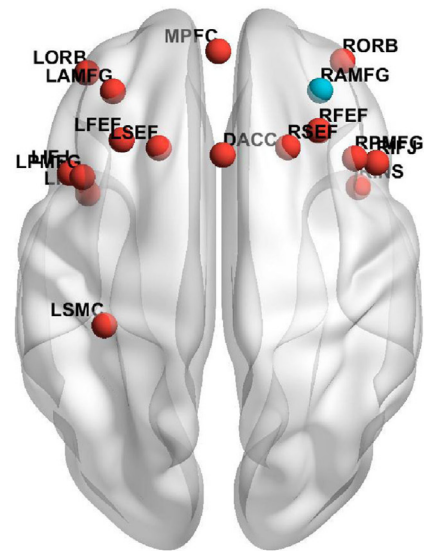


Fig. 1. Power envelope connectivity (PEC) in the beta band at baseline predicted the improvement of sleep quality after repetitive transcranial magnetic stimulation (rTMS) treatment. (top) The network of right anterior division of middle frontal gyrus (RAMFG) seeded in the beta band which associated with the relative change of Pittsburgh Sleep Quality Index from Exam 1 to Exam 2 ($PSQI_{21change}$). The related brain regions in the network include the left orbitofrontal cortex (LORB), left anterior division of middle frontal gyrus (LAMFG), left frontal eye field (LFEF), left supplementary eye field (LSEF), left posterior division of middle frontal gyrus (LPMFG), left inferior frontal junction (LIJ), left insular cortex (LINS), left sensorimotor cortex (LSMC), medial prefrontal cortex (MPFC), dorsal anterior cingulate cortex (DACC), right orbitofrontal cortex (RORB), right frontal eye field (RFEF), right supplementary eye field (RSEF), right posterior division of middle frontal gyrus (RPMFG), right inferior frontal junction (RIFJ), and right insular cortex (RINS). The cyan dot indicates the seed, and the red dots indicate the related brain regions comprising the network. (bottom) The correlation between the mean connectivity within the network and the $PSQI_{21change}$.

Both age and gender were not significant variables. The mean connectivity strength of the network was also related to $HAMD_{21change}$ ($r = -0.48, p = 0.02$) but not $HAMA_{21change}$ ($p = 0.95$).

The alpha PLS model ($R^2 = 0.74, cross-validated R^2 = 0.60$) identified a RAMFG-whole brain network that predicted the $PSQI_{21change}$ response to rTMS. The network approximated the bilateral frontal cortex, left insular cortex, and the limbic cortex. All brain regions within the network are shown in Fig. 2. Connectivity between the RAMFG and other regions in the network was negatively associated with $PSQI_{21change}$ ($r = -0.59, p = 0.01, Fig. 2$). Multiple linear regression showed that the mean connectivity in this network ($\beta = -0.503, t = -2.656, p = 0.015$) negatively predicts $PSQI_{21change}$. Both age and gender were not significant variables. The mean connectivity was also related to $HAMD_{21change}$ ($r = 0.45, p = 0.03$) but not $HAMA_{21change}$ ($p = 0.96$).

