Effects of Transcranial Magnetic Stimulation on the Default Mode Network in Minimal Cognitive Impairment and Alzheimer's disease: An ALE meta-analysis and systematic review

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September 2023

Abstract

Objective: This systematic review and meta-analysis sought to comprehensively assess the efficacy of repetitive transcranial magnetic stimulation (rTMS) on the default mode network (DMN) through functional magnetic resonance imaging (fMRI) among individuals diagnosed with mild cognitive impairment (MCI) and Alzheimer's disease (AD). The primary objective was to unravel the neuroimaging mechanism underpinning cognitive intervention.

Methods: A search encompassing English articles published until July 30, 2023, was conducted across prominent databases, including PubMed, Web of Science, Embase, and Cochrane Library. The study specifically focused on randomized controlled trials utilizing resting-state fMRI to investigate the impact of rTMS within the MCI and AD populations. The analysis of fMRI data was executed using GingerALE.

Results: Our meta-analysis encompassed a total of seven studies focusing on AD, collectively 116 patients in the treatment group and 90 patients in the sham group. Additionally, in MCI group comprised 34 patients in the treatment groups and 39 patients in the sham group. The combined ALE quantitative analyses on group contrasts between Alzheimer's patients and the sham group showed no significant clusters of convergence. A similar outcome was observed when conducting meta-analyses of the MCI group. The restricted pool of eligible studies may have hindered our ability to detect meaningful clusters of convergence.

Conclusions: The outcomes of this meta-analysis and systematic review collectively underscore the potential effectiveness and safety of rTMS intervention in addressing the needs of patients coping with MCI and AD. These improvements could likely be attributed to the favorable modulation that rTMS imparts upon spontaneous neural activity and cognitive networks. By elucidating the intricate neural mechanisms involved, this study contributes insights to the burgeoning field of cognitive intervention strategies.

KEYWORDS

Alzheimer's disease, fMRI, mild cognitive impairment, repetitive transcranial magnetic stimulation

1. Introduction

Alzheimer's disease (AD), the prevalent form of dementia among the elderly population, presents as an incurable chronic neurodegenerative disease that profoundly impacts cognitive function and essential life skills, eventually leading to fatality (Qu et al., 2021). The disease progression follows the initial stages of cognitive decline, including subjective cognitive decline and mild cognitive impairment (MCI), prior to culminating in full-blown dementia (Jessen et al., 2014). Given MCI's prodromal nature with a high likelihood of progressing into AD, the consensus underscores the significance of targeting interventions and treatments towards this population to stave off cognitive deterioration (Jia et al., 2020).

Presently available drugs for AD offer only limited short-term symptomatic relief (Hughes et al., 2016). Attempts at developing disease-modifying therapies for AD dementia patients have yielded little success, likely due to intervention at a stage when the neurodegenerative process is too advanced. The current focus revolves around therapeutic strategies applied during the MCI and/or preclinical phases, with the postponement of dementia onset serving as a pivotal clinical trial endpoint (Sperling et al., 2011). This paradigm shift hinges on the identification of biomarkers for early AD diagnosis (Sperling et al., 2011; Matthews and Hampshire, 2016).

Resting-state functional magnetic resonance imaging (rsfMRI) has emerged as a promising possible biomarker for early diagnosis of AD, reflecting its potential for uncovering neural connectivity alterations (Sperling et al., 2011; Matthews et al., 2016; Vemuri et al., 2012). This technique assesses resting-state brain activation, encompassing functional integration and segregation, and is a recommended modality for gauging neuroplasticity (Reid et al., 2016). As a valuable tool in exploring human functional neural networks, rs-fMRI indirectly measures neural processing through blood oxygenation, identifying spatially distributed networks (Logothetis et al., 2002). Notably, this method enables the identification of large-scale spatiotemporal networks during rest, including the default mode network (DMN), salience network, frontoparietal network, sensorimotor network, and visual network, among others (Barkhof et al., 2014). Among these, the DMN has drawn substantial cognitive neuroscience attention (Rektorova, 2014). Comprising functionally linked yet anatomically separated brain regions, the DMN typically

involves the posterior cingulate cortices (PCC), adjacent precuneus and retrosplenial cortices, medial prefrontal cortices, inferior parietal lobules (IPL), and medial temporal lobes (MTL), often encompassing lateral temporal and dorsolateral prefrontal areas as well (Buckner et al., 2008; Qi et al., 2010; Yan et al., 2013). Active at rest and suppressed during cognitive tasks, the DMN has been associated with self-reference and memory processing (Rektorova, 2014; Kim, 2012).

