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A Systematic Review and Meta-Analysis of rTMS Effects on Cognitive Enhancement in Mild Cognitive Impairment and Alzheimer's Disease

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Abstract

Repetitive transcranial magnetic stimulation (rTMS), a non-invasive brain stimulation technique, has emerged as a promising treatment for mild cognitive impairment (MCI) and Alzheimer's disease (AD). Currently, however, the effectiveness of this therapy is unclear due to the low statistical power and heterogeneity of previous trials. The purpose of the meta-analysis was to systematically characterize the effectiveness of various combinations of rTMS parameters on different cognitive domains in patients with MCI and AD. Thirteen studies comprising 293 patients with MCI or AD were included in this analysis. Random effects analysis revealed an overall medium-to-large effect size (0.77) favoring active rTMS over sham rTMS in the improvement of cognitive functions. Subgroup analyses revealed that 1) high-frequency rTMS over the left dorsolateral prefrontal cortex (DLPFC) and low-frequency rTMS at the right DLPFC significantly improved memory functions; 2) high-frequency rTMS targeting the right inferior frontal gyrus significantly enhanced executive performance; and 3) the effects of 5–30 consecutive rTMS sessions could last for 4–12 weeks. Potential mechanisms of rTMS effects on cognitive functions are discussed.

Keywords

mild cognitive impairment; Alzheimer's disease; transcranial magnetic stimulation; plasticity; dorsolateral prefrontal cortex; intervention; memory; treatment; therapy; cognition

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INTRODUCTION

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique that is increasingly utilized for a growing number of research and clinical applications. To perform TMS, a magnetic field that reaches a strength of up to 2 Tesla is rapidly generated in <1 ms. Typically, this transient magnetic field is focally applied with a Figure-of-Eight coil that is carefully placed on the surface of the scalp over a targeted stimulation site. Leveraging Faraday's principle of electromagnetic induction, this magnetic field penetrates the skull and generates an electric current in the more conductive brain tissue in a direction that is perpendicular to the applied magnetic field (Barker, et al., 1985, Hallett, 2007). If this orthogonal electrical current is strong enough to surpass a physiological threshold, it can depolarize neurons in the targeted cortical tissue. Due to the nature of the exponentially decaying electromagnetic field, the penetration depth is limited to 2–3 centimeters. Thus, only superficial brain tissue can be directly stimulated by TMS, but this excitation can be propagated to distal targets through circuits that are structurally and/or functionally connected to the stimulation site (Chou, et al., 2015b, Liston, et al., 2014, Wang, et al., 2014). In the corticospinal system, for example, when the motor cortex is stimulated with a suprathreshold TMS pulse, this direct excitation evokes a series of descending corticospinal volleys in the form of Direct (D-) and Indirect (I-) waves, which ultimately elicits a motor response in the corresponding limb (Bestmann and Krakauer, 2015).

Contrary to single-pulse TMS, patterned repetitive TMS (rTMS) can produce long-lasting effects on neural activity and behavior beyond the stimulation period (Chou, et al., 2015a, Fitzgerald, et al., 2006). Careful manipulation of the parameters comprising these patterned rTMS pulse trains can induce neuroplastic changes that resemble either Long-Term Potentiation (LTP) or Depression (LTD) (Chen, et al., 1997, Pascual-Leone, et al., 1994). Early studies targeting the motor cortex helped elucidate which rTMS parameters promote particular responses and their neurophysiological underpinnings (Klomjai, et al., 2015). More recently, this ability to evoke distinct long-lasting changes in neural activity has been leveraged for therapeutic applications in neuropsychiatric disease. In 2008, for example, TMS devices were cleared for market by the Food and Drug Administration (FDA) for the clinical treatment of medication-resistant Major Depression Disorder. The specific FDA approved protocol is comprised of a high-frequency stimulation protocol, which is known to produce an excitatory LTP-like effect, over the Left Dorsolateral Prefrontal Cortex (DLFPC) (O'Reardon, et al., 2007). However, as an extension of the prefrontal asymmetry phenomenon, it has also been reported that inhibitory LTD-like low-frequency rTMS over the Right DLPFC is equally efficacious in producing anti-depressive outcomes in this patient population (Fitzgerald, et al., 2009, Sutton and Davidson, 1997). In other words, prefrontal activity in patients with MDD is abnormally imbalanced with right-sided hyperactivity and left-sided hypoactivity. Thus, distinct rTMS protocols that are known to produce opposite neurophysiological effects must be specifically applied depending on the targeted site of stimulation. This interaction between rTMS protocol and stimulation site has also been documented in the treatment of neurodegenerative disease (Chou, et al., 2015a). Accordingly, it is necessary to carefully discern the rTMS parameters when evaluating its potential efficacy in all neurologic and psychiatric conditions.

In recent years, rTMS has been closely investigated to evaluate its potential to modulate cognitive functions in AD and MCI. Here, we extend previous important reviews (Birba, et al., 2017, Cheng, et al., 2017, Dong, et al., 2018, Hsu, et al., 2015, Liao, et al., 2015, Nardone, et al., 2014) by including rTMS studies among both patients with AD or MCI to evaluate and update the efficacy of rTMS intervention compared to sham controls. Additionally, we sought to give greater attention to the methodological components of these existing studies. Considerable heterogeneity exists among the various rTMS treatment protocols that have been reported for cognitive enhancement for AD and MCI in the literature (e.g., different combinations of stimulation site, pulse frequency, stimulation intensity, number of stimuli delivered, and number of treatment sessions). A systematic and quantitative review that delineates rTMS effects based on various rTMS treatment protocols is not available. It is important to integrate these findings in a manner that accounts for this methodological heterogeneity to more accurately estimate the effects of rTMS in AD and MCI. Furthermore, we systematically characterize the effectiveness of various combinations of rTMS parameters on different cognitive domains in patients with AD and MCI. The distilled findings presented herein can be used to improve the experimental design of future rTMS clinical trials.