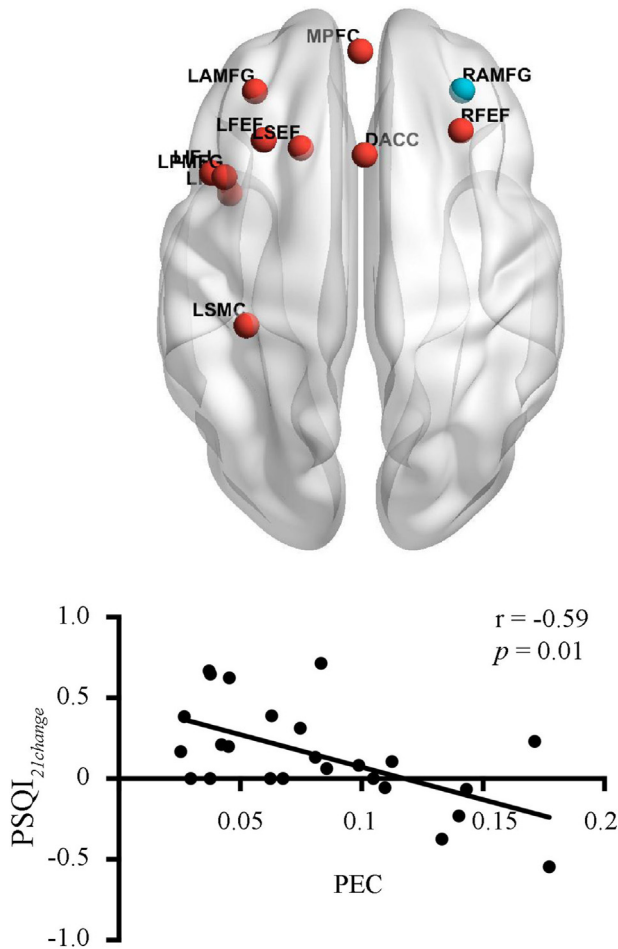


Fig. 2. Power envelope connectivity (PEC) in the alpha band at baseline predicted the improvement of sleep quality after repetitive transcranial magnetic stimulation (rTMS) treatment. (top) The network of right anterior division of middle frontal gyrus (RAMFG) seeded in the alpha band which associated with the relative change of Pittsburgh Sleep Quality Index from Exam 1 to Exam 2 ($PSQI_{21change}$). The related brain regions in the network include the left anterior division of middle frontal gyrus (LAMFG), left frontal eye field (LFEF), left supplementary eye field (LSEF), left posterior division of middle frontal gyrus (LPMFG), left inferior frontal junction (LIJ), left insular cortex (LINS), left sensorimotor cortex (LSMC), medial prefrontal cortex (MPFC), dorsal anterior cingulate cortex (DACC), and right frontal eye field (RFEF). The cyan dot indicates the seed, and the red dots indicate the related brain regions comprising the network. (bottom) The correlation between the mean connectivity within the network and the $PSQI_{21change}$.

The gamma PLS model ($R^2 = 0.67$, cross-validated $R^2 = 0.66$) identified a RAMFG whole brain network that predicted $PSQI_{21change}$ to rTMS. The network involved the bilateral frontal and limbic cortex. However, the mean connectivity within the network was not significantly associated with response to rTMS ($r = -0.35$, $p = 0.08$, Fig. 3).

The theta PLS model ($R^2 = 0.63$, cross-validated $R^2 = 0.58$) identified a RAMFG whole brain network that predicted $PSQI_{21change}$ to rTMS. The network involved the left frontal and parietal cortex, and right temporal cortex. However, the mean connectivity within the network was not significantly associated with response to rTMS ($r = -0.32$, $p = 0.12$, Fig. 4).

PLS models for delta frequencies showed a low proportion of variance of $PSQI_{21change}$ in the rTMS response (delta: $R^2 = 0.46$, cross validated $R^2 = 0.44$).

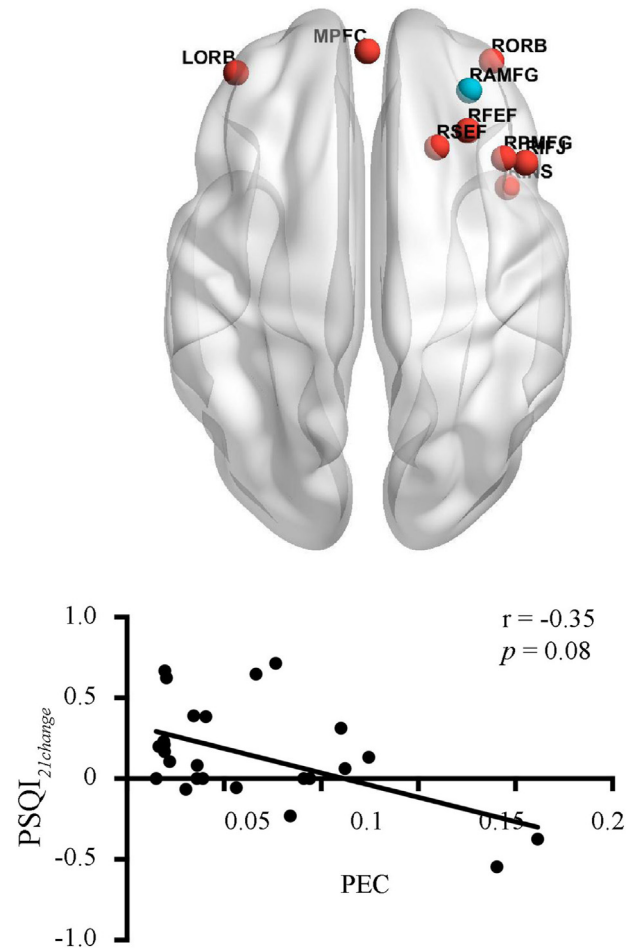


Fig. 3. Power envelope connectivity (PEC) in the gamma band at baseline predicted the improvement of sleep quality after repetitive transcranial magnetic stimulation (rTMS) treatment. (top) The network of right anterior division of middle frontal gyrus (RAMFG) seeded in the gamma band which associated with the relative change of Pittsburgh Sleep Quality Index from Exam 1 to Exam 2 ($PSQI_{21change}$). The related brain regions in the network include the left orbitofrontal cortex (LORB), medial prefrontal cortex (MPFC), right orbitofrontal cortex (RORB), right frontal eye field (RFEF), right supplementary eye field (RSEF), right inferior frontal junction (RIFJ), right posterior division of middle frontal gyrus (RPFMG), and right insular cortex (RINS). The cyan dot indicates the seed, and the red dots indicate the related brain regions comprising the network. (bottom) The correlation between the mean connectivity within the network and the $PSQI_{21change}$.

