Research Article

Neuroimaging mechanisms of high-frequency repetitive transcranial magnetic stimulation for treatment of amnestic mild cognitive impairment: a double-blind randomized sham-controlled trial

https://doi.org/10.4103/1673-5374.295345

Received: October 11, 2019

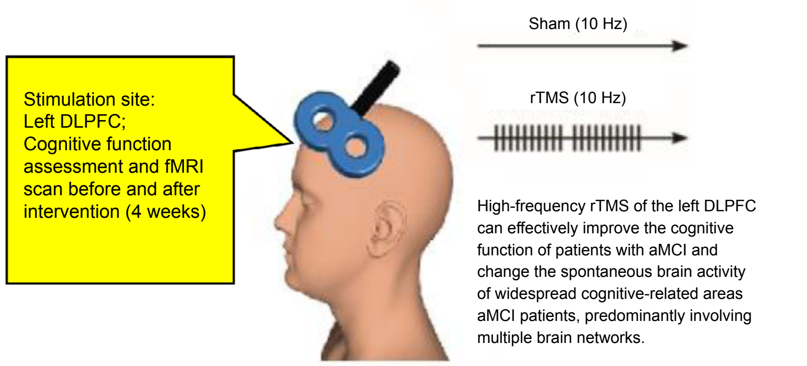
Peer review started: October 25, 2019

Accepted: May 13, 2020

Published online: October 9, 2020

Li-Qiong Yuan[1, #], Qing Zeng[1, #], Dan Wang[2], Xiu-Yun Wen[2], Yu Shi[1], Fen Zhu[2], Shang-Jie Chen[2, *], Guo-Zhi Huang[1, 3, *]

Graphical Abstract *Neuroimaging mechanisms of high frequency rTMS (10 Hz) in patients with amnestic mild cognitive impairment (aMCI)*



Abstract

Individuals with amnestic mild cognitive impairment (aMCI) have a high risk of developing Alzheimer's disease. Although repetitive transcranial magnetic stimulation (rTMS) is considered a potentially effective treatment for cognitive impairment in patients with aMCI, the neuroimaging mechanisms are poorly understood. Therefore, we performed a double-blind randomized sham-controlled trial in which rTMS was applied to the left dorsolateral prefrontal cortex of aMCI patients recruited from a community near the Third Hospital Affiliated to Sun Yat-sen University, China. Twenty-four patients with aMCI were randomly assigned to receive true rTMS (treatment group, n = 12, 6 men and 6 women; age 65.08 ± 4.89 years) or sham stimulation (sham group, n = 12, 5 men and 7 women; age 64.67 ± 4.77 years). rTMS parameters included a stimulation frequency of 10 Hz, stimulation duration of 2 seconds, stimulation interval of 8 seconds, 20 repetitions at 80% of the motor threshold, and 400 pulses per session. rTMS/sham stimulation was performed five times per week over a period of 4 consecutive weeks. Our results showed that compared with baseline, Montreal Cognitive Assessment scores were significantly increased and the value of the amplitude of low-frequency fluctuation (ALFF) was significantly increased at the end of treatment and 1 month after treatment. Compared with the sham group, the ALFF values in the right inferior frontal gyrus, triangular part of the inferior frontal gyrus, right precuneus, left angular gyrus, and right supramarginal gyrus were significantly increased, and the ALFF values in the right superior frontal gyrus were significantly decreased in the treatment group. These findings suggest that high-frequency rTMS can effectively improve cognitive function in aMCI patients and alter spontaneous brain activity in cognitive-related brain areas. This study was approved by the Ethics Committee of Shenzhen Baoan Hospital of Southern Medical University, China (approval No. BYL20190901) on September 3, 2019, and registered in the Chinese Clinical Trials Registry (registration No. ChiCTR1900028180) on December 14, 2019.

Key Words: Alzheimer's disease; clinical trial; cognitive function; cognitive impairment; functional magnetic resonance imaging; neurological function; repetitive transcranial magnetic stimulation

Chinese Library Classification No. R454.1; R741; R445

[1]Department of Rehabilitation Medicine and Physiotherapy, Zhujiang Hospital of Southern Medical University, Guangzhou, Guangdong Province, China; [2]Department of Rehabilitation Medicine and Physiotherapy, Shenzhen Baoan Hospital of Southern Medical University, Shenzhen, Guangdong Province, China; [3]Rehabilitation School of Southern Medical University, Guangzhou, Guangdong Province, China

*__Correspondence to:__ Guo-Zhi Huang, PhD, drhuang66@163.com; Shang-Jie Chen, PhD, csjme@163.com.

https://orcid.org/0000-0003-2797-1387 (Li-Qiong Yuan)

#Both authors contributed equally to this study.

Funding: *This work was supported by the National Natural Science Foundation of China, No. 81874032 (to GZH); the Science and Technology Planning Project of Shenzhen of China, No. JCYJ20160427191726109 (to FZ); the Science and Technology Planning Project of Guangdong Province of China, No. 2016A020215202 (to SHC); and Shenzhen Health and Family Planning System Research Project of China, No. SZXJ2017069 (to SHC).*

How to cite this article: *Yuan LQ, Zeng Q, Wang D, Wen XY, Shi Y, Zhu F, Chen SJ, Huang GZ (2021) Neuroimaging mechanisms of high-frequency repetitive transcranial magnetic stimulation for treatment of amnestic mild cognitive impairment: a double-blind randomized sham-controlled trial. Neural Regen Res 16(4):707-713.*

Introduction

Mild cognitive impairment (MCI) is considered a transitional phase between normal cognition and early dementia in elderly individuals (Petersen et al., 2018). Indeed, one study found that 2/3 of patients with Alzheimer's disease (AD) first present with MCI (Petersen et al., 2018). Among forms of MCI, amnestic MCI (aMCI) is characterized by memory dysfunction (Petersen, 2016; Song et al., 2019). aMCI accounts for the largest proportion of MCI cases, and patients have the highest risk of conversion to AD, i.e., about 50% (Gauthier et al., 2006). However, early intervention in aMCI patients can delay disease progression (Li et al., 2020). Although medications are the most common method of treating cognitive impairment, evidence does not support the use of examined pharmacological treatments for cognitive protection in persons with MCI (Fink et al., 2018). Furthermore, over-the-counter medicines have not been found to supplement cognitive protection in adults with MCI (Butler et al., 2018a). A systematic review reported that evidence regarding the effects of cognitive training on cognitive performance and dementia outcomes in adults with MCI is insufficient (Butler et al., 2018b). Therefore, there is an urgent need to explore better treatments for aMCI patients.

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique that has been found to be effective in treating a variety of neuropsychiatric conditions (Gu et al., 2013; Iimori et al., 2019) such as AD, refractory major depression, and chronic pain (Perera et al., 2016; Nardone et al., 2018; Iimori et al., 2019). Although rTMS is thought to be effective in alleviating cognitive symptoms in patients with aMCI, the mechanisms related to such network modification are poorly understood. High-frequency rTMS generates a more whole-brain reaction compared with low-frequency rTMS (Curtin et al., 2017; Zhang et al., 2020), and has been demonstrated via functional magnetic resonance imaging (fMRI) to affect the function of intrinsic brain connections (Cui et al., 2019).

