Intervention Effects of Repetitive Transcranial Magnetic Stimulation on Mild Cognitive Impairment

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Date: 2021-05-30T00:00:00+00:00

Abstract

Mild cognitive impairment (MCI) is an intermediate state between normal cognitive aging and dementia, for which no effective pharmacological treatment currently exists. Repetitive transcranial magnetic stimulation (rTMS) can improve cognitive function by inducing changes in synaptic plasticity. The efficacy and neural mechanisms of rTMS intervention for cognitive function in MCI are analyzed. Future research should optimize localization methods, extend follow-up assessments of intervention effects, investigate the impact of different stimulation parameters and target sites on intervention efficacy, and combine brain imaging techniques to explore the intervention mechanisms of rTMS.

Full Text

Effects of Repetitive Transcranial Magnetic Stimulation on Patients with Mild Cognitive Impairment

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Abstract: Mild cognitive impairment (MCI) represents an intermediate state between normal cognitive aging and dementia, for which no effective pharmacological treatments currently exist. Repetitive transcranial magnetic stimulation (rTMS) can improve cognitive function by inducing changes in synaptic plasticity. This systematic review analyzes the efficacy and neural mechanisms of rTMS interventions for cognitive function in MCI. Future research should optimize localization techniques, extend follow-up assessments of intervention effects, examine the impact of different stimulation parameters and target regions on treatment efficacy, and combine brain imaging technologies to explore the underlying mechanisms of rTMS intervention.

Keywords: mild cognitive impairment, non-pharmacological intervention, transcranial magnetic stimulation, TMS

Received: November 10, 2020
Funding: This work was supported by the Shenzhen Basic Research Program (Natural Science Foundation) General Project (JCYJ20190808121415365), Guangdong Provincial Natural Science Foundation Project (2020A1515011394), National Natural Science Foundation of China General Project (32071100), and National Key R&D Program of China (2018YFC1315200).

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Mild cognitive impairment (MCI) is an intermediate state between normal cognitive aging and dementia that does not impair daily activities (Petersen et al., 1999). In addition to Petersen (1999), who first proposed the MCI concept, the National Institute on Aging and Alzheimer' s Association (NIA-AA), Alzheimer' s Disease Neuroimaging Initiative (ADNI), and American Psychological Association (APA) have each established their own diagnostic criteria for MCI (Albert et al., 2011; Weiner et al., 2016; APA, 2000). These standards share common features: they use neuropsychological tests to assess cognitive function, exclude cognitive decline caused by dementia, and emphasize that daily activities remain unaffected in MCI individuals. The differences lie in that NIA-AA does not include subjective memory complaints and incorporates cognitive impairments beyond memory damage into the diagnostic criteria (Albert et al., 2011), whereas Petersen (1999) and APA (2000) provide detailed classifications of MCI patients' functional capacities, including general cognitive function, activities of daily living, and social functioning.

Cognitive impairments in MCI patients are primarily manifested in the memory domain, affecting episodic memory, semantic memory, and working memory, characterized by reduced memory capacity and diminished memory retention and consolidation abilities (Leukocyte & Summers, 2014; Supasitthumrong et al., 2019). Episodic memory impairment in MCI is associated with decreased hippocampal gray matter density, reduced posterior cingulate activation, and decreased default mode network activity (Venneri et al., 2019; Chetelat et al., 2003; Ries et al., 2006; Brier et al., 2014). Semantic memory impairment correlates with middle temporal gyrus atrophy (Venneri et al., 2019). Furthermore, when performing semantic memory tasks, MCI patients show enhanced functional connectivity in the anterior temporal network (primarily composed of the perirhinal cortex, entorhinal cortex, hippocampal head, amygdala, and lateral temporal lobe), which may represent a compensatory mechanism developed in response to cognitive impairment (Gour et al., 2011). During working memory tasks, MCI patients exhibit lower oxygenated hemoglobin concentrations in the left frontal lobe, right superior frontal gyrus, and left temporal lobe (Niu et al., 2013).