3.3. Baseline EEG connectivity and rTMS clinical response at Exam 3

PLS regression analyses were used to identify models of connectivity between RAMFG and the whole brain that maximally predicted $PSQI_{31change}$. Models were generated for delta, theta, alpha, beta, and gamma frequencies with the strongest relationship observed in beta frequency (fitted PLS model $R^2 = 0.62$), which also had a high predictive value (cross-validated $R^2 = 0.62$).

The beta PLS model identified a RAMFG whole brain network that predicted $PSQI_{31change}$ to rTMS. This network involved the bilateral frontal cortex, right parietal cortex, and limbic cortex. The lower connectivity between the RAMFG and the identified brain regions was associated with a greater improvement of $PSQI_{31change}$ ($r = -0.57$, $p = 0.01$; Fig. 5). However, the mean strength of the connectivity did not reach statistical significance ($p = 0.227$) when age and gender were added as covariates in the regression model.

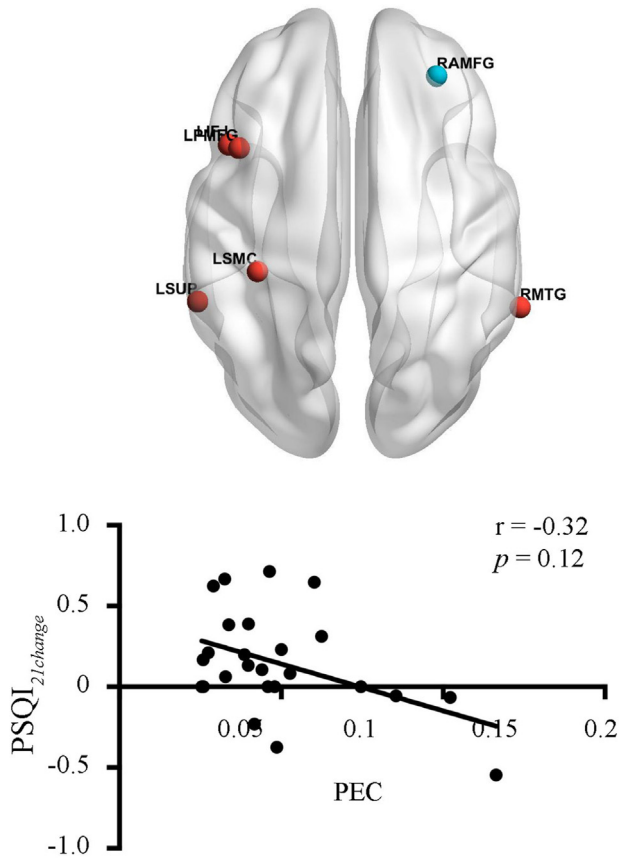


Fig. 4. Power envelope connectivity (PEC) in the theta band at baseline predicted the improvement of sleep quality after repetitive transcranial magnetic stimulation (rTMS) treatment. (top) The network of right anterior division of middle frontal gyrus (RAMFG) seeded in the theta band which associated with the relative change of Pittsburgh Sleep Quality Index from Exam 1 to Exam 2 (PSQI_{21change}). The related brain regions in the network include the left inferior frontal junction (LIFJ), left posterior division of middle frontal gyrus (LPMFG), left sensorimotor cortex (LSMC), left supramarginal gyrus (LSUP), and right middle temporal gyrus (RMTG). The cyan dot indicates the seed, and the red dots indicate the related brain regions comprising the network. (bottom) The correlation between the mean connectivity within the network and the PSQI_{21change}.

The theta PLS model ($R^2 = 0.62$, cross-validated $R^2 = 0.55$) identified a RAMFG whole brain network that predicted PSQI_{31change} to rTMS. The network involved bilateral frontal and occipital cortex, left parietal and right temporal cortex. However, the mean connectivity within the network was not significantly associated with response to rTMS ($r = -0.06$, $p = 0.79$, Fig. 6).

PLS models for other frequencies identified a low proportion of variance of the PSQI_{31change} in the rTMS response (delta: $R^2 = 0.28$, cross-validated $R^2 = 0.28$; alpha: $R^2 = 0.52$, cross-validated $R^2 = 0.42$; gamma: $R^2 = 0.31$, cross-validated $R^2 = 0.31$).

4. Discussion

This study investigated whether electroencephalographic connectivity could predict the clinical outcomes of LF rTMS treatment in patients with ID. The results demonstrated that (1) LF rTMS improved sleep quality and depressive mood, and maintained clinical benefits up to one month after treatment; (2) weaker connectivity of the beta and alpha bands between the RAMFG, a seed approximating the stimulated right DLPFC, and brain regions involving the frontal, insular, and limbic cortices was strongly associated with the improvement of sleep quality and depressive mood after LF rTMS.