METHODS

Search Strategy

Our meta-analysis was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement (Moher, et al., 2009) (Figure 1). To identify studies for inclusion in this meta-analysis we searched PubMed, Web of Science, Current Contents Connect, and SciELO Citation Index through March 2019. Databases were searched using combinations of the following terms: Alzheimer's disease or mild cognitive impairment and repetitive transcranial magnetic stimulation (or rTMS or repetitive TMS). Additionally, we searched reference lists of previous reviews on rTMS for AD/MCI (Birba, et al., 2017, Cheng, et al., 2017, Dong, et al., 2018, Hsu, et al., 2015, Liao, et al., 2015, Nardone, et al., 2014) to identify additional relevant articles.

Inclusion Criteria for the Selection of Studies

We included studies that met all of the following criteria: 1) clinical population of patients previously diagnosed with AD or MCI; 2) rTMS was the only intervention being investigated; 3) cognitive functions were assayed as a behavioral outcome measure; 4) parallel or cross-over design that utilized a sham-controlled group or condition; and 5) articles written in English. Studies identified through database searches were initially screened on the basis of their title and abstract. They were subsequently excluded if it was clear from the title or abstract that the study was not relevant or did not meet the inclusion criteria (see Supplementary Table 1). If it remained unclear, the paper was assessed in its entirety. Additionally, studies were excluded if they were conference abstracts/papers.

Data Extraction

Two authors (YHC and VTT) independently performed the data extraction and any disagreements were resolved by joint discussion. Extracted data included sample size,

sample characteristics, study design, rTMS protocol, statistical data of the score of cognitive performance for effect size estimation, and timing of outcome measurements (short-term: within 1 hour of the final rTMS session or long-term: ≥ 4 weeks post-rTMS). When published data were insufficient for data analysis, the original study author(s) were contacted with requests for access to additional data.

Statistical Analysis

Effect size calculation.—We used standardized mean difference (SMD, also known as *Cohen's d*) to express the effect size of rTMS on cognitive functions. A random-effects model was used to calculate pooled effect sizes and examine whether the averaged effect size was significantly different from zero ($p < 0.05$, two-tailed). The mean effect was expressed as SMD with 95% confidence intervals. Generally, one effect size was derived from each study. If a study had multiple effect sizes from the same patient group (e.g., short-term and long-term rTMS effects; or different cognitive measures), we obtained one averaged effect size across multiple effect sizes within that particular study. If the effect sizes were reported from mild AD and severe AD separately within a single study or if the effect sizes were estimated from 2 independent subgroups of patients who received rTMS with different protocols, then the data were included as 2 independent units in the meta-analysis.

Due to the heterogeneity of cognitive measures included in each study, we first derived an effect size from the main outcome measures reported in each study. We then performed a sensitivity analysis that included additional secondary or exploratory cognitive measures (Please refer to the Sensitivity Analysis Section below). The cognitive tasks used for the estimation of effect size (i.e., the main outcome measures reported in each study) included the mini-mental status evaluation (MMSE), AD assessment scale cognitive subscale (ADAS-cog), Rey auditory verbal learning test (RAVLT), Rivermead behavioral memory test (RBMT), Battery for analysis of aphasic deficits, trail making task, Stroop color-word task, word-image association task, recognition memory task, and action naming and object naming task.

Additionally, although our overall effect was estimated across diagnosis (AD and MCI), number of rTMS sessions (i.e., short and long rTMS manipulation), rTMS site, rTMS frequency (i.e., low frequency: ≤ 1 Hz and high frequency: ≥ 5 Hz), cognitive measures, and timing of outcome measurements (i.e., short-term: within 1 hour of the final rTMS session and long-term: ≥ 4 weeks post-rTMS), these potential rTMS moderating effects were investigated in the subgroup analyses (Please refer to the Subgroup Analyses Section below).

Heterogeneity analysis.—We used the Q statistics and the I^2 index to assess heterogeneity. A probability value less than 0.05 and I^2 greater than 40% is indicative of heterogeneity between included studies as it exceeds what is expected by chance (Higgins, et al., 2003).

Publication or selection bias.—Publication/selection bias was evaluated with Egger's Test of Asymmetry (Egger, et al., 1997) and Orwin's *fail-safe N* approach (Borenstein, et al.,

2009). In the absence of publication/selection bias, effect sizes are symmetrically distributed around the overall average effect size, since the sampling error is random. Egger's test evaluated whether the amount of asymmetry is significant. In addition, studies that demonstrated lack of benefit might not have been submitted and/or accepted for publication. Therefore, we used the Orwin's *fail-safe N* to estimate the number of missing studies (with a mean effect size of 0) that would need to be incorporated in our meta-analysis to make the summary effect become trivial.

Subgroup analyses.—Our pre-specified categories for subgroup analyses included diagnosis (AD and MCI), rTMS site, rTMS frequency (low: ≤ 1 Hz and high: ≥ 5 Hz), cognitive measures, timing of outcome measurements (short-term: within 1 hour of the final rTMS session vs. long-term: ≥ 4 weeks post-rTMS), number of rTMS sessions (i.e., short vs. long rTMS manipulation), and the interaction between rTMS site, rTMS frequency and outcome measures.

Sensitivity analysis.—The process of undertaking a meta-analysis involves making decisions about which outcome measures to include in the analysis. We performed a sensitivity analysis to examine whether our results would have differed if we had included other secondary or exploratory cognitive measures in our estimation of effect sizes.

Risk of Bias Assessment in Individual Studies

We used the Physiotherapy Evidence Database (PEDro) scale (de Morton, 2009, Maher, et al., 2003) to quantify the quality of included studies. The PEDro scale scored 11 items (Supplementary Table 1) as either present or absent. The final score is the number of positive answers on all questions. We considered a PEDro score of 11 to represent an excellent-quality study, a score between 8 and 10 a good-quality study, a score of 6 and 7 a fair-quality study, and a score of ≤ 5 a low-quality study (Franssen, et al., 2014).

Risk of Bias Assessment across Studies

We utilized the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach to assess the quality of evidence (Atkins, et al., 2004). Four levels of quality of evidence are specified: high quality, moderate quality, low quality, and very low quality. A high level of evidence is initially assumed, and subsequently downgraded for meeting any of the following criteria (O'Connell, et al., 2014):

- Risk of bias: downgrade once if less than 75% of included studies are excellent or good quality.
- Heterogeneity: downgrade once if heterogeneity between the included studies is significant and the I^2 value is greater than 40%.
- Indirectness: downgrade once if more than 50% of the participants were outside the target group.
- Imprecision: downgrade once if fewer than 400 participants (Guyatt, et al., 2011).