Beyond memory functions, MCI patients also demonstrate impairments in attention, language and speech, and executive function. Attention deficits in MCI primarily involve attention switching and orienting abilities, selective attention, and attention allocation (Okonkwo et al., 2008; Fernández et al., 2011; Charette et al., 2020). Attention impairment is associated with reduced prefrontal activity (Dannhauser et al., 2005). Evidence from electroencephalography (EEG) studies shows that MCI patients exhibit weakened beta-band oscillatory power during attention orienting tasks (Caravaglios et al., 2018). MCI also affects patients' language and speech functions, manifesting as slowed speech rate, longer syllable duration, and reduced pronunciation clarity (Mueller et al., 2018; Themistocleous et al., 2020), which is related to decreased frontal glucose metabolism (Kim et al., 2010). Additionally, executive function deficits such as impaired learning, intertemporal decision-making, and risky decision-making represent important clinical manifestations of MCI (Wu et al., 2016; Nemeth et al., 2013; Seo et al., 2016; Geng et al., 2020; Pertl et al., 2015; Sun et al., 2020). Existing evidence indicates that executive dysfunction is associated with atrophy of the hippocampus and anterior cingulate cortex (McGough et al., 2018). Moreover, the salience network, which includes the anterior cingulate cortex, plays a critical role in executive function (Dosenbach et al., 2008; Goulden et al., 2014). Recent evidence shows that MCI patients exhibit abnormalities in functional connectivity between the salience network and large-scale brain networks such as the default mode network and central executive network, as well as whole-brain functional connectivity (Chand et al., 2017; Cai et al., 2020).

MCI patients have a high conversion rate to Alzheimer' s disease (AD), with an annual AD conversion rate ten times higher than that of cognitively normal elderly individuals (陶雪琴 et al., 2016; Breton et al., 2019). The latest research data indicate that the prevalence of MCI in China has reached 14% (张惠玲 et al., 2020). However, the more 严峻 reality is that pharmacological treatments show limited efficacy in improving MCI (Luber et al., 2013). Consequently, researchers and clinicians have begun to focus on non-invasive physical therapies for functional neuromodulation (Cui et al., 2019). Repetitive transcranial magnetic stimulation (rTMS) is a neural stimulation and modulation technique based on the principle of electromagnetic induction in the brain' s electric field (Rossi et al., 2009). It generates pulsed magnetic fields on the scalp of awake subjects through a coil, creating painless induced currents that directly modulate neuronal function in the stimulated brain region, inducing changes in synaptic plasticity and cortical reorganization to promote modulation of cortical circuits (Luber et al., 2013), thereby improving overall brain function (Lefaucheur, 2019).

In recent years, rTMS has been increasingly applied to treat conditions such as depression, post-traumatic stress disorder, movement disorders, and chronic pain (Blades et al., 2020; Brys et al., 2016; Eijndhoven et al., 2020; Nardon et al., 2017; Perera et al., 2016). Indeed, previous studies have demonstrated that rTMS can improve multiple cognitive functions including working memory (Beynel et al., 2019; Yang et al., 2019), language (Zhao et al., 2017; Myczkowski et al., 2018), and decision-making (Rahnev et al., 2016; Guillaume et al., 2018), with improvements lasting for days or even weeks (Cotelli et al., 2012; Drumond et al., 2015). rTMS features adjustable pulse frequencies and relatively high spatial precision, allowing researchers to administer excitatory or inhibitory rTMS to impaired brain regions in MCI patients to improve their cognitive function.

Furthermore, from a neuroplasticity perspective, rTMS may have therapeutic effects on MCI. On one hand, rTMS can modulate synaptic plasticity (Strafella et al., 2001), which constitutes the neural basis of memory and learning—the primary cognitive domains impaired in MCI (Bliss & Lomo, 1973). On the other hand, MCI individuals retain synaptic plasticity (D' Antonio et al., 2019), making it possible for them to improve cognitive function through neuromodulation.

The first rTMS study on MCI was published in 2006 (Solé-Padullés et al., 2006). Although the number of publications in this field has shown a growth trend in recent years, the overall volume remains small, and controversies persist regarding the selection of primary stimulation sites, cognitive domains showing improvement, duration of treatment effects, and adverse reactions. The main points of debate concern which cognitive functions can be improved by rTMS intervention in MCI patients, how sustained the rTMS treatment effects are, and whether adverse reactions occur. In light of this, this article reviews empirical studies in this field to clarify the efficacy of rTMS in intervening with cognitive functions in MCI and its potential mechanisms of action, and to provide evidence for rTMS treatment of MCI.