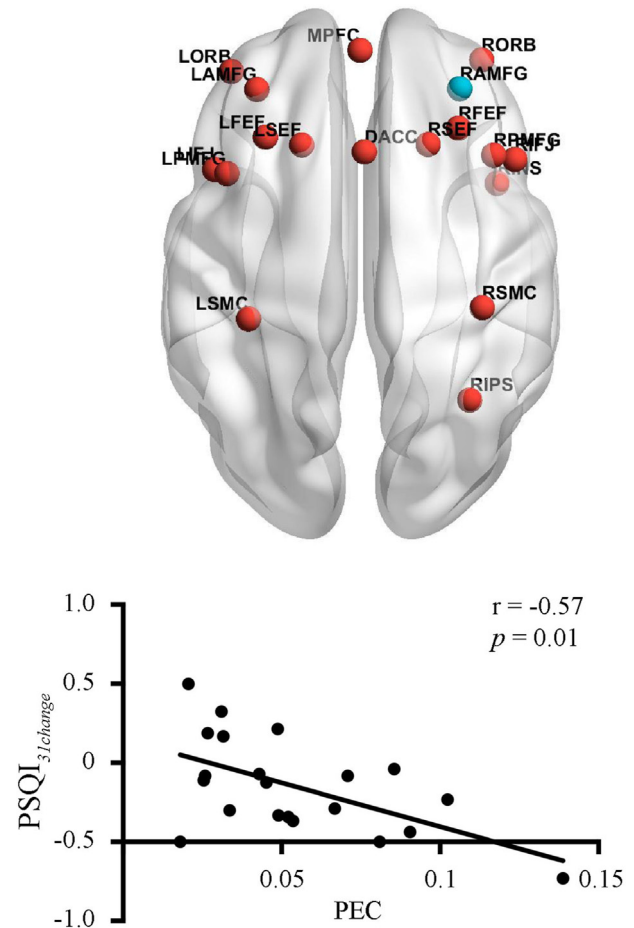


Fig. 5. Power envelope connectivity (PEC) in the beta band at baseline predicted the improvement of sleep quality one month after repetitive transcranial magnetic stimulation (rTMS) treatment. (top) The network of right anterior division of middle frontal gyrus (RAMFG) seeded in the beta band which associated with the relative change of Pittsburgh Sleep Quality Index from Exam 1 to Exam 3 (PSQI_{31change}). The related brain regions in the network include the left orbitofrontal cortex (LORB), left anterior division of middle frontal gyrus (LAMFG), left frontal eye field (LFEF), left supplementary eye field (LSEF), left posterior division of middle frontal gyrus (LPMFG), left inferior frontal junction (LIFJ), left sensorimotor cortex (LSMC), medial prefrontal cortex (MPFC), dorsal anterior cingulate cortex (DACC), right orbitofrontal cortex (RORB), right frontal eye field (RFEF), right supplementary eye field (RSEF), right posterior division of middle frontal gyrus (RPMFG), right inferior frontal junction (RIFJ), right insular cortex (RINS), right left sensorimotor cortex (RSMC), and right intraparietal sulcus (RIPS). The cyan dot indicates the seed, and the red dots indicate the related brain regions comprising the network. (bottom) The correlation between the mean connectivity within the network and the PSQI_{31change}.

Insomnia is conceptualized as a hyperarousal model of structural and functional psychobiological disorder [19]. LF rTMS, which generally decreases cortical excitability, has been demonstrated could trigger slow waves and spindles, enhance stage III sleep cycle, and increase the serum brain-derived neurotrophic factor and gamma-aminobutyric acid level in ID [34–36]. The present study found that LF rTMS effectively improved the sleep quality in patients with ID. Previous work reported that two weeks of daily 1 Hz rTMS over the right DLPFC improved stage III sleep and REM sleep cycle with the lowest relapse and recurrence rates within three months when compared with control conditions of psychotherapy or medication treatment [36]. Acupuncture combined with 12 sessions of 1 Hz rTMS over the left DLPFC also had better efficacy of improving sleep quality than combination with sham rTMS in patients with ID [37]. All these suggested the efficacy of LF rTMS and its potential in clinical transition for treating ID.