In the context of AD, the DMN garners attention due to its heightened susceptibility to neurodegeneration and early involvement in AD pathophysiology (Pasaquini et al., 2015). Notably, the distribution of amyloid beta (Aβ) deposition, a hallmark of AD, significantly overlaps with the DMN (Buckner et al., 2005). Numerous studies have consistently reported disrupted DMN function in AD, particularly evident in the functional connectivity of the PCC/precuneus, which strongly correlates with impaired cognitive function (Pievani et al., 2017; Cha et al., 2013; Binnewijzend et al., 2012).

Repetitive transcranial magnetic stimulation (rTMS) (Hartwigsen and Volz, 2021) stands as a potent tool for modulating brain network connectivity by harnessing neural plasticity mechanisms. This technique employs potent, brief magnetic pulses to induce changes in neuronal polarization within the targeted cortical region, leading to transitory alterations in cortical excitability (Bradley et al., 2016; Sarasso et al., 2020; Balderston et al., 2020). Notably, the influence of rTMS extends beyond the stimulated area to encompass distant brain regions interconnected with the site of stimulation (Ruff et al., 2009). These 'network' effects of rTMS can evolve in response to the functional state of the targeted network, offering fresh insights into the role of remote yet interlinked brain areas in supporting cognitive processes (Du et al., 2018; Philip et al., 2018). Clinical trial models focusing on AD (Choung et al., 2021; Chou et al., 2020) have highlighted the therapeutic potential of transcranial magnetic stimulation (TMS) for addressing neurodegenerative disorders. Meta-analysis results by Lin et al. (2019) provided compelling evidence that rTMS therapy can significantly enhance cognitive abilities in individuals with mild to moderate AD. Furthermore, the findings from Menardi et al. (2022) reinforce the efficacy of TMS in improving global cognitive functioning among patients with mild-to-moderate AD. Empirical research indicates that rTMS effectively enhances neuroplasticity, cortical excitability, and the cognitive impairment trajectory among patients with mild cognitive impairment (MCI)

and AD (Heath et al., 2018). The growing body of evidence suggests that rTMS could enable more precise modulation of neurochemical and neurophysiological functions (Bashir et al., 2022).

Initial findings lend support to the potential role of neuro-navigated rTMS targeted at key nodes within the DMN to reshape network dynamics and ameliorate cognitive impairments in early AD patients (Koch et al., 2018; Abellaneda-Pérez et al., 2019). Halko et al. (2014) demonstrated that intermittent theta burst stimulation which is a complex, high-frequency excitatory TMS protocol applied to the lateral cerebellum enhanced DMN functional connectivity in healthy individuals. Furthermore, intermittent theta burst stimulation led to increased connectivity in the proximal DMN region among elderly adults (Abellaneda-Pérez et al., 2019). In a study by Xue et al. (2017), rTMS directed at the left dorsolateral prefrontal cortex (DLPFC) evoked significant activity changes in several areas, including the right frontal gyrus, right precuneus, and inferior parietal lobule. Notably, Yuan et al. (2020) highlighted that rTMS holds the potential to elevate the amplitude of low-frequency fluctuation (ALFF) values within the frontal lobe, precuneus, and inferior parietal cortex (IPC) among individuals with amnestic mild cognitive impairment (aMCI). This underscores rTMS interventions in aMCI by impacting the modulation of functional connectivity across brain networks.