2.1 Search Strategy

We searched Web of Science, PubMed, PsycINFO, and the China National Knowledge Infrastructure (CNKI) academic journal database to collect Chinese and English literature on rTMS intervention for MCI, with the search period extending from database inception to November 2020. Additionally, we traced the references of included studies to supplement relevant literature and ensure comprehensive retrieval. The search employed a combination of subject headings and free terms. English search terms included transcranial magnetic stimulation, TMS, repetitive transcranial magnetic stimulation, rTMS, cognitive disorder, mild cognitive impairment, and cognitive dysfunction. Chinese search terms included 经颅磁刺激, 轻度认知障碍, 轻度认知损害, 认知障碍, 认知损害, TMS, rTMS, and MCI. A total of 1,437 English articles and 29 Chinese articles were retrieved.

2.2 Inclusion and Exclusion Criteria

Inclusion criteria: (1) Study subjects: aged over 50 years, non-illiterate, with no geographical or gender restrictions; met diagnostic criteria for MCI (as established by Petersen, NIA-AA, ADNI, or APA (Petersen et al., 1999; Albert et al., 2011; Weiner et al., 2016; APA, 2000)); no other neurological or psychiatric conditions causing cognitive impairment; no rTMS contraindications such as metal implants. (2) Intervention measures: experimental subjects received rTMS (i.e., using a specific stimulator model to administer repetitive transcranial magnetic stimulation to a brain region after measuring subjects' motor thresholds; stimulation parameters such as pulse number, sequence, intensity, frequency, and duration were fixed), while control groups received sham stimulation (e.g., using a sham coil); or different brain regions were stimulated in experimental and control groups, such as dorsolateral prefrontal cortex, temporal lobe, or precuneus; or different intensities and frequencies of rTMS were administered to experimental and control groups. (3) Outcome measures: primary indicators included cognitive test scores such as Trail Making Test, Complex Figure Test, Verbal Fluency Test, Montreal Cognitive Assessment, and Mini-Mental State Examination; secondary indicators included adverse reactions. (4) Study types: randomized controlled trials (RCTs) and case studies.

Exclusion criteria: (1) Study subjects were only animals or healthy participants. (2) rTMS combined with pharmacological intervention. (3) Duplicate publications. (4) Lack of necessary outcome indicators for evaluating intervention effects.

Based on these criteria, 11 articles met the requirements. The screening process is shown in Figure 1 [Figure 1: see original paper].

2.3 Literature Quality Assessment

We used the Cochrane Risk of Bias Assessment Tool to evaluate the risk of bias in 10 RCT studies that met the criteria (Higgins et al., 2019). The remaining study was a case study (Cotelli et al., 2012), which did not meet the criteria for bias risk assessment and was therefore excluded from this quality evaluation. The quality assessment included random sequence generation, allocation concealment, blinding of researchers and participants, blinded outcome assessment, completeness of outcome data, selective reporting, and other biases. Risk of bias was classified into three levels: "low risk," "unclear risk," and "high risk." The risk of bias assessment chart is shown in Figure 2 [Figure 2: see original paper].

2.4 Literature Classification

To investigate the specific effects of rTMS on cognitive function in MCI patients, the included articles were categorized according to the cognitive functions improved by rTMS, identifying six aspects: attention and cognitive processing speed, executive function, episodic memory, long-term memory, short-term memory, and associative memory. Relevant research methods and results are detailed in Table 1 . The methods and results of the 11 studies are analyzed and summarized below.

Table 1 Basic Information of Included Studies

Regarding stimulation site selection, most researchers targeted the dorsolateral prefrontal cortex, while a small number stimulated regions such as the parietal lobe, precuneus, inferior frontal gyrus, and superior temporal gyrus. Two main localization methods were employed: one used neuronavigation for precise targeting, while the other used the relatively simple "5 cm rule," which involves stimulating the brain approximately 5/5.5 cm anterior to the cortical stimulation point corresponding to the abductor pollicis brevis muscle—this serves as the stimulation target for the dorsolateral prefrontal cortex.