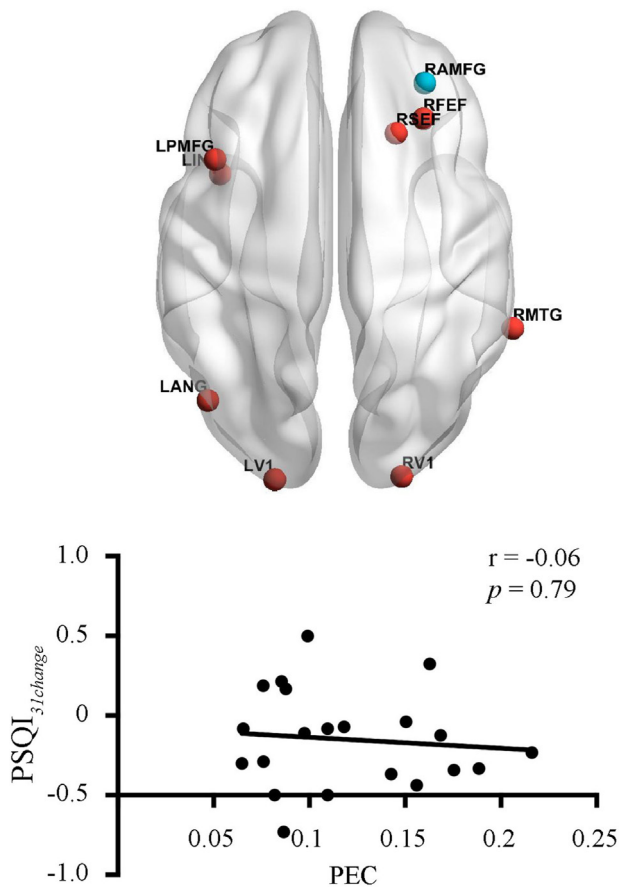


Fig. 6. Power envelope connectivity (PEC) in the theta band at baseline predicted the improvement of sleep quality one month after repetitive transcranial magnetic stimulation (rTMS) treatment. (top) The network of right anterior division of middle frontal gyrus (RAMFG) seeded in the theta band which associated with the relative change of Pittsburgh Sleep Quality Index from Exam 1 to Exam 3 ($PSQI_{31change}$). The related brain regions in the network include the left posterior division of middle frontal gyrus (LPMFG), left insular cortex (LINS), left angular gyrus (LANG), left primary visual cortex (LV1), right frontal eye field (RFEF), right supplementary eye field (RSEF), right middle temporal gyrus (RMTG), and right primary visual cortex (RV1). The cyan dot indicates the seed, and the red dots indicate the related brain regions comprising the network. (bottom) The correlation between the mean connectivity within the network and the $PSQI_{31change}$.

Abnormal functional connectivity of ID has been reported widely in fMRI studies, such as lower connection between the amygdala and insula, the striatum and thalamus, the medial prefrontal cortex and right medial temporal lobe, and the left medial temporal lobe and the left inferior parietal cortices [38]. Some of these changes contributed to the severity of sleep quality [39]. A concurrent TMS-EEG study showed that the information outflow from the left occipital, the frontal mid-line and the right posterior temporal region was excessive, and that in the right central, parietal, and temporal regions was inadequate in patients with ID compared with healthy controls [40]. While complicated alterations of brain networks are involved in ID, rTMS was considered a circuit-targeting neuromodulation strategy. Animal models demonstrated that LF rTMS modulated dentate gyrus morphological plasticity in neurons while high frequency rTMS induced remarkable changes in dendritic complexity in primary motor cortex [41,42]. The DLPFC is a functionally heterogeneous brain region and a key node of several brain networks, involved in cognitive, affective, and sensory processing [43]. Stimulation over DLPFC could induce changes of functional connectivity widely across the brain [44]. In healthy subjects, right DLPFC inhibition by

theta-burst stimulation induced enhanced occipito-parietal brain activity [45], and transcranial direct current stimulation over left DLPFC could induce changes in the activation of the motor cortex [46]. Moreover, rTMS over DLPFC leads to clinical improvement in patients with neuropsychological diseases such as major depressive disorder, stroke, and Alzheimer's Disease partially by modifying brain connection [44,47]. Meanwhile, predicting value of connectivity characters has been investigated. rsEEG theta connectivity could predict rTMS response in depression [48]. The present study demonstrated that rsEEG alpha and beta functional connectivity, which was associated with the improvement of sleep quality after LF rTMS over right DLPFC in patients with ID, and multiple brain regions across the frontal, insular, and limbic cortices were involved in the prognosis predication.

Elevated beta EEG activity during sleep has been important pathophysiological evidence for the characterization of insomnia by central nervous system hyperarousal [49]. A consistent increase in alpha activity during deep nonrapid eye movement sleep was found in patients with insomnia compared to good-sleeping controls [50]. Though these features were reported in sleep EEG studies, wake EEG has been shown to provide valuable physiological features of insomnia with greater feasibility than sleep recording devices [51]. In this study, we found the relationship between awake connectivity in the alpha and beta bands with the sleep quality improvement after rTMS. The predictive value of EEG connectivity for rTMS outcomes observed in the beta and alpha bands of the functional connectivity is possibly due to the intrinsic activity changes in these bands in ID. Another hypothesis could be formed from the bandwidth sensitivity of the PEC, with which the strongest correlations between brain regions were found in the alpha and beta frequency ranges [28]. This could indicate that it is favorable to preselect the desired bandwidth in concurrence with the frequency-specific sensitivity of the chosen functional connectivity measure. Further research to determine which frequency band is the most valid in ID is needed to answer these questions.