- Publication/selection bias: downgrade once if the publication/selection bias is significant.

RESULTS

Search Results

Our initial search of all databases retrieved 124 studies and 1 additional article was identified from previous reviews (Figure 1). After rejecting articles based off the contents of the title and abstract, the full texts of 28 articles were obtained for further examination. Of these, 15 studies were excluded (see Supplementary Table 1). The remaining 13 studies (Ahmed, et al., 2012, Anderkova, et al., 2015, Cotelli, et al., 2011, Cotelli, et al., 2008, Drumond Marra, et al., 2015, Eliasova, et al., 2014, Koch, et al., 2018, Padala, et al., 2018, Rutherford, et al., 2015, Sole-Padulles, et al., 2006, Turriziani, et al., 2012, Wu, et al., 2015, Zhao, et al., 2017) that met the inclusion criteria were included for this meta-analysis. Among the 13 included studies, Cotelli et al. (2008) separately reported statistics from mild AD and moderate-to-severe AD, and Ahmed et al. (2012) distinctly described statistics from independent subgroups of AD patients who received rTMS with different protocols (i.e., inhibitory or excitatory). Therefore, those data (Ahmed, et al., 2012, Cotelli, et al., 2008) were included as multiple independent units in the meta-analysis. We only needed to request additional data from one group of authors to calculate effect sizes for the sensitivity analysis. The authors responded to our request within 10 days. Thus, no study was excluded due to the lack of data required for the effect size estimation

Study Characteristics

The 13 eligible studies included 293 participants (age range = 50–87 years, 45% males). The total effect size (pooled across all parameters) of rTMS on cognitive performance was 0.77 (95% CI = [0.57, 0.97]), indicating a medium-to-large effect size favoring active rTMS over sham rTMS ($z = 7.69$, $p < 0.0001$). The main characteristics of the included studies are described in Tables 1, 2, 3, and the distribution of effect sizes is illustrated in Figure 2.

Heterogeneity between the included studies did not exceed that expected by chance, $Q = 14.55$, $df(Q) = 16$, $p = 0.56$, $I^2 = 0.00$, which indicate that the results across the included studies were statistically homogeneous. Publication bias was evaluated using Egger's Test of Asymmetry and Orwin's *fail-safe N* approach. Egger's Test did not reveal significant asymmetry across included studies (intercept = 0.76, $df = 15$, $t = 1.08$, two-tailed $p = 0.30$, Supplementary Figure 1). Orwin's *fail-safe N* analysis showed that 239 studies with a mean effect size of 0 would be needed to offset the conclusion that we are able to draw from the 13 studies included in this analysis (i.e., to bring p-value greater than 0.05). This suggests that our findings are robust, and it reduces concerns of potential publication bias.

Subgroup Analyses

Patient population.—Six studies reported rTMS effects in AD (Ahmed, et al., 2012, Cotelli, et al., 2011, Cotelli, et al., 2008, Rutherford, et al., 2015, Wu, et al., 2015, Zhao, et al., 2017), 5 studies presented rTMS efficacy in MCI (Drumond Marra, et al., 2015, Koch, et al., 2018, Padala, et al., 2018, Sole-Padulles, et al., 2006, Turriziani, et al., 2012), and 2

studies included data on both AD and MCI (Anderkova, et al., 2015, Eliasova, et al., 2014) (Table 1). Our subgroup analysis revealed that the effect sizes of rTMS estimated from both MCI (SMD = 0.91, $p < 0.0001$) and AD (SMD = 0.75, $p < 0.0001$) were significant.

Stimulation site x frequency x outcome measures.—For the *stimulation site*, 9 studies stimulated left, right, or bilateral DLPFC, 2 studies targeted the right inferior frontal gyrus (IFG), and the remaining 2 studies stimulated the temporo-parietal regions (Table 2). Pertaining to the *stimulation frequency*, the majority of included studies (12/13) used high-frequency (≥ 5 Hz) rTMS protocols, while only 2 studies employed low-frequency (≤ 1 Hz) rTMS protocols (Table 2). Regarding the *outcome measures*, memory, executive, language, and general cognitive functions have been included for the assessments of the rTMS effects. Please see Table 3 for a complete list of neuropsychological tests that were administered in each study, and the respective time points at which each was assessed.

To parse the effectiveness of various combinations of rTMS parameters on different cognitive domains, we ran *Stimulation site x frequency x outcome measures* subgroup analyses across the included studies. The estimated effect sizes and *p* values are illustrated in Figure 3. First, the effects of rTMS at the DLPFC were lateralized. High-frequency rTMS over the left DLPFC (SMD = 0.68, $p < 0.005$) and low-frequency rTMS at the right DLPFC (SMD = 1.53, $p < 0.005$) significantly improved memory functions. Second, high-frequency rTMS targeting the right IFG significantly improved executive functions. Additionally, the effects of high-frequency rTMS over the left DLPFC on language (SMD = 1.33, $p = 0.06$) and general cognitive function (SMD = 1.24, $p = 0.06$) were marginally significant. Although the effects of high-frequency rTMS at bilateral DLPFC on memory and general cognitive function were not significant, it should be noted that all of these effect sizes were greater than 0.8, which may be indicative of a large effect of active rTMS over the sham-condition. Future studies are warranted to further investigate these rTMS protocols in patients with AD or MCI.

Number of rTMS sessions (i.e., short vs. long rTMS manipulation).—Most of the included studies administered rTMS for multiple sessions on consecutive days, but 5 studies only consisted of a single rTMS session (Anderkova, et al., 2015, Cotelli, et al., 2008, Eliasova, et al., 2014, Sole-Padulles, et al., 2006, Turriziani, et al., 2012) (Table 2). Our subgroup analysis showed that both single-session rTMS (SMD = 0.83, $p < 0.001$) and multi-session rTMS (SMD = 0.72, $p < 0.001$) improved cognitive functions.