Regarding rTMS stimulation frequency settings, parameters varied across studies but could be divided into two categories: excitatory stimulation (high frequency, $ $5 Hz) and inhibitory stimulation (low frequency, $ $1 Hz), with high-frequency rTMS promoting neuronal excitability and low-frequency rTMS reducing it (Lage et al., 2016). Stimulation intensity mostly ranged from 80% to 120% of subjects' resting motor thresholds.

The results of the included studies indicate that rTMS can improve cognitive function in MCI patients to some extent, and the intervention effects can be maintained for 1-6 months in certain cognitive domains (Cotelli et al., 2012; Drumond et al., 2015). Regarding adverse reactions, two studies reported that subjects experienced scalp pain during stimulation (Anderkova et al., 2015; Eliasova et al., 2014). Drumond (2015) found that adverse reactions gradually decreased during the later stages of stimulation, while other studies observed no potential adverse effects of rTMS.

4 Effects of rTMS Intervention on MCI

4.1 Attention and Cognitive Processing Speed Cognitive processing speed is one of the key indicators for measuring individual cognitive function (Moll et al., 2016). Studies have confirmed that rTMS applied to the inferior frontal gyrus and superior temporal gyrus in MCI patients can effectively improve their performance on attention and cognitive processing speed tasks, whereas stimulation of the vertex did not produce any cognitive changes (Anderkova et al., 2015; Eliasova et al., 2014). The inferior frontal gyrus and superior temporal gyrus, as important components of the ventral attention network, are involved in attentional orienting and switching processes (Corbetta & Shulman, 2002), and decreased activity in the inferior frontal gyrus leads to attention deficits (Weissman et al., 2006). Additionally, research has shown that rTMS applied to the right inferior frontal gyrus in Parkinson' s disease patients results in shortened latency of the event-related potential P3 component during cognitive tasks, indicating that rTMS can improve cognitive processing speed (Balaz et al., 2010). These results suggest that attention decline in MCI patients may be related to damage to attention networks including the inferior frontal gyrus and superior temporal gyrus (Liang et al., 2012), and rTMS can improve MCI patients' performance on attention tasks by enhancing the excitability of attention networks.

4.2 Executive Function Executive function comprises a series of higher-order cognitive processes responsible for regulating individuals' thinking and behavior patterns, with three core components: working memory, inhibitory control, and cognitive flexibility (Diamond, 2013). Taylor et al. (2019) found that excitatory rTMS applied to the dorsolateral prefrontal cortex in MCI patients could improve their executive function, consistent with the findings of Angius et al. (2019), who reported that enhanced dorsolateral prefrontal cortex activity was associated with improved Stroop test performance. Moreover, studies have shown that larger volume and cortical thickness of the dorsolateral prefrontal cortex in MCI patients correlate with better executive function performance (Shaked et al., 2018; Zhu et al., 2018), and the influence of the dorsolateral prefrontal cortex on executive function shows lateralization, with the left dorsolateral prefrontal cortex related to attention and the right to inhibition (Vanderhasselt et al., 2009). Recent research suggests that reduced cognitive control function may be a key impairment in MCI (He et al., 2019), and executive dysfunction largely contributes to emotional and cognitive deficits in AD patients (Chainay & Gaubert, 2020). However, current research on rTMS intervention for executive function in MCI individuals remains limited, and future studies should increase attention to this area.

4.3 Episodic Memory Episodic memory refers to memory for events occurring at specific times and places, and its functional impairment is a core clinical symptom in the pre-dementia stage of AD (Dubois et al., 2007). Koch et al. (2018) applied rTMS to the precuneus of 14 MCI patients while recording brain activity with EEG. The results showed that MCI patients' episodic memory improved significantly after stimulation compared to pre-stimulation baseline. The brain network involved in episodic memory retrieval consists of the ventral precuneus, ventral prefrontal cortex, and medial temporal lobe (Kaboodvand et al., 2018). In Koch et al.' s study, high-frequency rTMS to the precuneus may have facilitated retrieval of episodic memory information in MCI patients, thereby improving their episodic memory performance. Additionally, Koch et al. (2018) found enhanced beta-band oscillations in the precuneus after rTMS administration in MCI patients. Since increased precuneus activity is one of the characteristics of episodic memory learning (Gilmore et al., 2015), Koch et al.' s rTMS intervention on the precuneus in MCI patients may have enhanced long-term potentiation of neural cells in this region (Lorenzo et al., 2016), thereby promoting learning and memory of episodic information.