In addition to improved sleep quality after rTMS, depressive and anxiety symptoms ameliorated in this study. Moreover, the improvement of sleep quality strongly correlated with the bettered depressive mood. Insomnia, depression, and anxiety commonly co-occur and might have overlapping neural substrates [52,53]. In practice, most patients visiting the clinic complaining of insomnia have depressive and/or anxious symptoms but do not meet the diagnostic criteria for any depressive or anxiety disorders. The clinical features of participants of this study are in accordance with real-world situations. While the 1 Hz rTMS over the right DLPFC could also be a treatment protocol for depression [54], it is uncertain whether the rTMS reversed the insomnia by remitting the depressive and anxious mood, or vice versa. The relation between the improvement of sleep quality and depressive mood after LF rTMS over right DLPFC deserves further studies.

There are several limitations of this study. A neuro-navigated system was not used to locate therapeutic targets that may influence the accuracy of the effects. However, targeting the stimulation site based on anatomical landmarks is common in clinical practice and may reduce the significance of this limitation. In addition, we used PSQI as the measure for sleep quality at three time points. The PSQI asks for sleep quality in the past month, so the questionnaire might not fully disclose the clinical benefit during the immediate post-treatment assessment, which is only 2 weeks after treatment started. However, assessment at one month post-treatment did not demonstrate an enhanced benefit over the post-treatment test. Further, the sample size was small. Future studies with a more rigorous design and larger sample size should be conducted to address these issues.

5. Conclusion

Patients with ID who underwent LF rTMS over the right DLPFC could have the benefit on their sleep quality and depressive symptoms. rsEEG functional connectivity between the stimulation site and multiple regions across the whole brain in the beta and alpha bands is a robust and specific biomarker for predicting these therapeutic effects. The results contribute to the current knowledge on factors that modulate responses to rTMS and provide further insight into the complex intrinsic characteristics associated with sleep amelioration in people with ID.

Author contributions

Xue Shi contributed to data acquisition, data analysis, manuscript drafting and revising. Xiaolin Su, Qian Wang, Xiaoxia Chen and Xiaoyong Lan contributed to data acquisition. Lin Zhu contributed to data analysis. Wei Wu and Brenton Hordacre contributed to manuscript revising. Yi Guo and Ge Dang contributed to study design, study supervision and manuscript revising.

Study fundings

This study was supported by the Natural Science Foundation of China (grant number 81901208 and 61876063), the Medical Science and Technology Research Foundation of Guangdong Province (grant number A2019174), the Natural Science Foundation of Guangdong Province (grant number 2021A1515010983), the National Health and Medical Research Council of Australia (grant number 1125054).

Conflict of interest

None declared.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: <https://doi.org/10.1016/j.sleep.2021.10.017>.