To comprehensively unravel the neural underpinnings of rTMS treatments, a growing body of studies employed rs-fMRI within clinical trials. A spectrum of analytical methods, including the amplitude of low-frequency fluctuations (ALFF), regional homogeneity (ReHo), and functional connectivity (FC), is furnishing neurologists and researchers with fresh insights into the rTMS therapy landscape for dementia. However, despite these advancements, a complete understanding of the precise neural mechanisms fueling rTMS effects remains elusive. The absence of a consensus could stem from factors such as small sample sizes or disparities in experimental outcomes across studies. Additionally, diverse affected brain regions have been observed in prior investigations, further contributing to the complexity of the field.

Therefore, aiming to elucidate which brain areas play a crucial role in the therapeutic effect of rTMS, this systematic review and meta-analysis integrates the results of individual neuroimaging studies to assess the clinically meaning of rTMS for patients with MCI and AD. Another aim is to

test the hypothesis that rTMS can enhance connectivity and perfusion of the DMN, which is affected in the early stages of AD. Understanding the mechanism of rTMS-induced neuroplasticity can not only elucidate the core mechanism of rTMS but also provide novel ideas for the application of rTMS in the treatment of neurodegenerative diseases.

2. Methods

2.1 Search strategy and study selection

This study was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009). Systematic literature research was performed from January 2010 to July 2023 in Scopus, Science Direct, PubMed, PsycINFO, and ISI Web. The search terms were organized into strings A, B, and C. String A: “prodromal Alzheimer”, “Alzheimer’s diseases”; “Mild Cognitive Disorder”, and “MCI”. for string B: “brain networks”, “default mode network”, “DMN”. for string C: “transcranial magnetic stimulation”, “TMS”, “Repetitive transcranial magnetic stimulation”, “rTMS”. The operator that regulated the relationship between the words within each string was OR; the operator that linked the two strings was AND. The research was extended to all fields (title, abstract, keywords, full text, and bibliography).

The focus was on original, randomized, double-blind clinical trials designed for therapeutic purposes, with either parallel or crossover designs. Review papers and the references cited in the identified studies were used to extend the search for further relevant literature. Only studies written in English were considered. Furthermore, a manual search of the reference sections of the retrieved studies and review articles was carried out. The final search identified a total of 1105 articles. The titles and abstracts of the remaining records were screened for eligibility, which led to the exclusion of 591 for either being animal model studies or with an inappropriate scope. Afterwards, the full text of each publication was assessed and eligible studies were selected. In sum, 20 full-text articles were excluded due to the absence sham condition. Thus 10 articles remained for full-text assessment and data extraction (Fig. 1).