The dorsolateral prefrontal cortex (DLPFC) is considered a key part of the executive control network (ECN) and frontoparietal network (FPN). It acts as a modulator of cognitive function and plays an important role in cognitive functions, such as attention, working memory, and executive function (Lara and Wallis, 2015). The DLPFC, which anatomically corresponds to Brodmann areas 9 and 46, is one of the most popular rTMS targets for treating cognitive impairment. Although high-frequency rTMS of the left DLPFC has been found to be effective in alleviating cognitive symptoms in patients with MCI (Drumond Marra et al., 2015; Cheng et al., 2018) and AD (Luber and Lisanby, 2014; Vacas et al., 2019), the neuroimaging mechanisms are poorly understood. Uncovering the mechanisms of action of TMS is critical to improving treatment efficacy and developing new therapeutic stimulation parameters.

Resting-state fMRI (RS-fMRI) is an effective way to explore changes in brain structure and function (Zhang et al., 2018; Zhao et al., 2020). Recently, increasing numbers of RS-fMRI studies have investigated neural plasticity and treatment responses (Pascual-Leone et al., 2011) associated with rTMS. Furthermore, functional connectivity (Philip et al., 2018) has been used to assess responses to rTMS. The amplitude of low-frequency fluctuations (ALFF) (Zang et al., 2007) is used as a biomarker of cerebral spontaneous activity (Yang et al., 2007). However, few studies have explored the after-effects of high-frequency rTMS over the left DLPFC applied during the resting state with respect to cognitive impairment. Thus, how rTMS affects spontaneous brain activity and the specific brain region(s) involved remain unclear.

We hypothesized that rTMS over the left DLPFC would modulate widespread cognitive-related regional spontaneous brain activity in aMCI patients that could be measured by RS-fMRI analysis. Accordingly, we investigated the neuroimaging mechanisms of high-frequency rTMS in patients with aMCI using ALFF.

Subjects and Methods

Subjects

aMCI subjects were recruited from a community near the Third Hospital Affiliated to Sun Yat-sen University of China from August 2016 to December 2018. All patients understood the study and signed an informed consent form (**Additional file 1**) prior to participation. The study was approved by the Ethics Committee of the Shenzhen Baoan Hospital of Southern Medical University, China (approval No. BYL20190901) on September 3, 2019 (**Additional file 2**), and registered in the Chinese Clinical Trial Registry (registration No. ChiCTR1900028180) on December 14, 2019.

In this study, the inclusion criteria were as follows: aMCI as diagnosed via Petersen's diagnostic criteria (Petersen, 2004); aged 55–75 years; memory complaint provided by the patient or family; memory impairment relative to age; right-handed; Montreal Cognitive Assessment (MoCA) score ≤ 26; Clinical Dementia Rating Scale of 0.5 points or total decline scale (Global Deterioration Scale) of 2–3; and normal level of daily living ability. Patients were excluded if they had: comorbid diseases that cause cognitive decline (e.g., stroke, vascular disease, Parkinson's disease, traumatic head injury, other relevant medical history); a Hachinski ischemic score of > 4 and/or Hamilton Depression Scale score > 8; claustrophobia or disorders such as deafness, language impairment, or blindness such that they could not perform the fMRI and cognitive function test; or contraindications for TMS, such as metal implants, electronic devices, or pacemakers.

Based on the TMS and fMRI literature, combined with the efficacy of TMS and the test efficacy, we calculated that it would be possible to detect a significant difference with a sample size of 12 aMCI patients per group (Padala et al., 2018). A researcher who did not participate in the study divided the 24 participants into a treatment and sham group (n = 12) using the random number table method, and generated the relevant random numbers. Using the double-blind method, the assessor, data analysts and participants were blinded to the grouping. The assessor and data analysts did not participate in the clinical intervention. The flow chart of the study procedure is shown in **Figure 1**.

rTMS

rTMS was performed using a CCYIA Stimulator (Yiruide Medical Equipment Co., Wuhan, China) connected to a 70-mm diameter figure-8 coil. DLPFC positioning was 5.5 cm anterior to M1 (Pascual-Leone et al., 1996). All patients received rTMS sessions for 4 weeks, five times per week, on consecutive days. According to a previous meta-analysis (Xu et al., 2019) and application guidelines for TMS (Rossi et al., 2009), the rTMS parameters were: 10-Hz frequency with a 2-second stimulation time and 8-second intermittent period, repeated 20 times for a total of 400 pulses per session. The entire session lasted about 200 seconds. The stimulus intensity was set at 80% of the resting motor threshold. The resting motor threshold was defined as the lowest intensity that produced motor evoked potentials of > 50 μV in the relaxed first dorsal interosseous muscle in the right hand in at least five out of 10 trials (Rossini et al., 2015).

For sham stimulation, the coil was tilted 90° relative to the skull (Berlim et al., 2013). At this position, the magnetic field is tangential to the scalp and does not cause cortical irritation. The remaining instruments, stimulation parameters, stimulation sites, and other parameters were the same as in the treatment group.

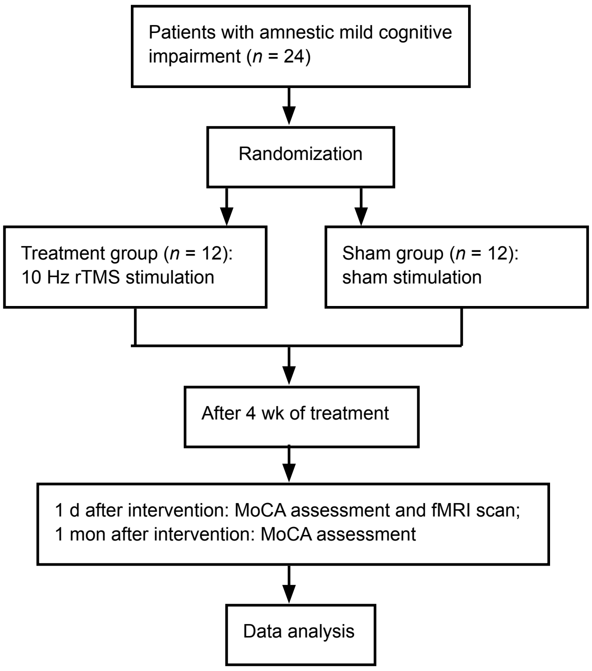


Figure 1 | Flow chart of the study procedure.
fMRI: Functional magnetic resonance imaging; MoCA: Montreal Cognitive Assessment; rTMS: repetitive transcranial magnetic stimulation.

Neuropsychological assessment
To assess the overall cognitive function of the patients before and after the intervention, a trained assessor examined all participants using the Clinical Dementia Rating Scale (Morris, 1993), Global Deterioration Scale (Reisberg et al., 1982), and MoCA (Nasreddine et al., 2005). To evaluate the effects of the rTMS session, the MoCA was repeated 1 day and 1 month after the intervention. The MoCA (Nasreddine et al., 2005) includes eight cognitive areas—executive function, naming, memory, attention, language, abstraction, delayed recall, and orientation—and has a maximum score of 30 points.

Image acquisition
fMRI scans were conducted before and after the rTMS intervention using a 3.0-T GE scanner (MR-750; General Electric, Milwaukee, WI, USA). The scan sequence included structural images and functional images. Before the scan, patients were familiarized with the functional nuclear magnetic equipment and the scanning environment. During the scan, they were asked to close their eyes, maintain natural relaxation without thinking of anything in particular, and to keep their head as static as possible. The structural image was generated using a 3D brain volume imaging sequence. The main parameters were repetition time = 8.2 ms, echo time = 3.2 ms, flip angle = 90°, field of view = 25.6 cm, matrix = 256 × 256, and slice thickness = 1 mm, 130 slices. Functional image scanning in the resting state was conducted used a gradient-recalled echo planar imaging sequence. The main parameters were repetition time = 2500 ms, echo time = 30 ms, field of view = 21.6 cm, matrix = 72 × 72, slice thickness = 3.0 mm, slice space = 0, and flip angle = 90°, 52 slices.