Timing of outcome measurements.—All 13 studies assessed cognitive functions acutely (≤ 1 hour after the final rTMS session), and 3 studies additionally reported follow-up behavioral assessments as a long-term outcome measure (≥ 4 weeks) (Ahmed, et al., 2012, Drumond Marra, et al., 2015, Zhao, et al., 2017). The acute assessment was administered within 1 hour of the final rTMS session, while the chronic assessment occurred either at 4 weeks, 6 weeks, or 12 weeks after the final rTMS session (Table 3). Results of our subgroup analysis revealed that both short-term (SMD = 0.71, $p < 0.0001$) and long-term rTMS effects on cognitive functions (SMD = 0.71, $p < 0.0001$) were significant, suggesting that with 5–30 consecutive rTMS sessions, the effects could last 4–12 weeks.

Sensitivity Analysis

We included secondary or exploratory cognitive measures from 8 studies (Anderkova, et al., 2015, Cotelli, et al., 2011, Drumond Marra, et al., 2015, Eliasova, et al., 2014, Koch, et al., 2018, Padala, et al., 2018, Rutherford, et al., 2015, Zhao, et al., 2017) into our meta-analysis to examine whether the results would change (Table 3). The pooled rTMS effect remained medium-to-large and significant (SMD = 0.65, 95% CI = [0.46, 0.84], $z = 6.61$, $p < .0001$), as did the pooled effect from the primary cognitive measures (SMD = 0.77, 95% CI = [0.57, 0.97], $z = 7.69$, $p < .0001$).

Adverse Events

No incidents of seizure were reported in this patient population across the 13 studies. Eight studies further assessed the incidence of other minor adverse responses related to the application of rTMS. Among them, patients in the Ahmed et al. (2012) and Cotelli et al. (2011) studies did not report any adverse events during or after rTMS sessions. The minor adverse events reported due to rTMS are summarized in Supplementary Table 2.

Risk of Bias Assessment in Individual Studies

The risk of bias assessment for all included studies is summarized in Supplementary Table 1. Overall, our analysis indicates that 2 studies were of excellent methodological quality (PEDro scale 11/11), 10 studies were of good methodological quality (8– 10/11), and one study was of fair methodological quality (7/11).

Risk of Bias Assessment across Studies

Using the GRADE criteria, we characterized the quality of evidence presented in this meta-analysis as *moderate* quality. The initial presumption for a high level of evidence was downgraded once because fewer than 400 participants were included in this meta-analysis. Despite this imperfection, our meta-analysis exhibited low risk of bias, adequate homogeneity, directedness (i.e., all participants were patients with AD or MCI), and it is free from publication/selection bias across included studies.

DISCUSSION

Overall, our meta-analysis provides evidence supporting a beneficial effect of rTMS on cognitive functions in both patients with MCI and AD. Subgroup analyses indicate that 1) high-frequency rTMS over the left DLPFC and low-frequency rTMS at the right DLPFC significantly improved memory functions; 2) high-frequency rTMS targeting the right IFG significantly enhanced executive performance; and 3) the effects of 5–30 consecutive rTMS sessions could last for 4–12 weeks.

What are the potential mechanisms underlying the rTMS effects on cognitive functions?

Previous animal models of dementia indicate that both high-frequency (Ma, et al., 2017, Wang, et al., 2010, Zhang, et al., 2015) and low-frequency (Huang, et al., 2017, Wang, et al., 2010, Yang, et al., 2015, Zhang, et al., 2018) rTMS (daily sessions for 2–4 weeks) can significantly improve hippocampal dependent functions of learning and memory. These

findings are congruent with those presented in this meta-analysis, and a closer examination of such experimental models may yield additional insights as to the underlying mechanisms of rTMS. Here, we will explore the multifaceted neurobiological effects of rTMS that may be interacting in some capacity to influence cognitive functions.

Numerous in vitro and in vivo experimental models provide evidence that rTMS can increase long-term potentiation (LTP) (Thickbroom, 2007). Of particular relevance, this has been documented in various murine models of dementia where rTMS rescues LTP deficits (Tan, et al., 2013, Wang, et al., 2015, Zhang, et al., 2015, Zhen, et al., 2017). These improvements in neural plasticity are observed in conjunction with improved performance on hippocampal dependent measures of spatial cognition (Huang, et al., 2017, Ma, et al., 2014, Tan, et al., 2013, Wang, et al., 2015). Further, in murine models of AD, the increase in LTP and improvement in spatial cognition following rTMS are observed concomitantly with reduced amyloid-β load (Huang, et al., 2017, Tan, et al., 2013, Wang, et al., 2015). Reported mechanisms to explain this reduction in pathology by rTMS include 1) the reduction of amyloid precursor protein (APP) (Huang, et al., 2017), and 2) facilitation of the large-conductance calcium-activated potassium channel via increased expression of the Homer1a scaffold protein (Wang, et al., 2015).

On more granular level, there are numerous rTMS induced effects that likely mediate this enhanced synaptic function. Numerous studies, for example, report that hippocampal expression of brain derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) are increased following rTMS (Gersner, et al., 2011, Ma, et al., 2014, Muller, et al., 2000, Shang, et al., 2016, Zhang, et al., 2015). In addition to these neurotrophic factors, rTMS reportedly increases expression of N-methyl-D-aspartate (NMDA) receptors and other proteins that facilitate synaptic plasticity (e.g., synaptophysin, post-synaptic density protein-95, cyclin dependent kinase 5, GAP43) (Etievant, et al., 2015, Kole, et al., 1999, Ma, et al., 2017, Ma, et al., 2014, Shang, et al., 2016, Wang, et al., 2010, Yang, et al., 2015, Zhang, et al., 2015).

Relatedly, there are reports of rTMS increases hippocampal neurogenesis in the dentate gyrus (Ueyama, et al., 2011), which plays a critical role in pattern separation (Clelland, et al., 2009). In addition to the neurotrophic mediators listed above, rTMS may promote neurogenesis via the increased expression of cholecystokinin (CCK) (Muller, et al., 2000). In addition to its neuroprotective effects in rodent models of AD (Sugaya, et al., 1992), CCK has been shown to increase cell proliferation and neurogenesis in the dentate gyrus (Reisi, et al., 2015). CCK is the most abundant peptide in the mammalian brain, and there is a dipropionate density of CCK receptors found in the hippocampus (Zarbin, et al., 1983). In numerous rodent models, increased expression of CCK corresponds with increased performance on hippocampal dependent tasks of learning and memory (Croll, et al., 1999, Reisi, et al., 2015, Sebret, et al., 1999, Taghzouti, et al., 1999). In a recent human study from the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset, CCK concentration in the cerebrospinal fluid was identified as a novel biomarker that was associated with both cognitive status and gray matter volume in key anatomical regions associated with AD pathology (Plagman, et al., 2019).