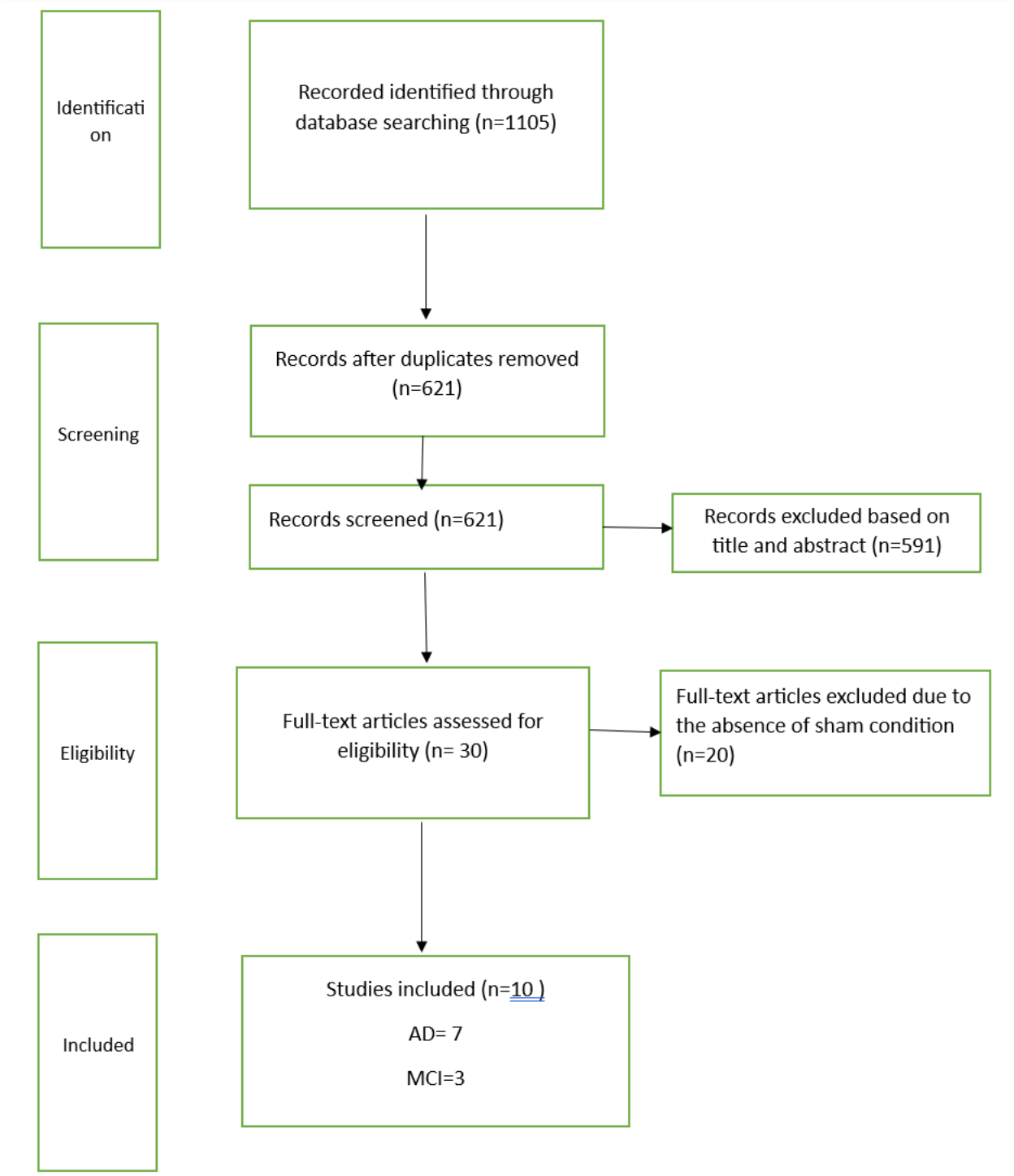

Figure 1: Diagram flow. Search strategy and study selection for the present meta-analytical study

2.2 Eligibility Criteria

The screened articles were carefully reviewed by researcher and included in the meta-analysis if they met the following criteria: (1) randomized controlled trials (RCTs) were conducted in patients who were previously diagnosed with MCI or AD according to eligible criteria (e.g., Petersen's criteria, National Institute on Aging Alzheimer's Association [NIA-AA], National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association [NINCDS-ADRDA], Diagnostic and Statistical Manual of Mental Disorders, 5th edition [DSM-V]); (2) rTMS was the main intervention being investigated for the outcome differences in the treatment group while sham stimulation in the control group; (3) the use of high-frequency (≥5 Hz) rTMS protocols; (4) article was published in English; (5) involved whole-brain functional imaging in resting-state; (6) fMRI data for quantitative analysis were displayed as three-dimensional coordinates (x, y, z) in standard stereotactic space Montreal Neurological Institute.

The exclusion criteria were as follows: (1) single-arm studies or studies without sham conditions, to ensure control over placebo effects; (2) case reports, to ensure greater generalizability of the findings; (3) AD patients with other concomitant forms of dementia (e.g., vascular dementia) or other comorbidities (e.g., depression) to ensure homogeneity across samples, as well as to limit unwanted confounding factors; (4) 1 Hz rTMS, that is, inhibitory stimulation protocols, to further reduce the heterogeneity across studies, and (5) studies without available data for analysis.