Image pre-processing and ALFF analysis
The data were pre-processed using the Data Processing Assistant for RS-fMRI (http://www.rfmri.org/DPARSF) (Chao-Gan and Yu-Feng, 2010). First, the data format was converted from DICOM to NIFTI and the first 10 volumes of data were excluded to remove the initial unstable signal. Then, slice timing correction, realignment, and normalization were sequentially performed. Next, the functional images were smoothed using a Gaussian kernel of 4 mm with the full width at half-maximum. Finally, we regressed out nuisance covariates, including head motion parameters, white matter signal, and cerebrospinal fluid signal. After preprocessing, ALFF was obtained by filtering (0.01–0.08 Hz).

Statistical analysis
The statistical analyses were performed using SPSS version 20.0 software (IBM SPSS, Inc., Chicago, IL, USA). For clinical variables, we performed non-parametric paired signed rank tests with $P < 0.05$ indicating a significant value. To compare the MoCA score, we used a two-sample *t*-test for between-group comparisons, and a paired *t*-test for within-group comparisons. To assess the between-group differences in ALFF between the two groups before and after the rTMS intervention, we performed a two-sample *t*-test with sex, age, and education as covariates. Then, we performed a paired *t*-test to evaluate the differences in within-group comparisons of ALFF. The significance threshold was set to $P < 0.05$ for false discovery rate correction, with a minimum cluster size of 85 voxels.

We performed correlation analysis between MoCA scores and each ALFF signal map in the aMCI patients. The analysis was performed using the Correlation Analysis module of the REST software (http://restfmri.net/forum/rest), and results were corrected via false discovery rate correction ($P < 0.05$).

Results
Clinical characteristics of aMCI patients with rTMS or sham stimulation
A total of 45 cases were screened in this study. For each group, we randomly selected 13 aMCI patients for each group after receiving informed consent. One patient from each group discontinued the study because of poor treatment efficacy. Throughout the study, a total of three patients in the treatment group reported mild headaches at the beginning of treatment. The patients reported that they were able to tolerate the headaches and opted to continue the treatment. Finally, 24 patients were included in the analysis. The baseline characteristics of the patients in the two groups are shown in **Table 1**, and there were no statistically significant differences between the groups before the intervention ($P > 0.05$).

Neuropsychological scores of aMCI patients with rTMS or sham stimulation
Figure 2 shows the MoCA scores for the three assessment periods. The MoCA scores of the treatment group had significantly improved at the end of the treatment and 1 month after the treatment ($P < 0.05$, *vs*. pre-treatment), and were higher than those in the sham group ($P < 0.05$). However, there were no statistical differences in MoCA scores in the sham group among different time points.

ALFF values in aMCI patients with rTMS or sham stimulation
There were no significant differences in ALFF values between the treatment and sham groups before treatment ($P > 0.05$). After treatment, the ALFF values in the right middle frontal gyrus had significantly increased compared with the baseline vales in the treatment group ($P < 0.05$; **Figure 3A** and **Table 2**).

Table 1 | Characteristics of amnestic mild cognitive impairment patients after repetitive transcranial magnetic stimulation or sham stimulation

Characteristics	Treatment group	Sham group	*P*-value
Sex (male/female, *n*)	6/6	5/7	0.698
Age (yr)	65.08±4.89	64.67±4.77	0.835
Education (yr)	11.83±2.37	11.33±2.15	0.500
Course of disease (yr)	4.25±2.26	3.50±2.23	0.423
Montreal Cognitive Assessment	22.83±1.11	22.00±1.28	0.103

Data are expressed as the mean ± SD ($n = 12$), except sex. All data were analyzed via a two-sample *t*-test.

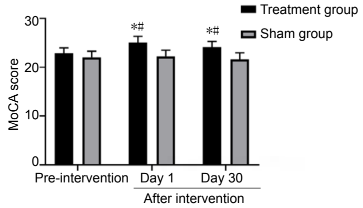


Figure 2 | MoCA scores of amnestic mild cognitive impairment patients after repetitive transcranial magnetic stimulation or sham stimulation.
Data are expressed as the mean ± SD (n = 12 per group). All data were analyzed via a two-sample t-test. *P < 0.05, *vs.* pre-intervention; #P < 0.05, *vs*. sham group. MoCA: Montreal Cognitive Assessment; Day1: 1 day after the intervention; Day30: 1 month after the intervention.

In the sham group, the ALFF values in the right middle frontal gyrus, inferior parietal lobule, and precuneus had significantly decreased compared with the baseline values (P < 0.05; **Figure 3B** and **Table 2**). Compared with the sham group, the ALFF values in the right inferior frontal gyrus, triangular part of the inferior frontal gyrus, right precuneus, left angular gyrus, and right supramarginal gyrus had significantly increased, and the ALFF values in the right superior frontal gyrus had significantly decreased in the treatment group after the intervention (P < 0.05; **Figure 3C** and **Table 2**).

Relationship between MoCA scores and ALFF signal maps in aMCI patients with rTMS or sham stimulation

The correlation analysis failed to find a statistically significant association between MoCA scores and ALFF signal maps.

Discussion

TMS uses a pulsed magnetic field to act on the central nervous system. TMS can affect not only the area stimulated, but also distant brain areas that are interconnected with the stimulation site (Ruff et al., 2009). These 'network' effects of TMS can change with the functional state of the targeted network and provide new perspectives on how remote but interconnected brain areas support cognition (Du et al., 2018; Philip et al., 2018). In the present study, we investigated the effects of high-frequency rTMS on cognitive function and brain spontaneous activity in patients with aMCI. After stimulation, neuropsychological tests showed that MoCA scores improved in the treatment group, but not in the sham group. We used ALFF values to assess spontaneous activity in the brain after a 4-week rTMS intervention. The results showed that ALFF in the right middle frontal gyrus increased in the treatment group. However, we only observed decreases in ALFF in the sham group. Significant differences in ALFF in the right frontal gyrus, right precuneus, and inferior parietal lobule were also observed between the treatment and sham groups.

aMCI is characterized by widespread abnormal ALFF. A recent meta-analysis showed a decrease in ALFF values in the bilateral frontoinsular cortices, right supramarginal gyrus, and bilateral precuneus/posterior cingulate cortex of patients with aMCI (Pan et al., 2017). The frontal lobe is one of the most complex brain regions and is responsible for decision-making, regulating behavior, learning, and memory storage. It is even considered to be the memory-processing center in individuals with MCI (Yao et al., 2010). The imbalance among neural networks in aMCI patients may be caused by decreases in ALFF in the bilateral frontal cortex, which could negatively affect the efficiency of processes that control cognitive function. The precuneus has been strongly implicated in visuo-spatial imagery, episodic memory retrieval, and self-processing operations (Cavanna and Trimble, 2006). Pathologically, the precuneus is important for determining the dementia state in early AD (Yokoi et al., 2018). The severity of cognitive impairment has been shown to be inversely related to activity in the precuneus cortices. The supramarginal and angular gyri are part of the inferior parietal cortex. The supramarginal gyrus is involved in language learning, attention (Verga and Kotz, 2019), emotional processing (Flasbeck et al., 2019), and other important functions. The angular gyrus is not only responsible for semantic processing, but has also been long regarded as an area in which cortical multisensory convergence takes place (Xie et al., 2019). In our study, as ALFF increased in multiple regions in aMCI patients following rTMS, the intervention may have affected cognitive function. Additionally, the right frontal lobe, inferior parietal cortex, and precuneus are regarded as key nodes of the default mode network (DMN), ECN, and FPN, and these regions may be essential structures that interconnect different brain networks that interact and collectively control attention, working memory, and other cognitive operations (Chen et al., 2013).