These microscopic alterations from rTMS may also interact to produce network level changes in brain function that are more readily detected in human trials. As an example, consider the findings reported by Solé-Padullés and colleagues in their clinical trial of AD patients that utilized task-based fMRI before and after rTMS. They report that improvements in associative memory following rTMS corresponded with compensatory recruitment of additional neural networks (Sole-Padulles, et al., 2006). Similar compensatory brain activity has been previously documented in older adults who retain high cognitive functions as they age (Bangen, et al., 2012, Cabeza, et al., 2002).

Why does the DLPFC rTMS enhance memory functions in AD and MCI?

The DLPFC is a core region involved in executive functions, such as working memory and cognitive flexibility (Blumenfeld, et al., 2011, Blumenfeld and Ranganath, 2007). Previous research reported that patients with MCI and AD have executive function deficits (Baudic, et al., 2006, Chen, et al., 1998, Guarino, et al., 2018, Guarino, et al., 2019) and the impairments in executive functions are considered to exacerbate memory deficits in this population (Buckner, 2004, Zheng, et al., 2012). Our subgroup analyses provide evidence showing that the DLPFC rTMS significantly improved memory functions in patients with MCI or AD. One possible explanation for this effect is that the DLPFC may contribute to long-term memory formation through its interaction with regions within the medial temporal network (e.g., hippocampus) during memory encoding (Blumenfeld and Ranganath, 2006, Murray and Ranganath, 2007, Ranganath, et al., 2005, Simons and Spiers, 2003, Yuan, et al., 2016) and retrieval (Achim and Lepage, 2005, Balconi and Ferrari, 2012, Balconi and Ferrari, 2013, Manenti, et al., 2010, Simons and Spiers, 2003). Consistent with this idea, studies of patients with focal prefrontal lesion have reported that damage to the DLPFC can disrupt recognition memory (Duarte, et al., 2005, Gershberg and Shimamura, 1995); activity in the DLPFC during the early stage of working memory maintenance was predictive of subsequent long-term memory (Ranganath, et al., 2005); and disruption of working memory processing resulted in impaired long-term memory formation (Ranganath, et al., 2005). Collectively, previous behavioral and imaging studies suggest that successful long-term memory may depend on effective control of information in working memory (Blumenfeld and Ranganath, 2007), and this relationship might be mediated by the DLPFC (Ranganath, et al., 2005, Yuan, et al., 2016).

Additionally, our subgroup analyses revealed that both high-frequency rTMS over the left DLPFC and low-frequency rTMS at the right DLPFC significantly improved memory functions in patients with MCI or AD. These two rTMS protocols have also been examined in major depressive disorder (MDD), and previous meta-analyses in MDD show that these two rTMS protocols exhibited similarly lateralized clinical efficacy on response rate and remission rate (Cao, et al., 2018, Chen, et al., 2013). Previous brain imaging studies in MDD found reduced cerebral blood flow and metabolism in the left DLPFC and hypermetabolism in the right DLPFC in acute MDD (Mayberg, 2003, Phillips, et al., 2003). Thus, it is postulated that patients with MDD benefit from high-frequency rTMS over the left DLPFC due to increasing cortical activity and benefit from low-frequency rTMS over the right DLPFC because the cortical activity is suppressed (Avery, et al., 2006, Cao, et al., 2018, Chen, et al., 2013, George, et al., 2010). Currently, it is not clear whether patients with MCI

or AD exhibit similar prefrontal asymmetry as patients with MDD do. Furthermore, functional brain imaging data examining how each rTMS protocol modulates brain activity of the DLPFC and other connected regions in MCI and AD is very limited. Future studies that integrate rTMS and brain imaging techniques will be needed to understand the prefrontal functions in MCI and AD, and better explain the DLPFC rTMS effects.

Notably, the same rTMS protocols over the respective DLPFC targets elicit positive clinical outcomes in both patients with depression and those with MCI/AD. As an additional consideration, this might also be suggestive that the reported rTMS influence on cognition may be an indirect consequence of improved affect. Scholars have long discussed the appreciable interaction and marginal phenomenological distinction between affect and cognition (Duncan and Barrett, 2007). The two behavioral phenotypes are increasingly intertwined with age (Crocco, et al., 2010), which may speak to enmeshed neurobiological mechanisms (e.g., inflammation) or it may be driven by a bidirectional interaction of the phenomenology of the conditions. Only a single study included in our analysis reported outcome measures pertaining to both affect and cognition (Ahmed, et al., 2012). Interestingly, these authors report that the cohort with appreciable improvement in cognition also exhibited a concomitant decrease in depressive symptoms (Ahmed, et al., 2012). This possibility is met with conflicting evidence in the literature. Generally, cognitive improvements are not observed in clinical trials applying rTMS for depression (Martin, et al., 2017). However, this potential effect is likely influenced by the baseline cognitive status of patients receiving DLPFC rTMS. As such, the association between neurocognitive and mood improvement following rTMS may be more likely to emerge in populations where baseline cognition is more vulnerable (Ilieva, et al., 2018).