References

- Morin CM, Drake CL, Harvey AG, et al. Insomnia disorder. *Nat Rev Dis Primers* 2015 Sep 3;1:15026.
- Fernandez-Mendoza J, Vgontzas AN. Insomnia and its impact on physical and mental health. *Curr Psychiatr Rep* 2013 Dec;15(12):418.
- Kyle SD, Henry AL. Sleep is a modifiable determinant of health: implications and opportunities for health psychology. *Br J Health Psychol* 2017 Nov;22(4):661–70.
- Qaseem A, Kansagara D, Forcica MA, et al. Clinical Guidelines Committee of the American College of P. Management of chronic insomnia disorder in adults: a Clinical Practice Guideline from the American College of Physicians. *Ann Intern Med* 2016 Jul 19;165(2):125–33.
- Buyssse DJ, Germain A, Moul DE, et al. Efficacy of brief behavioral treatment for chronic insomnia in older adults. *Arch Intern Med* 2011 May 23;171(10):887–95.
- Nardone R, Sebastianelli L, Versace V, et al. Effects of repetitive transcranial magnetic stimulation in subjects with sleep disorders. *Sleep Med* 2020 Jul;71:113–21.
- Lanza G, Cantone M, Lanuzza B, et al. Distinctive patterns of cortical excitability to transcranial magnetic stimulation in obstructive sleep apnea syndrome, restless legs syndrome, insomnia, and sleep deprivation. *Sleep Med Rev* 2015 Feb;19:39–50.
- Sun N, He Y, Wang Z, et al. The effect of repetitive transcranial magnetic stimulation for insomnia: a systematic review and meta-analysis. *Sleep Med* 2021 Jan;77:226–37.
- Castrillon G, Sollmann N, Kurcys K, et al. The physiological effects of noninvasive brain stimulation fundamentally differ across the human cortex. *Sci Adv* 2020 Jan;6(5):eay2739.
- Lanza G. Repetitive TMS for sleep disorders: are we ready? *Sleep Med* 2020 Jul;71:111–2.
- Lanza G, Ferri R. The neurophysiology of hyperarousal in restless legs syndrome: hints for a role of glutamate/GABA. *Adv Pharmacol* 2019;84:101–19.
- Spampinato C, Aguglia E, Concerto C, et al. Transcranial magnetic stimulation in the assessment of motor cortex excitability and treatment of drug-resistant major depression. *IEEE Trans Neural Syst Rehabil Eng* 2013 May;21(3):391–403.
- Wu W, Zhang Y, Jiang J, et al. An electroencephalographic signature predicts antidepressant response in major depression. *Nat Biotechnol* 2020 Apr;38(4):439–47.
- Metin SZ, Balli Altuglu T, Metin B, et al. Use of EEG for predicting treatment response to transcranial magnetic stimulation in obsessive compulsive disorder. *Clin EEG Neurosci* 2020 May;51(3):139–45.
- Corlier J, Wilson A, Hunter AM, et al. Changes in functional connectivity predict outcome of repetitive transcranial magnetic stimulation treatment of major depressive disorder. *Cerebr Cortex* 2019 Dec 17;29(12):4958–67.
- Zandvakili A, Philip NS, Jones SR, et al. Use of machine learning in predicting clinical response to transcranial magnetic stimulation in comorbid post-traumatic stress disorder and major depression: a resting state electroencephalography study. *J Affect Disord* 2019 Jun 1;252:47–54.
- Nardone R, Golaszewski S, Frey V, et al. Altered response to repetitive transcranial magnetic stimulation in patients with chronic primary insomnia. *Sleep Med* 2020 Aug;72:126–9.
- Li C, Dong M, Yin Y, et al. Abnormal whole-brain functional connectivity in patients with primary insomnia. *Neuropsychiatric Dis Treat* 2017;13:427–35.
- Riemann D, Spiegelhalter K, Feige B, et al. The hyperarousal model of insomnia: a review of the concept and its evidence. *Sleep Med Rev* 2010 Feb;14(1):19–31.
- Drysdale AT, Grosenick L, Downar J, et al. Resting-state connectivity biomarkers define neurophysiological subtypes of depression. *Nat Med* 2017 Jan;23(1):28–38.
- Rossi S, Hallett M, Rossini PM, et al. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol* 2009 Dec;120(12):2008–39.
- Zulkifly MFM, Merkohtaj O, Brockmoller J, et al. Confounding effects of caffeine on neuroplasticity induced by transcranial alternating current stimulation and paired associative stimulation. *Clin Neurophysiol* 2021 Jun;132(6):1367–79.
- Rossini PM, Burke D, Chen R, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. *Clin Neurophysiol* 2015 Jun;126(6):1071–107.
- Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Methods* 2004 Mar 15;134(1):9–21.
- Tadel F, Baillet S, Mosher JC, et al. Brainstorm: a user-friendly application for MEG/EEG analysis. *Comput Intell Neurosci* 2011;2011:879716.
- Gramfort A, Papadopoulos T, Olivi E, et al. OpenMEEG: opensource software for quasistatic bioelectromagnetics. *Biomed Eng Online* 2010 Sep 6;9:45.
- Chen AC, Oathes DJ, Chang C, et al. Causal interactions between fronto-parietal central executive and default-mode networks in humans. *Proc Natl Acad Sci U S A* 2013 Dec 3;110(49):19944–9.
- Hipp JF, Hawellek DJ, Corbetta M, et al. Large-scale cortical correlation structure of spontaneous oscillatory activity. *Nat Neurosci* 2012 Jun;15(6):884–90.
- Krishnan A, Williams LJ, McIntosh AR, et al. Partial least squares (PLS) methods for neuroimaging: a tutorial and review. *Neuroimage* 2011 May 15;56(2):455–75.
- Andersson CA, Bro R. The N-way toolbox for MATLAB. *Chemometr Intell Lab Syst* 2000;52(1):1–4.
- Menzies L, Achard S, Chamberlain SR, et al. Neurocognitive endophenotypes of obsessive-compulsive disorder. *Brain* 2007 Dec;130(Pt 12):3223–36.
- Hordacre B, Moezzi B, Goldsworthy MR, et al. Resting state functional connectivity measures correlate with the response to anodal transcranial direct current stimulation. *Eur J Neurosci* 2017 Mar;45(6):837–45.
- Hordacre B, Moezzi B, Ridding MC. Neuroplasticity and network connectivity of the motor cortex following stroke: a transcranial direct current stimulation study. *Hum Brain Mapp* 2018 Aug;39(8):3326–39.
- Massimini M, Ferrarelli F, Esser SK, et al. Triggering sleep slow waves by transcranial magnetic stimulation. *Proc Natl Acad Sci U S A* 2007 May 15;104(20):8496–501.
- Feng J, Zhang Q, Zhang C, et al. The Effect of sequential bilateral low-frequency rTMS over dorsolateral prefrontal cortex on serum level of BDNF and GABA in patients with primary insomnia. *Brain Behav* 2019 Feb;9(2):e01206.
- Jiang CG, Zhang T, Yue FG, et al. Efficacy of repetitive transcranial magnetic stimulation in the treatment of patients with chronic primary insomnia. *Cell Biochem Biophys* 2013 Sep;67(1):169–73.
- Zhang YP, Liao WJ, Xia WG. Effect of acupuncture cooperated with low-frequency repetitive transcranial magnetic stimulation on chronic insomnia: a randomized clinical trial. *Curr Med Sci* 2018 Jun;38(3):491–8.
- Huang Z, Liang P, Jia X, et al. Abnormal amygdala connectivity in patients with primary insomnia: evidence from resting state fMRI. *Eur J Radiol* 2012 Jun;81(6):1288–95.
- Khazaie H, Veronese M, Noori K, et al. Functional reorganization in obstructive sleep apnoea and insomnia: a systematic review of the resting-state fMRI. *Neurosci Biobehav Rev* 2017 Jun;77:219–31.
- Song P, Lin H, Li S, et al. Repetitive transcranial magnetic stimulation (rTMS) modulates time-varying electroencephalography (EEG) network in primary insomnia patients: a TMS-EEG study. *Sleep Med* 2019 Apr;56:157–63.
- Cambiaghi M, Crupi R, Bautista EL, et al. The effects of 1-Hz rTMS on emotional behavior and dendritic complexity of mature and newly generated dentate gyrus neurons in male mice. *Int J Environ Res Publ Health* 2020 Jun 8;17(11).