The DMN participates in the retrieval of autobiographical episodic memory and self-referential mental processing (Joo et al., 2016). The DMN includes the posterior cingulate cortex/precuneus, medial prefrontal cortex, inferior parietal lobule, lateral temporal cortex, and hippocampal formation (Buckner et al., 2008). It has been implicated in higher cognitive functions and is the most extensively explored brain network in MCI and AD patients (Krajcovicova et al., 2014). The DMN is vulnerable to neuropathology and converging evidence suggests that aberrant spontaneous brain activity in the posterior DMN occurs in aMCI patients. In individuals with MCI, the central executive system has been found to exhibit hypoactivation of the right frontoparietal regions and attenuation of the DMN (Melrose et al., 2018). As the hub of the brain network, the precuneus not only has widespread connections with other brain regions, but is also a key node in the DMN (Utevsky et al., 2014; Li et al., 2019). In AD patients, connectivity has been found to significantly decrease between the precuneus and widespread brain regions (Yokoi et al., 2018). Over time, progressive damage in the DMN was found in patients with aMCI (Bai et al., 2011). Therefore, the DMN

Table 2 | The specific values of the clusters with significant differences in amnestic mild cognitive impairment patients after rTMS or sham stimulation

				MNI coordinates (mm)			
	Clusters	Brodmann area	Voxels	*X*	*Y*	*Z*	*t*-value
Treatment group	Right middle frontal	46	102	45	30	21	3.9699
Sham group	Right middle frontal	46	173	39	48	0	–5.3776
	Right supramarginal	40	121	66	–39	33	–8.8384
	Left precuneus	31	342	0	–60	33	–13.5093
Intergroup	Right inferior frontal gyrus, triangular part	46	380	48	30	18	6.3389
	Right precuneus	31	285	15	–63	45	5.8361
	Lift angular	39	152	–48	–51	27	4.6104
	Right supramarginal	40	173	63	–42	33	5.2888
	Right superior frontal gyrus	6	159	21	3	63	–5.4426

MNI: Montreal Neurological Institute; rTMS: repetitive transcranial magnetic stimulation. All clusters in Table 2 were P < 0.05.

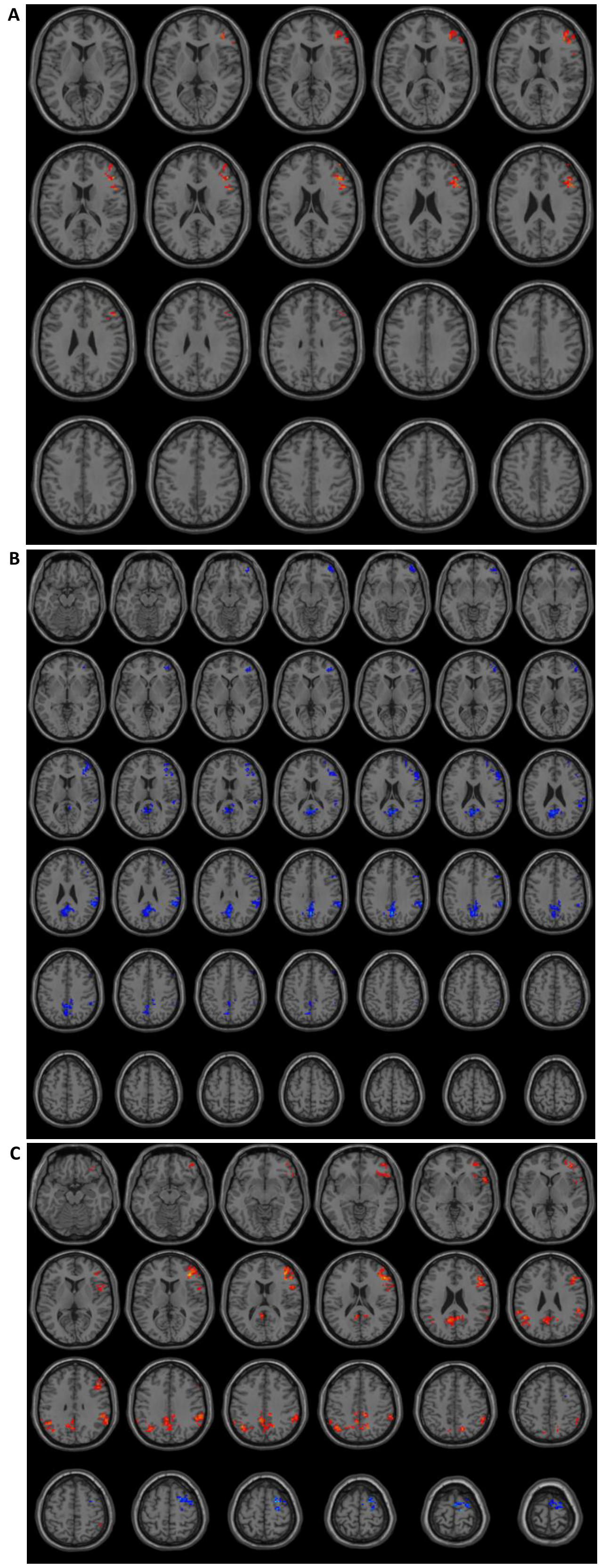


Figure 3 | **ALFF analysis of amnestic mild cognitive impairment patients after rTMS or sham stimulation.**

(A, B) The ALFF values in the different brain regions in the rTMS treatment (A) and sham groups (B). (C) Differences in ALFF values between the treatment and sham groups after the rTMS intervention. Red represents an increase and blue represents a decrease. The *P*-value, corrected by topological FDR, was set to $P < 0.05$. ALFF: Amplitude of low-frequency fluctuation; FDR: false discovery rate; rTMS: repetitive transcranial magnetic stimulation.

may be useful in monitoring aMCI progress (Serra et al., 2016) and may be a potential target for treating cognitive decline (Huang et al., 2016). Halko et al. (2014) found that intermittent theta burst stimulation of the lateral cerebellum enhanced functional connectivity of the DMN in healthy humans. Additionally, the proximal DMN region in elderly adults was found to exhibit increased connectivity after intermittent theta burst stimulation (Abellaneda-Pérez et al., 2019b). Xue et al. (2017) showed that rTMS of the left DLPFC enhanced functional connectivity between DMNs. The current finding that rTMS applied over the left DLPFC significantly changed activity in several areas, including the right frontal gyrus, right precuneus, and inferior parietal lobule, is consistent with the above findings.