Limitations and future directions

Regarding the limitations of the present meta-analysis, our results could be constrained by insufficient number of patients (i.e., less than 400 patients with MCI or AD) included in this meta-analysis. In addition, very few studies have stimulated brain regions other than the DLPFC, therefore, the non-significant rTMS effects of other brain regions should be interpreted with caution. Future studies should focus on establishing a more precise relationship between stimulation site, rTMS frequency, and function of cognitive domains enhanced by rTMS; as well as 2) establishing a procedure to tailor the rTMS parameters for each individual patient.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Repetitive TMS is a promising tool to enhance cognitive functions in AD and MCI
- High-frequency L-DLPFC and low-frequency R-DLPFC rTMS may improve memory function
- High-frequency R-IFG rTMS may enhance executive performance
- rTMS effects on cognition are documented at both acute and chronic time points
- Chronic effects of consecutive rTMS sessions reportedly persist at 12 weeks

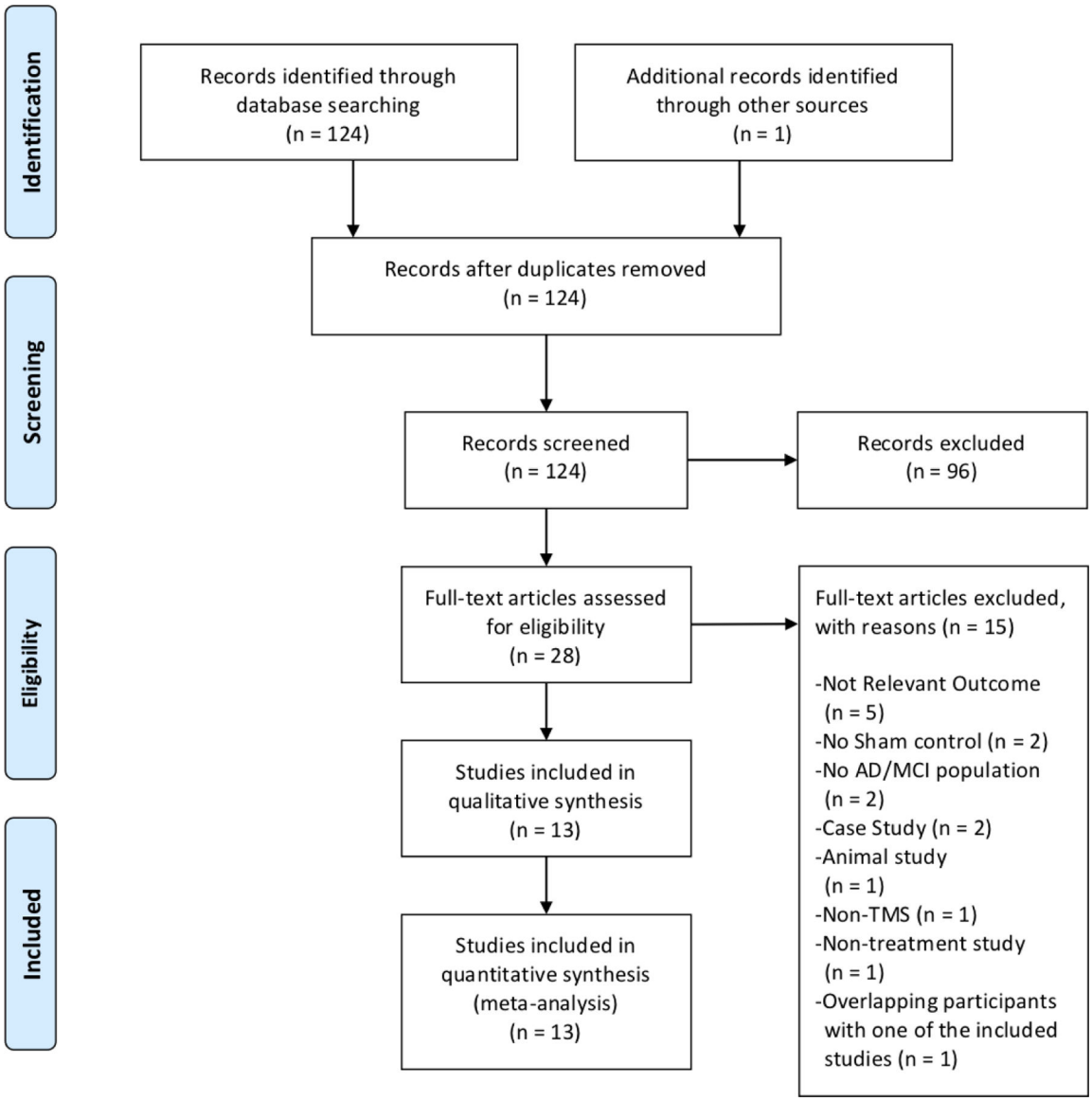

Figure 1.

Flow diagram showing the search and selection procedure that was used for this meta-analysis. Diagram adapted from Moher et al.(Moher, et al., 2009).

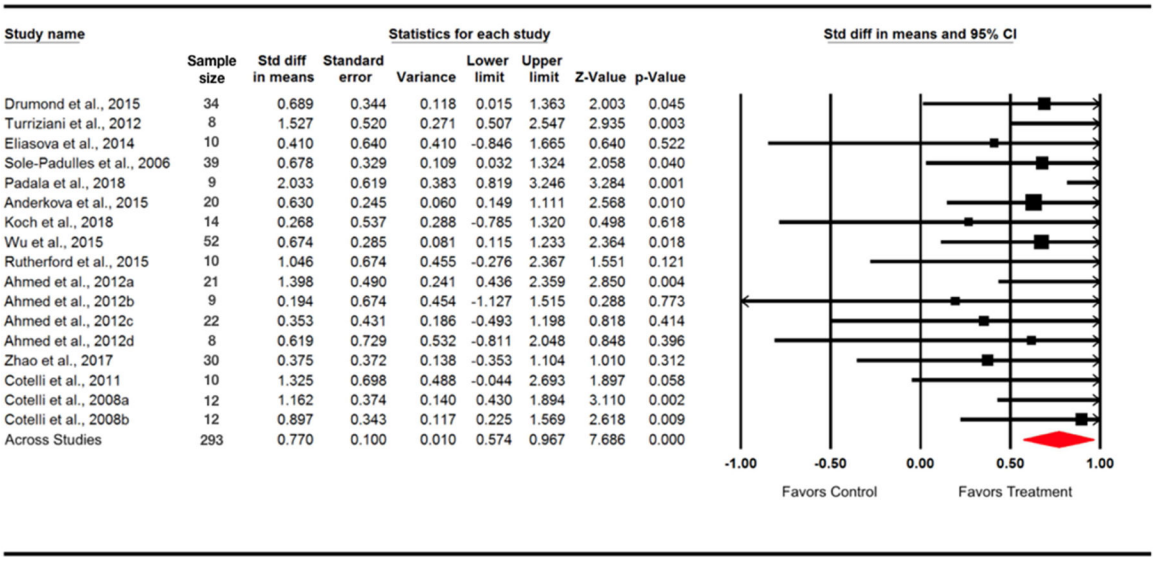

Figure 2.