- [42] Cambiaghi M, Cherchi L, Masin L, et al. High-frequency repetitive transcranial magnetic stimulation enhances layer II/III morphological dendritic plasticity in mouse primary motor cortex. *Behav Brain Res* 2021 Jul 23;410:113352.
- [43] Glasser MF, Coalson TS, Robinson EC, et al. A multi-modal parcellation of human cerebral cortex. *Nature* 2016 Aug 11;536(7615):171–8.
- [44] Beynel L, Powers JP, Appelbaum LG. Effects of repetitive transcranial magnetic stimulation on resting-state connectivity: a systematic review. *Neuroimage* 2020 May 1;211:116596.
- [45] Keuper K, Terrighena EL, Chan CCH, et al. How the dorsolateral prefrontal cortex controls affective processing in absence of visual awareness - insights from a combined EEG-rTMS study. *Front Hum Neurosci* 2018;12:412.
- [46] Mineo L, Fetterman A, Concerto C, et al. Motor facilitation during observation of implied motion: evidence for a role of the left dorsolateral prefrontal cortex. *Int J Psychophysiol* 2018 Jun;128:47–51.
- [47] Guo Y, Dang G, Hordacre B, et al. Repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex modulates electroencephalographic functional connectivity in Alzheimer's disease. *Front Aging Neurosci* 2021;13:679585.
- [48] Bailey NW, Krepel N, van Dijk H, et al. Resting EEG theta connectivity and alpha power to predict repetitive transcranial magnetic stimulation response in depression: a non-replication from the ICON-DB consortium. *Clin Neurophysiol* 2021 Feb;132(2):650–9.
- [49] Perlis ML, Merica H, Smith MT, et al. Beta EEG activity and insomnia. *Sleep Med Rev* 2001 Oct;5(5):363–74.
- [50] Riedner BA, Goldstein MR, Plante DT, et al. Regional patterns of elevated alpha and high-frequency electroencephalographic activity during nonrapid eye movement sleep in chronic insomnia: a pilot study. *Sleep* 2016 Apr 1;39(4):801–12.
- [51] Colombo MA, Ramautar JR, Wei Y, et al. Wake high-density electroencephalographic spatio-spectral signatures of insomnia. *Sleep* 2016 May 1;39(5):1015–27.
- [52] Bagherzadeh-Azbari S, Khazaie H, Zarei M, et al. Neuroimaging insights into the link between depression and Insomnia: a systematic review. *J Affect Disord* 2019 Nov 1;258:133–43.
- [53] Pace-Schott EF, Zimmerman JP, Bottary RM, et al. Resting state functional connectivity in primary insomnia, generalized anxiety disorder and controls. *Psychiatry Res Neuroimaging* 2017 Jul 30;265:26–34.
- [54] Cao X, Deng C, Su X, et al. Response and remission rates following high-frequency vs. Low-frequency repetitive transcranial magnetic stimulation (rTMS) over right DLPFC for treating major depressive disorder (MDD): a meta-analysis of randomized, double-blind trials. *Front Psychiatr* 2018;9:413.