The ECN typically comprises the DLPFC (Damoiseaux et al., 2006; Vincent et al., 2008), anterior cingulate cortex, and inferior parietal cortex (Zhao et al., 2018), and plays a key role in cognitive function (Zhao et al., 2019). aMCI is characterized by memory deficits and patients typically exhibit abnormal functional connectivity between the frontal lobe and other brain regions. For instance, one study found decreased connectivity in the DMN and ECN in the frontoinsular cortices of aMCI patients (He et al., 2014). Reduced functional connectivity in AD (Zhao et al., 2018) and MCI has been found to be related not only to activity in the DMN and ECN, but also the FPN. Indeed, many network interactions appear to be disrupted in aMCI patients (Chand et al., 2018). The FPN consists of the anterior prefrontal cortex, DLPFC, and other areas that correspond with cognitive function such as decision-making and language (Vincent et al., 2008). Hafkemeijer et al. (2017) found decreased connectivity between the precuneus and right FPN in AD patients. Functional connectivity in the FPN and ECN was also significantly decreased in AD patients (Zhao et al., 2018), and so may be useful as a potential non-invasive biomarker of early AD (Zhao et al., 2019). Indeed, maintaining an optimal dynamic between networks is essential for successful cognition (Abellaneda-Pérez et al., 2019a), and abnormal functional connectivity of networks may be the main cause of morbidity (Godwin et al., 2017).

TMS interacts with neural networks that participate in cognitive processing, rather than isolated hubs (Abellaneda-Pérez et al., 2019a). Results from a study by Ge et al. (2019) suggest that the ECN may play a role in mediating the efficacy of rTMS in the treatment of depression. Gratton et al. (2013) showed that after TMS of the left DLPFC, connectivity in the left DLPFC to the medial superior frontal gyrus, anterior insula/inferior frontal gyrus, and angular gyrus increased. High-frequency rTMS of the left DLPFC might selectively strengthen resting-state functional connectivity within the right FPN in obese adults (Kim et al., 2019). However, no previous studies have demonstrated the impact of rTMS on the brain network of aMCI patients. The present study indicates that rTMS can enhance ALFF values in the frontal lobe, precuneus, and IPC in aMCI patients. This may indicate that rTMS interventions have potential as a therapeutic approach for aMCI, via alteration of functional connectivity among brain networks. Stimulating the DLPFC might enhance functional connectivity in the DMN, ECN, and FPN, as well as the connections between these three networks. rTMS was found to have significant effects on the whole-brain functional network in postherpetic neuralgia patients, with potential improvements in cognition and memory function (Pei et al., 2019). A systematic review showed that the efficacy of TMS for treating major depression was associated with distal rather than proximal changes in the TMS stimulation site (Philip et al., 2018). Our results are consistent with these studies. However, Richieri et al. (2017) found a decrease in connectivity between the left DLPFC and the cingulate/medial frontal cortex in treatment-resistant depression, which contrasts with our findings. This may be because of differences between the diseases studied and treatment mechanisms tested. In the present study, the observed increase in brain activity in the frontal lobe, precuneus, and IPC indicated that rTMS stimulation was effective in improving cognitive function, and these RS-fMRI results were consistent with the changes in MoCA score. However, that the MOCA score was not related to the ALFF value was consistent with Weiler's results (Weiler et al., 2014), but contradicted Liang's findings (Liang et al., 2014). Our results may be explained by the small and heterogeneous nature of the sample.

In contrast, there were no significant improvements in MoCA score before *vs*. after stimulation in the sham group. Furthermore, the ALFF values in the right frontal gyrus, anterior "wedge" gyrus, and the superior anterior gyrus were significantly lower after *vs*. before treatment. Studies have shown that if effective interventions are not carried out in aMCI patients, the disease will continue to progress and brain connectivity will decline over time (Wang et al., 2012). Although we found no statistical difference in MoCA score, cognitive function decreases at a slow rate, and changes may not have been captured in the study time period. Thus, these results may be associated with decreased memory function in aMCI patients. Additionally, the sham group did not show an enhanced ALFF area, which may be related to the severity of the disease (Yang et al., 2018). Successful cognition in elderly adults may depend on the maintenance of prefrontal activity rather than compensation (Abellaneda-Pérez et al., 2019a). Therefore, when normal activities are not maintained, cognitive function may decrease. Alternatively, these findings may have been caused by variability in compensation processes, the heterogeneity of the sample, or an insufficient sample size.

This study had several limitations. First, the sample size was relatively small. Second, the DLPFC is an important brain area for cognitive function, and depending on the asymmetry of the brain, TMS may have different effects on the left or right DLPFC. However, this study only explored stimulation of the left DLPFC. Additionally, positioning the coil perpendicular to the scalp may not be sufficient to achieve the condition of a completely false stimulation. A control coil should be used to perform sham stimulation in future studies.

TMS stimulation involves multiple parameters such as stimulation target, stimulation frequency, intensity, pulse, stimulation treatment course, and stimulation mode. The frontal lobe, temporal lobe, anterior wedge lobe, and other brain areas can be used as stimulation targets for TMS treatment. These brain regions all show initial efficacy, which is the key goal of optimizing aMCI stimulation programs. Low-frequency (≤ 1 Hz) and high-frequency rTMS (> 1 Hz) have been found to reduce and increase cortical excitability, respectively. Studies have shown that 5–20 Hz high-frequency rTMS is more effective than low-frequency rTMS in treating aMCI. Therefore, different stimulation parameters may modulate brain regions in unique ways, with diverse clinical effects. The adverse reactions in this test were slightly transient and resolved without special treatment. In trials and clinical applications, it is necessary to exclude patients with certain contraindications, such as metallic implants, according to TMS application guidelines.

In summary, our data indicate that rTMS of the right DLPFC improved cognitive function in aMCI patients, and also modulated widespread cognitive-related regional spontaneous brain activity, mainly involving the DMN, ECN, and FPN. This could indicate that rTMS improves cognitive function in aMCI patients by altering the functional connectivity of brain networks. These findings provide an objective basis for the effectiveness of rTMS in the treatment of cognitive dysfunction in aMCI patients. Future studies could expand upon this research, for example, by assessing the effects of rTMS within functional connections and the impact on multiple brain networks, to better understand the effects of brain stimulation on the cortical network.

Acknowledgments: *We thank all the doctors of the Zhujiang Hospital and Shenzhen Baoan Hospital of Southern Medical University, China for critical discussion of this study.*
Author contributions: *Study concept: SJC, GZH; experiment implementation: LQY, QZ, DW, XYW; data collection and analysis: LQY, QZ; data interpretation: DW, XYW, YS, FZ, SJC, GZH; manuscript preparation: SJC, GZH; manuscript drafting: LQY, QZ, DW, XYW, YS, FZ. All authors approved the final version of the manuscript.*
Conflicts of interest: *The authors declare no conflict of interest.*
Financial support: *This work was supported by the National Natural Science Foundation of China, No. 81874032 (to GZH); the Science and Technology Planning Project of Shenzhen of China, No. JCYJ20160427191726109 (to FZ); the Science and Technology Planning Project of Guangdong Province of China, No. 2016A020215202 (to SHC); and Shenzhen Health and Family Planning System Research Project of China, No. SZXJ2017069 (to SHC). The funding sources had no role in study conception and design, data analysis or interpretation, paper writing or deciding to submit this paper for publication.*
Institutional review board statement: *This study was approved by the Ethics Committee of Shenzhen Baoan Hospital of Southern Medical University, China (approval No. BYL20190901) on September 3, 2019, and registered in the Chinese Clinical Trials Registry (registration No. ChiCTR1900028180) on December 14, 2019.*
Declaration of patient consent: *The authors certify that they have obtained the consent forms from patients. In the form, patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published.*
Reporting statement: *The writing and editing of the article were performed in accordance with the CONsolidated Standards Of Reporting Trials (CONSORT) Statement.*
Biostatistics statement: *The statistical methods of this study were reviewed by the epidemiologist of Zhujiang Hospital of Southern Medical University, China.*
Copyright license agreement: *The Copyright License Agreement has been signed by all authors before publication.*
Data sharing statement: *Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices). Data will be available immediately following publication, with no end date. Results will be disseminated through presentations at scientific meetings and/or by publication in a peer-reviewed journal. Anonymized behavioral data will be available indefinitely at www.figshare.com.*
Plagiarism check: *Checked twice by iThenticate.*
Peer review: *Externally peer reviewed.*