Forest plot. Individual and pooled rTMS effect sizes (SMDs) for cognitive function in patients with MCI or AD. The size of the squares increases with increasing sample size. Cotelli et al. (2008) reported statistics from mild AD (Cotelli et al., 2008a) and moderate-to-severe AD (Cotelli et al., 2008b) separately, and Ahmed et al. (2012) described statistics from 4 groups (Ahmed et al., 2012a = high-frequency rTMS in mild AD; Ahmed et al., 2012b = high-frequency rTMS in severe AD; Ahmed et al., 2012c = low-frequency rTMS in mild AD; Ahmed et al., 2012d = low-frequency rTMS in severe AD;), therefore, those data were included as multiple independent units in the meta-analysis.

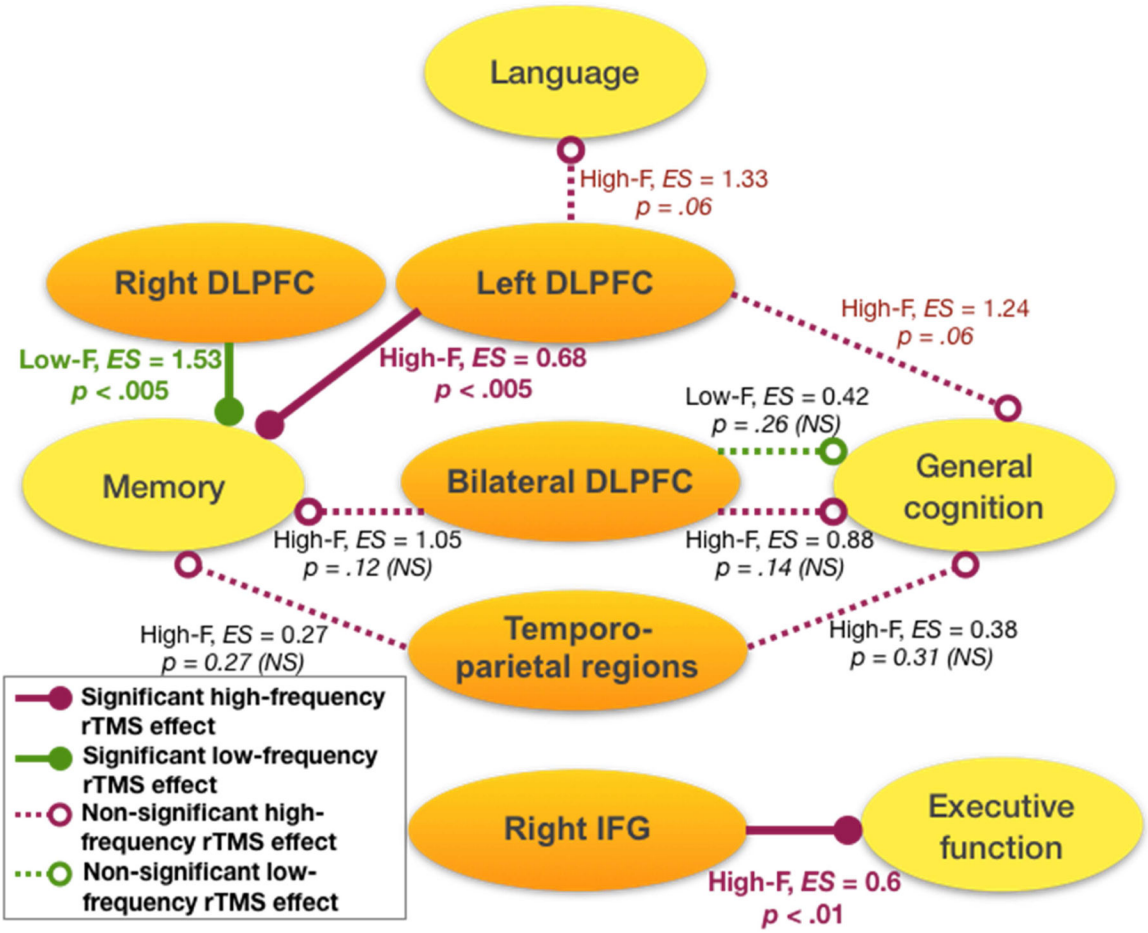

Figure 3.

rTMS effect sizes for various combinations of stimulation site, frequency, and outcome measures. DLPFC = dorsolateral prefrontal cortex; ES = effect size; High-F = high-frequency rTMS; IFG = inferior frontal gyrus; Low-F = low-frequency rTMS.

Table 1.

Characteristics of included studies – participants and design

Source	Sample size	Diagnosis	Age (years)	Gender (M/F)	DD (years)	Study design
Padala et al., 2018	9[a]	MCI	66 ± 9	8/1	NA	RAN_CO_DB_SC
Koch et al., 2018	14	aMCI	70 ± 5	7/7	1	RAN_CO_DB_SC
Zhao et al., 2017	30	AD	71 ± 6	15/15	NA	RAN_PA_DB_SC
Anderkova et al., 2015	20	12 AD, 8 MCI	73 ± 7	9/11	3 ± 2	RAN_CO_SB_SC
Wu et al., 2015	52	AD	72 ± 5	21/31	5 ± 2	RAN_PA_DB_SC
Rutherford et al., 2015	10	AD	57 – 87	3/7	NA	RAN_CO_DB_SC
Drumond Marra et al., 2015	34	MCI	60 – 74	12/22	NA	RAN_PA_DB_SC
Eliasova et al., 2014	10	7 Mild AD, 3 aMCI	75 ± 8	6/4	~4	RAN_CO_SC
Ahmed et al., 2012	45	Probable AD	68 ± 6	16/29	NA	RAN_PA_SB_SC
Turriziani et al., 2012	8	aMCI	66 ± 6	8/0	1–2	RAN_CO_SC
Cotelli et al., 2011	10	AD	76 ± 5	NA	NA	RAN_PA_SB_SC
Cotelli et al., 2008, mAD	12	mild AD	75 ± 6	NA	NA	RAN_CO_SC
Cotelli et al., 2008, msAD	12	moderate to severe AD	78 ± 6	NA	NA	RAN_CO_SC
Sole-Padulles et al., 2006	39	aMCI	> 50	1½8	>1 year	RAN_PA_DB_SC

Note. AD = Alzheimer's disease; aMCI = amnestic mild cognitive impairment; CO = cross-over; DB = double-blind; DD = Disease duration; mAD = mild AD; ms AD = moderate to severe AD; MCI = mild cognitive impairment; NA = not available; PA = parallel; RAN = randomized; SB = single-blind; SC = sham-controlled.