In addition to the precuneus, stimulating the dorsolateral prefrontal cortex in MCI patients can also enhance episodic memory, with intervention efficacy lasting up to 30 days (Drumond et al., 2015; 温秀云 et al., 2018). Previous studies have shown that the left and right prefrontal cortices are responsible for processing verbal and visual information in episodic memory, respectively (Balconi, 2013), and activating the dorsolateral prefrontal cortex during information processing can facilitate encoding and promote the formation of long-term episodic memory (Blumenfeld & Ranganath, 2006).

4.4 Long-Term Memory Turriziani et al. (2012) compared the effectiveness of inhibitory rTMS (1 Hz) and excitatory rTMS (50 Hz) on long-term memory by administering rTMS to the dorsolateral prefrontal cortex in both MCI patients and cognitively normal elderly individuals. The results showed that inhibitory stimulation applied to the right dorsolateral prefrontal cortex after stimulus presentation significantly improved long-term memory task performance in MCI patients. Research has demonstrated that inhibiting prefrontal activity during the interference task period before long-term memory assessment can enhance long-term memory (Karlsson et al., 2015; Keresztes et al., 2014). Additionally, Marián et al. (2018) found that anodal transcranial direct current stimulation (tDCS) applied to the right dorsolateral prefrontal cortex decreased long-term memory performance in subjects. In Turriziani et al.' s (2012) study, MCI patients were forced to suppress memories of previously presented stimulus materials during the interference task, which was detrimental to long-term memory formation.

A functional magnetic resonance imaging (fMRI) study showed that during interference tasks, the right dorsolateral prefrontal cortex was activated while hippocampal activity decreased, suggesting that suppressing previous memories may disrupt functional connectivity between the dorsolateral prefrontal cortex and hippocampus, thereby impairing long-term memory (Anderson et al., 2004). Therefore, the reason inhibitory stimulation of the dorsolateral prefrontal cortex improved long-term memory task performance in Turriziani et al.' s (2012) study may be that inhibitory rTMS interfered with this memory suppression mechanism.

Furthermore, 祝本菊 et al. (2012) applied low-frequency rTMS to bilateral anterior temporal regions in both vascular MCI (vMCI) and non-vascular MCI (nvMCI) patients and evaluated intervention effects using the Clinical Memory Scale. They found that both types of MCI patients showed improved scores on the Clinical Memory Scale, manifested electrophysiologically as shortened P3 latency and increased amplitude in event-related potentials. Moreover, the improvement in various indicators was significantly greater in the vMCI group than in the nvMCI group, while healthy control subjects showed age-related cognitive decline without any intervention. Since rTMS intervention can increase local cerebral blood flow and promote neuronal growth (Nadeau et al., 2002), and given the presence of vascular factors in the vMCI group, the intervention effects were more pronounced in this group.

4.5 Short-Term Memory Cui et al. (2019) found that applying high-frequency rTMS to the right dorsolateral prefrontal cortex could improve short-term memory performance in amnestic MCI patients, with follow-up assessments indicating that intervention effects could last for 8 weeks. The prefrontal cortex plays an important role in short-term memory. An animal study demonstrated that neuropeptide S could be used to increase prefrontal activity in mice, thereby improving short-term memory impairment caused by sleep restriction (Thomasson et al., 2017). Tian et al. (2018) used two-photon imaging in mice and found that there exists a neuronal subpopulation composed of excitatory neurons in the medial prefrontal cortex that can maintain connections for several minutes to encode short-term memory. Therefore, Cui et al.' s (2019) use of rTMS to stimulate the dorsolateral prefrontal cortex in MCI patients may have improved short-term memory performance by promoting connections among these neuronal subpopulations.

4.6 Associative Memory Associative memory involves learning and storing two unrelated pieces of information and plays an important role in daily life (Konkel & Cohen, 2009). Cotelli et al. (2012) used a face-name associative memory task to assess associative memory performance in amnestic MCI patients and found that applying high-frequency rTMS to the left inferior parietal lobule improved accuracy on the associative memory task, with this improvement maintained 6 months after stimulation ended. This suggests that the left inferior parietal lobule may play a role in the encoding and recognition processes of associative memory. Bjekić et al. (2019) applied tDCS to the parietal lobe in healthy subjects and similarly improved associative memory, further supporting Cotelli et al.' s (2012) findings. Stimulating the parietal lobe may also activate the hippocampus, which plays a central role in associative memory formation (Horecka et al., 2018), because the posterior parietal lobe has strong functional connectivity with the hippocampus, and parietal lobe activity' s contribution to memory performance is related to activation levels in the posterior hippocampus and adjacent regions (Hoppstädter et al., 2015).