Open peer reviewer: *Sergio Bagnato, Giuseppe Giglio Foundation, Italy.*
Additional files:
Additional file 1: *Informed consent form (Chinese).*
Additional file 2: *Hospital ethics approval (Chinese).*
Additional file 3: *Open peer review report 1.*
Additional file 4: *Original data.*

References

Abellaneda-Pérez K, Vaqué-Alcázar L, Solé-Padullés C, Bartrés-Faz D (2019a) Combining non-invasive brain stimulation with functional magnetic resonance imaging to investigate the neural substrates of cognitive aging. J Neurosci Res doi: 10.1002/jnr.24514.
Abellaneda-Pérez K, Vaqué-Alcázar L, Vidal-Piñeiro D, Jannati A, Solana E, Bargalló N, Santarnecchi E, Pascual-Leone A, Bartrés-Faz D (2019b) Age-related differences in default-mode network connectivity in response to intermittent theta-burst stimulation and its relationships with maintained cognition and brain integrity in healthy aging. Neuroimage 188:794-806.
Bai F, Watson DR, Shi Y, Wang Y, Yue C, YuhuanTeng, Wu D, Yuan Y, Zhang Z (2011) Specifically progressive deficits of brain functional marker in amnestic type mild cognitive impairment. PLoS One 6:e24271.
Berlim MT, Broadbent HJ, Van den Eynde F (2013) Blinding integrity in randomized sham-controlled trials of repetitive transcranial magnetic stimulation for major depression: a systematic review and meta-analysis. Int J Neuropsychopharmacol 16:1173-1181.
Buckner RL, Andrews-Hanna JR, Schacter DL (2008) The brain's default network: anatomy, function, and relevance to disease. Ann N Y Acad Sci 1124:1-38.
Butler M, Nelson VA, Davila H, Ratner E, Fink HA, Hemmy LS, McCarten JR, Barclay TR, Brasure M, Kane RL (2018a) Over-the-counter supplement interventions to prevent cognitive decline, mild cognitive impairment, and clinical Alzheimer-type dementia: a systematic review. Ann Intern Med 168:52-62.
Butler M, McCreedy E, Nelson VA, Desai P, Ratner E, Fink HA, Hemmy LS, McCarten JR, Barclay TR, Brasure M, Davila H, Kane RL (2018b) Does cognitive training prevent cognitive decline?: A systematic review. Ann Intern Med 168:63-68.
Cavanna AE, Trimble MR (2006) The precuneus: a review of its functional anatomy and behavioural correlates. Brain 129:564-583.
Chand GB, Hajjar I, Qiu D (2018) Disrupted interactions among the hippocampal, dorsal attention, and central-executive networks in amnestic mild cognitive impairment. Hum Brain Mapp 39:4987-4997.