[a]Data from enrolled participants

[b]Participants who completed the rTMS sessions and the 1-hour after-rTMS evaluation

[c]Median disease duration

[d]Data analyzed

Table 2.

Characteristics of included studies – rTMS parameters

Source	rTMS site	rTMS frequency	Intensity	No. of pulses[a]	Treatment duration	Sham rTMS
Padala et al., 2018	L-DLPFC	10 Hz	120% RMT	30000 (3000 × 10)	2 weeks	Tilted coil
Koch et al., 2018	L parietal region (precuneus)	20 Hz	100% RMT	16000 (1600 × 10)	1 weeks	Sham coil
Zhao et al., 2017	Bilateral parietal region and posterior temporal areas	20 Hz	NA	120000 (4000 × 30)	6 weeks	Inactive coil with sound
Anderkova et al., 2015	R IFG and R STG	10 Hz	90% RMT	2250 (2250 × 1)	1 session for each target	Stimulating vertex
Wu et al., 2015	L DLPFC	20 Hz	80% RMT	24000 (1200 × 20)	4 weeks	Tilted coil
Rutherford et al., 2015	Bilateral DLPFC	20 Hz	90%–100% RMT	26000 (2000 × 13)	4 weeks	Wooden block
Drumond Marra et al., 2015	L DLPFC	10 Hz	110% RMT	20000 (2000 × 10)	2 weeks	Sham coil
Eliasova et al., 2014	R IFG	10 Hz	90% RMT	2250 (2250 × 1)	1 day	Stimulating vertex
Ahmed et al., 2012, 20Hz Ahmed et al., 2012, 1Hz	Bilateral DLPFC	20 Hz	90% RMT	10000 (2000 × 5)	5 days	Elevated coil
	Bilateral DLPFC	1 Hz	100% RMT	10000 (2000 × 5)	5 days	Elevated coil
Turriziani et al., 2012	L DLPFC	1 Hz	90% RMT	600 (600 × 1)	1 day	Tilted coil
	R DLPFC	1 Hz	90% RMT	600 (600 × 1)	1 day	Tilted coil
Cotelli et al., 2008, mAD Cotelli et al., 2008, msAD	L and R DLPFC	20 Hz	90% RMT	NA	1 session for each target	Stimulating vertex
	L and R DLPFC	20 Hz	90% RMT	NA	1 session for each target	Stimulating vertex
Cotelli et al., 2011	L DLPFC	20 Hz	100% RMT	20000 (2000 × 10)	2 weeks	Sham coil
Sole-Padulles et al., 2006	L DLPFC	5 Hz	80% RMT	500 (500 × 1)	1 day	Tilted coil

Note. AMT = active motor threshold; M1 = primary motor cortex, mAD = mild Alzheimer's disease; msAD = mild to severe Alzheimer's disease; SMA = supplementary motor area; DLPFC = dorsolateral prefrontal cortex; PMd = dorsal premotor cortex; RMT = resting motor threshold

[a]Total number of pulses (number of pulses per session x number of sessions).

Table 3.

Characteristics of included studies – outcome measurements

Source	Cognitive measures used for the estimation of effect size (Type of cognitive domain)	Post-rTMS evaluation	Seizure due to rTMS
Padala et al., 2018	**MMSE (General cognitive function)** and *TMT (Executive function)*	1 hour after	No
Koch et al., 2018	**Delayed recall of the RAVLT (Memory)** and *MMSE (General cognitive function)*	Immediately after	No
Zhao et al., 2017	**ADAS-cog (General cognitive function)** and *MMSE (General cognitive function)*	Immediately after and 6 weeks after	No
Anderkova et al., 2015	**Stroop color-word task (Executive function)** and *TMT*	1 hour after	No
Wu et al., 2015	**ADAS-cog (General cognitive function)**	Immediately after	No
Rutherford et al., 2015	**Word-image association (Memory)**, *ADAS-cog (General cognitive function)*, and *associative memory (Memory)*	Immediately after	No
Drumond Marra et al., 2015	**RBMT (Memory)**, *letter-number sequencing test (Executive function)*, and *TMT-B (Executive function)*	Immediately after and 1 month after	No
Eliasova et al., 2014	**TMT-A, TMT-B (Executive function)** and *Stroop task (Executive function)*	Immediately after	No
Ahmed et al., 2012, 20Hz	**MMSE (General cognitive function)**	Immediately after, 1 month after, and 3 months after	No
Ahmed et al., 2012, 1Hz	**MMSE (General cognitive function)**	Immediately after, 1 month after, and 3 months after	No
Turriziani et al., 2012, LDLPFC	**Recognition memory test (Memory)**	Immediately after	No
Turriziani et al., 2012, RDLPFC	**Recognition memory test (Memory)**	Immediately after	No
Cotelli et al., 2008, mAD	**Action naming and object naming (Language)**	Immediately after	No
Cotelli et al., 2008, msAD	**Action naming and object naming (Language)**	Immediately after	No
Cotelli et al., 2011	**SC-BADA (Language)** and *MMSE (General cognitive function)*	Immediately after	No
Sole-Padulles et al., 2006	**Associative memory (Memory)**	Immediately after	No

Abbreviations. ADAS-cog = AD assessment scale cognitive subscale; MMSE = mini-mental status evaluation; RAVLT = Rey auditory verbal learning test; RBMT = Rivermead behavioral memory test; SC-BADA = Battery for analysis of aphasic deficits; TMT = trail making task. *Note.* Cognitive measures listed in this table were included in the sensitivity analysis. Cognitive measures in bold were the primary outcome measures used to derive the overall effect size. The italicized tasks were included in the sensitivity analysis.