High-frequency rTMS applied to the prefrontal cortex in MCI patients can also enhance associative memory performance. Solé-Padullés et al. (2006) used a face-surname memory task as an assessment tool and recorded changes in brain activity with fMRI during each evaluation. The results showed that before rTMS administration, brain regions activated during the face-surname task included the frontal lobe, parietal lobe, cingulate gyrus, and cerebellum, while after rTMS, higher activation was observed in the right inferior frontal gyrus, middle frontal gyrus, middle occipital gyrus, and inferior occipital gyrus, with associative memory performance also significantly improved. This suggests a compensatory brain network mechanism for associative memory in MCI patients.

5 Summary and Outlook

This article systematically reviewed recent rTMS studies in the MCI field and analyzed the main cognitive functions improved by rTMS and its potential mechanisms of action. The results indicate that rTMS intervention has good efficacy in improving cognitive function in MCI patients, with enhanced cognitive domains including attention and cognitive processing speed, executive function, episodic memory, long-term memory, short-term memory, and associative memory. Furthermore, the effects of rTMS intervention can be maintained for 30 days, 8 weeks, or 6 months. rTMS has attracted widespread attention from researchers due to its advantages of being safe, non-invasive, well-tolerated, and having sustained effects. However, current rTMS research in the MCI field still has some limitations, and future studies can be improved in the following four aspects.

First, optimize operational methods. Currently, some researchers still use the traditional "5 cm rule" to locate the dorsolateral prefrontal cortex. Although this method is simple and feasible, it has limitations in terms of inaccurate localization (Ahdab et al., 2010). Future studies should preferably use localization methods based on magnetic resonance structural imaging with neuronavigation or frameless stereotactic navigation systems. Additionally, some researchers use coil tilting in the sham stimulation group to create a control condition, but this method can still generate some voltage in the brain during actual operation (Lisanby et al., 2001). Future studies should use sham coils to establish control groups.

Second, examine the intervention effects of rTMS on MCI from both sample size and outcome assessment perspectives. The total sample size of the MCI rTMS intervention studies included in this review was 283 participants, with an average of only 25 subjects per study, which is insufficient for generalizing rTMS treatment for MCI. Future studies should increase sample sizes. Regarding follow-up assessment of intervention effects, different studies have varied greatly in tracking duration, with the longest follow-up being 6 months and the shortest being 1 week. Future research should conduct longer-term follow-up assessments of cognitive function improvements to more comprehensively evaluate the intervention effects of rTMS.

Third, explore the effects of different stimulation parameters and target sites on intervention efficacy. Currently, only one study has compared the effects of different stimulation parameters on cognitive function in MCI patients (Turriziani et al., 2012), and only two studies have compared the efficacy of different stimulation targets (Anderkova et al., 2015; Taylor et al., 2019). Most studies have used high-frequency stimulation, with only two implementing low-frequency stimulation (Turriziani et al., 2012; 祝本菊 et al., 2012), which also produced positive effects on cognitive function. Future research should systematically investigate the relationship between various rTMS parameter settings and intervention efficacy. Regarding stimulation targets, current studies have selected brain regions including the dorsolateral prefrontal cortex, parietal lobe, temporal lobe, and precuneus, with little known about the efficacy of stimulating other brain regions. Future research should thoroughly explore which set of stimulation parameters and which brain region yields optimal intervention effects.

Fourth, apply EEG and brain imaging technologies to investigate the neural mechanisms of rTMS intervention in MCI. EEG offers high temporal-frequency resolution and can reflect dynamic changes and band oscillations in various cortical activities (Bortoletto et al., 2015). Functional magnetic resonance imaging (fMRI) provides high spatial resolution and can reveal changes in brain activity and network states (Chandra et al., 2019). Future studies should consider how to reasonably and conveniently apply these technologies to rTMS research in MCI.

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