Chao-Gan Y, Yu-Feng Z (2010) DPARSF: A MATLAB toolbox for "Pipeline" data analysis of resting-state fMRI. Front Syst Neurosci 4:13.
Chen AC, Oathes DJ, Chang C, Bradley T, Zhou ZW, Williams LM, Glover GH, Deisseroth K, Etkin A (2013) Causal interactions between fronto-parietal central executive and default-mode networks in humans. Proc Natl Acad Sci U S A 110:19944-19949.
Cheng CPW, Wong CSM, Lee KK, Chan APK, Yeung JWF, Chan WC (2018) Effects of repetitive transcranial magnetic stimulation on improvement of cognition in elderly patients with cognitive impairment: a systematic review and meta-analysis. Int J Geriatr Psychiatry 33:e1-e13.
Cui H, Ren R, Lin G, Zou Y, Jiang L, Wei Z, Li C, Wang G (2019) Repetitive transcranial magnetic stimulation induced hypoconnectivity within the default mode network yields cognitive improvements in amnestic mild cognitive impairment: a randomized controlled study. J Alzheimers Dis 69:1137-1151.
Curtin A, Sun J, Ayaz H, Qian Z, Onaral B, Wang J, Tong S (2017) Evaluation of evoked responses to pulse-matched high frequency and intermittent theta burst transcranial magnetic stimulation using simultaneous functional near-infrared spectroscopy. Neurophotonics 4:041405.
Damoiseaux JS, Rombouts SA, Barkhof F, Scheltens P, Stam CJ, Smith SM, Beckmann CF (2006) Consistent resting-state networks across healthy subjects. Proc Natl Acad Sci U S A 103:13848-13853.
Drumond Marra HL, Myczkowski ML, Maia Memória C, Arnaut D, Leite Ribeiro P, Sardinha Mansur CG, Lancelote Alberto R, Boura Bellini B, Alves Fernandes da Silva A, Tortella G, Ciampi de Andrade D, Teixeira MJ, Forlenza OV, Marcolin MA (2015) Transcranial magnetic stimulation to address mild cognitive impairment in the elderly: a randomized controlled study. Behav Neurol 2015:287843.
Du L, Liu H, Du W, Chao F, Zhang L, Wang K, Huang C, Gao Y, Tang Y (2018) Stimulated left DLPFC-nucleus accumbens functional connectivity predicts the anti-depression and anti-anxiety effects of rTMS for depression. Transl Psychiatry 7:3.
Fink HA, Jutkowitz E, McCarten JR, Hemmy LS, Butler M, Davila H, Ratner E, Calvert C, Barclay TR, Brasure M, Nelson VA, Kane RL (2018) Pharmacologic interventions to prevent cognitive decline, mild cognitive impairment, and clinical Alzheimer-type dementia: a systematic review. Ann Intern Med 168:39-51.
Flasbeck V, Enzi B, Brüne M (2019) Enhanced processing of painful emotions in patients with borderline personality disorder: a functional magnetic resonance imaging study. Front Psychiatry 10:357.
Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, Belleville S, Brodaty H, Bennett D, Chertkow H, Cummings JL, de Leon M, Feldman H, Ganguli M, Hampel H, Scheltens P, Tierney MC, Whitehouse P, Winblad B (2006) Mild cognitive impairment. Lancet 367:1262-1270.
Ge R, Downar J, Blumberger DM, Daskalakis ZJ, Lam RW, Vila-Rodriguez F (2019) Structural network integrity of the central executive network is associated with the therapeutic effect of rTMS in treatment resistant depression. Prog Neuropsychopharmacol Biol Psychiatry 92:217-225.
Godwin CA, Hunter MA, Bezdek MA, Lieberman G, Elkin-Frankston S, Romero VL, Witkiewitz K, Clark VP, Schumacher EH (2017) Functional connectivity within and between intrinsic brain networks correlates with trait mind wandering. Neuropsychologia 103:140-153.
Gratton C, Lee TG, Nomura EM, D'Esposito M (2013) The effect of theta-burst TMS on cognitive control networks measured with resting state fMRI. Front Syst Neurosci 7:124.
Gu P, Zhang ZX, Ma QY, Geng Y, Wang YY, Zhang LN, Wang MW (2013) Transcranial magnetic stimulation promotes proliferation of endogenous neural stem cells of Parkinson's disease model mice. Zhongguo Zuzhi Gongcheng Yanjiu 17:7939-7946.
Hafkemeijer A, Möller C, Dopper EG, Jiskoot LC, van den Berg-Huysmans AA, van Swieten JC, van der Flier WM, Vrenken H, Pijnenburg YA, Barkhof F, Scheltens P, van der Grond J, Rombouts SA (2017) A longitudinal study on resting state functional connectivity in behavioral variant frontotemporal dementia and Alzheimer's disease. J Alzheimers Dis 55:521-537.
Halko MA, Farzan F, Eldaief MC, Schmahmann JD, Pascual-Leone A (2014) Intermittent theta-burst stimulation of the lateral cerebellum increases functional connectivity of the default network. J Neurosci 34:12049-12056.
He X, Qin W, Liu Y, Zhang X, Duan Y, Song J, Li K, Jiang T, Yu C (2014) Abnormal salience network in normal aging and in amnestic mild cognitive impairment and Alzheimer's disease. Hum Brain Mapp 35:3446-3464.
Huang P, Fang R, Li BY, Chen SD (2016) Exercise-related changes of networks in aging and mild cognitive impairment brain. Front Aging Neurosci 8:47.
Iimori T, Nakajima S, Miyazaki T, Tarumi R, Ogyu K, Wada M, Tsugawa S, Masuda F, Daskalakis ZJ, Blumberger DM, Mimura M, Noda Y (2019) Effectiveness of the prefrontal repetitive transcranial magnetic stimulation on cognitive profiles in depression, schizophrenia, and Alzheimer's disease: A systematic review. Prog Neuropsychopharmacol Biol Psychiatry 88:31-40.
Joo SH, Lim HK, Lee CU (2016) Three large-scale functional brain networks from resting-state functional MRI in subjects with different levels of cognitive impairment. Psychiatry Investig 13:1-7.
Kim SH, Park BY, Byeon K, Park H, Kim Y, Eun YM, Chung JH (2019) The effects of high-frequency repetitive transcranial magnetic stimulation on resting-state functional connectivity in obese adults. Diabetes Obes Metab 21:1956-1966.
Krajcovicova L, Marecek R, Mikl M, Rektorova I (2014) Disruption of resting functional connectivity in Alzheimer's patients and at-risk subjects. Curr Neurol Neurosci Rep 14:491.
Lara AH, Wallis JD (2015) The role of prefrontal cortex in working memory: a mini review. Front Syst Neurosci 9:173.
Li R, Utevsky AV, Huettel SA, Braams BR, Peters S, Crone EA, van Duijvenvoorde ACK (2019) Developmental maturation of the precuneus as a functional core of the default mode network. J Cogn Neurosci 31:1506-1519.
Li Y, Guan HT, Zhou Y (2020) Semantic memory impairment and neuroregulation in patients with mild cognitive impairment. Zhongguo Zuzhi Gongcheng Yanjiu 24:5236-5242.
Liang P, Xiang J, Liang H, Qi Z, Li K, Alzheimer's Disease NeuroImaging I (2014) Altered amplitude of low-frequency fluctuations in early and late mild cognitive impairment and Alzheimer's disease. Curr Alzheimer Res 11:389-398.
Luber B, Lisanby SH (2014) Enhancement of human cognitive performance using transcranial magnetic stimulation (TMS). Neuroimage 85 Pt 3:961-970.
Melrose RJ, Jimenez AM, Riskin-Jones H, Weissberger G, Veliz J, Hasratian AS, Wilkins S, Sultzer DL (2018) Alterations to task positive and task negative networks during executive functioning in Mild Cognitive Impairment. Neuroimage Clin 19:970-981.
Morris JC (1993) The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 43:2412-2414.
Nardone R, Brigo F, Höller Y, Sebastianelli L, Versace V, Saltuari L, Lochner P, Trinka E (2018) Transcranial magnetic stimulation studies in complex regional pain syndrome type I: A review. Acta Neurol Scand 137:158-164.
Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H (2005) The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 53:695-699.
Padala PR, Padala KP, Lensing SY, Jackson AN, Hunter CR, Parkes CM, Dennis RA, Bopp MM, Caceda R, Mennemeier MS, Roberson PK, Sullivan DH (2018) Repetitive transcranial magnetic stimulation for apathy in mild cognitive impairment: A double-blind, randomized, sham-controlled, cross-over pilot study. Psychiatry Res 261:312-318.
Pan P, Zhu L, Yu T, Shi H, Zhang B, Qin R, Zhu X, Qian L, Zhao H, Zhou H, Xu Y (2017) Aberrant spontaneous low-frequency brain activity in amnestic mild cognitive impairment: A meta-analysis of resting-state fMRI studies. Ageing Res Rev 35:12-21.
Pascual-Leone A, Rubio B, Pallardó F, Catalá MD (1996) Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. Lancet 348:233-237.
Pascual-Leone A, Freitas C, Oberman L, Horvath JC, Halko M, Eldaief M, Bashir S, Vernet M, Shafi M, Westover B, Vahabzadeh-Hagh AM, Rotenberg A (2011) Characterizing brain cortical plasticity and network dynamics across the age-span in health and disease with TMS-EEG and TMS-fMRI. Brain Topogr 24:302-315.
Pei Q, Zhuo Z, Jing B, Meng Q, Ma X, Mo X, Liu H, Liang W, Ni J, Li H (2019) The effects of repetitive transcranial magnetic stimulation on the whole-brain functional network of postherpetic neuralgia patients. Medicine (Baltimore) 98:e16105.
Perera T, George MS, Grammer G, Janicak PG, Pascual-Leone A, Wirecki TS (2016) The clinical TMS society consensus review and treatment recommendations for TMS therapy for major depressive disorder. Brain Stimul 9:336-346.
Petersen RC (2004) Mild cognitive impairment as a diagnostic entity. J Intern Med 256:183-194.
Petersen RC (2016) Mild Cognitive Impairment. Continuum (Minneap Minn) 22:404-418.
Petersen RC, Lopez O, Armstrong MJ, Getchius TSD, Ganguli M, Gloss D, Gronseth GS, Marson D, Pringsheim T, Day GS, Sager M, Stevens J, Rae-Grant A (2018) Practice guideline update summary: Mild cognitive impairment: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology 90:126-135.
Philip NS, Barredo J, Aiken E, Carpenter LL (2018) Neuroimaging mechanisms of therapeutic transcranial magnetic stimulation for major depressive disorder. Biol Psychiatry Cogn Neurosci Neuroimaging 3:211-222.
Reisberg B, Ferris SH, de Leon MJ, Crook T (1982) The Global Deterioration Scale for assessment of primary degenerative dementia. Am J Psychiatry 139:1136-1139.
Richieri R, Jouvenoz D, Verger A, Fiat P, Boyer L, Lançon C, Guedj E (2017) Changes in dorsolateral prefrontal connectivity after rTMS in treatment-resistant depression: a brain perfusion SPECT study. Eur J Nucl Med Mol Imaging 44:1051-1055.
Rossi S, Hallett M, Rossini PM, Pascual-Leone A (2009) Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 120:2008-2039.
Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, Di Lazzaro V, Ferreri F, Fitzgerald PB, George MS, Hallett M, Lefaucheur JP, Langguth B, Matsumoto H, Miniussi C, Nitsche MA, Pascual-Leone A, Paulus W, Rossi S, Rothwell JC, et al. (2015) 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 126:1071-1107.
Ruff CC, Driver J, Bestmann S (2009) Combining TMS and fMRI: from 'virtual lesions' to functional-network accounts of cognition. Cortex 45:1043-1049.
Serra L, Cercignani M, Mastropasqua C, Torso M, Spanò B, Makovac E, Viola V, Giulietti G, Marra C, Caltagirone C, Bozzali M (2016) Longitudinal changes in functional brain connectivity predicts conversion to Alzheimer's disease. J Alzheimers Dis 51:377-389.
Song GP, Yao TT, Wang D, Li YH (2019) Differentiating between Alzheimer's disease, amnestic mild cognitive impairment, and normal aging via diffusion kurtosis imaging. Neural Regen Res 14:2141-2146.
Utevsky AV, Smith DV, Huettel SA (2014) Precuneus is a functional core of the default-mode network. J Neurosci 34:932-940.
Vacas SM, Stella F, Loureiro JC, Simões do Couto F, Oliveira-Maia AJ, Forlenza OV (2019) Noninvasive brain stimulation for behavioural and psychological symptoms of dementia: A systematic review and meta-analysis. Int J Geriatr Psychiatry 34:1336-1345.
Verga L, Kotz SA (2019) Spatial attention underpins social word learning in the right fronto-parietal network. Neuroimage 195:165-173.
Vincent JL, Kahn I, Snyder AZ, Raichle ME, Buckner RL (2008) Evidence for a frontoparietal control system revealed by intrinsic functional connectivity. J Neurophysiol 100:3328-3342.
Wang Z, Liang P, Jia X, Jin G, Song H, Han Y, Lu J, Li K (2012) The baseline and longitudinal changes of PCC connectivity in mild cognitive impairment: a combined structure and resting-state fMRI study. PLoS One 7:e36838.
Weiler M, Teixeira CV, Nogueira MH, de Campos BM, Damasceno BP, Cendes F, Balthazar ML (2014) Differences and the relationship in default mode network intrinsic activity and functional connectivity in mild Alzheimer's disease and amnestic mild cognitive impairment. Brain Connect 4:567-574.
Xie YJ, Li YY, Xie B, Xu YY, Peng L (2019) The neural basis of complex audiovisual objects maintenances in working memory. Neuropsychologia 133:107189.
Xu Y, Qiu Z, Zhu J, Liu J, Wu J, Tao J, Chen L (2019) The modulation effect of non-invasive brain stimulation on cognitive function in patients with mild cognitive impairment: a systematic review and meta-analysis of randomized controlled trials. BMC Neurosci 20:2.
Xue SW, Guo Y, Peng W, Zhang J, Chang D, Zang YF, Wang Z (2017) Increased low-frequency resting-state brain activity by high-frequency repetitive TMS on the left dorsolateral prefrontal cortex. Front Psychol 8:2266.
Yang H, Long XY, Yang Y, Yan H, Zhu CZ, Zhou XP, Zang YF, Gong QY (2007) Amplitude of low frequency fluctuation within visual areas revealed by resting-state functional MRI. Neuroimage 36:144-152.
Yang L, Yan Y, Wang Y, Hu X, Lu J, Chan P, Yan T, Han Y (2018) Gradual disturbances of the amplitude of low-frequency fluctuations (ALFF) and fractional ALFF in Alzheimer spectrum. Front Neurosci 12:975.
Yao Z, Zhang Y, Lin L, Zhou Y, Xu C, Jiang T (2010) Abnormal cortical networks in mild cognitive impairment and Alzheimer's disease. PLoS Comput Biol 6:e1001006.
Yokoi T, Watanabe H, Yamaguchi H, Bagarinao E, Masuda M, Imai K, Ogura A, Ohdake R, Kawabata K, Hara K, Riku Y, Ishigaki S, Katsuno M, Miyao S, Kato K, Naganawa S, Harada R, Okamura N, Yanai K, Yoshida M, et al. (2018) Involvement of the precuneus/posterior cingulate cortex is significant for the development of Alzheimer's disease: A PET (THK5351, PiB) and Resting fMRI study. Front Aging Neurosci 10:304.
Zang YF, He Y, Zhu CZ, Cao QJ, Sui MQ, Liang M, Tian LX, Jiang TZ, Wang YF (2007) Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. Brain Dev 29:83-91.
Zhang H, Sollmann N, Castrillón G, Kurcyus K, Meyer B, Zimmer C, Krieg SM (2020) Intranetwork and internetwork effects of navigated transcranial magnetic stimulation using low- and high-frequency pulse application to the dorsolateral prefrontal cortex: a combined rTMS-fMRI approach. J Clin Neurophysiol 37:131-139.
Zhang S, Hu Q, Tang T, Liu C, Li C, Zang YY, Cai WX (2018) Changes in gray matter density, regional homogeneity, and functional connectivity in methamphetamine-associated psychosis: A resting-state functional magnetic resonance imaging (fMRI) study. Med Sci Monit 24:4020-4030.
Zhao J, Du YH, Ding XT, Wang XH, Men GZ (2020) Alteration of functional connectivity in patients with Alzheimer's disease revealed by resting-state functional magnetic resonance imaging. Neural Regen Res 15:285-292.
Zhao Q, Lu H, Metmer H, Li WXY, Lu J (2018) Evaluating functional connectivity of executive control network and frontoparietal network in Alzheimer's disease. Brain Res 1678:262-272.
Zhao Q, Sang X, Metmer H, Swati Z, Lu J (2019) Functional segregation of executive control network and frontoparietal network in Alzheimer's disease. Cortex 120:36-48.

P-Reviewer: Bagnato S; C-Editor: Zhao M; S-Editors: Yu J, Li CH; L-Editors: Yu J, Song LP; T-Editor: Jia Y

group	Age (yr)	Education (yr)	Sex	Course of disease (yr)	Pre-MoCA	1 day after	1 mon after MoCA
1	70	11	2	1	22	26	23
1	71	8	1	2	23	26	25
1	72	14	2	3	23	27	24
1	60	14	1	4	21	26	25
1	64	12	1	4	23	25	24
1	60	11	1	4	25	24	26
1	68	12	2	5	23	23	23
1	60	15	1	10	21	25	24
1	68	11	2	5	23	23	22
1	68	11	2	6	23	25	26
1	60	15	1	4	23	25	23
1	60	8	2	3	24	26	24
2	63	8	1	3	23	23	23
2	59	11	2	4	24	23	23
2	64	11	2	3	21	21	21
2	60	11	1	4	21	23	20
2	68	11	2	7	21	22	23
2	60	11	1	8	23	23	21
2	64	11	2	2	24	21	19
2	60	11	2	1	21	23	21
2	73	11	2	1	21	20	21
2	71	15	1	2	21	23	23
2	70	14	1	2	21	21	21
2	64	8	2	5	23	24	23

remark：group1=Treatment group, group2=Sham group;sex1=male, sex2=female