2.3 Activation likelihood estimation

The statistical analyses were performed using the revised version of the activation likelihood estimation (ALE) (Eickhoff et al., 2012) based on coordinate-based meta-analyses (CBMA) (Eickhoff et al., 2009; Laird et al., 2009a; Turkeltaub et al., 2002). ALE assessed the significant convergence between activation foci from different experiments (e.g. rTMS>sham, rTMS<sham) for a given study in comparison with a random distribution of foci. More specifically, as the first step, the ALE algorithm models the reported activation foci as center peaks of 3D Gaussian probability distributions that acknowledge the spatial uncertainty associated with each focus. The uncertainty is mainly due to between-subject variations (neuroanatomical variability and small sample sizes) and between-laboratory differences (various brain templates, normalization, and

analysis strategies). The number of participants per experiment determines the width of the spatial uncertainty of any focus (Eickhoff et al., 2012). As the second step, the probability distributions of all activation foci in a particular experiment are combined for each voxel, which creates a modeled activation map (MA map). Thus, these MA maps summarize localization probabilities of studies, and the final ALE map results from interpolation of these MA maps describing the convergence of results across all experiments. During the third step, an analytical approach based on a non-linear histogram integration is applied to test against the null hypothesis of randomly distributed foci and subsequently significant statistical threshold set at $p < 0.05$ family-wise error in cluster level (cFWE). The recent analysis approach tested for convergence by experiments (random effects) rather than foci (fixed effects) (Eickhoff et al., 2012); for further details and a summary of the ALE method please refer to (Eickhoff and Bzdok, 2013; Laird et al., 2009).

2.5. Whole-brain co-activation profiles

In order to map brain regions that feature significant co-activation with the regions identified in the Alzheimer's disease functional meta-analysis, we performed meta-analytic co-activation modeling (MACM). More specifically, we tested how likely it is that the experiments activating the particular region also activate other brain voxels above chance (Eickhoff et al., 2011; Robinson et al., 2010). In order to perform MACM, first we identified all experiments in the BrainMap database that activate the convergent seeds. Then, quantitative meta-analysis was applied to test for convergence across the foci reported in the experiments. Inevitably, the highest convergence will be observed in the seed regions because experiments are already selected by activation in those seeds. Significant convergence of reported foci in other brain areas represents consistent co-activation or functional connectivity of other voxels with the seeds. More specifically, MACM provides information on the functional interactions of cortical modules based on their whole-brain co-activation pattern across the BrainMap database (Eickhoff et al., 2011; Laird et al., 2013).

3. Results

3.1 Included studies and sample characteristics

Our meta-analysis encompassed a total of seven studies focusing on AD, collectively 116 patients in the treatment group and 90 patients in the sham group. These studies were carefully selected based on stringent inclusion and exclusion criteria to ensure the quality and relevance of the data. A summary of the demographic and clinical details for each of these studies can be found in Table 1. Additionally, our meta-analysis also incorporated three studies that specifically recruited MCI patients, comprising 34 patients in the treatment groups and 39 patients in the sham group, adhering to predefined inclusion and exclusion criteria. A summary of the demographic and clinical characteristics of each of these MCI-focused studies is provided in Table 2.

Table 1. Essential demographic and clinical characteristics of the AD studies.

	Study	participants	Gender(F/M)	Age(Y)	Education(Y)	disease	Design
1	Wei(2022)	rTMS=29	9/20	70	7.34	AD	Parallel
		Sham=27	7/20	71.67	6.63		
2	Yao(2022)	rTMS=15	7/8	63.87	10.53	AD	Parallel
		Sham=12	6/6	67.60	9.40		
3	Qin(2022)	rTMS=9	2/7	66.9	12.3	AD	Parallel
		Sham=8	3/5	66.3	11.5		
4	Liu(2022)	rTMS=25	12/13	67.28	10.44	AD	Parallel
		Sham=12	4/8	72.08	11.66		
5	Budak(2023)	rTMS=10	6/4	72	NR	AD	Parallel
		Sham=8	7/1	74.90	NR		

6	Qin(2023)	rTMS=10	8/2	65.60	11.80	AD	Parallel
		Sham=6	3/3	66.50	11.83		
7	Zhang(2023)	rTMS=18	8/10	84.8	NR	AD	Parallel
		Sham=17	6/11	83.4	NR		

Abbreviations: AD, Alzheimer's disease; F, female; M, male; NR, not reported; Y, year.

Table 2. Essential demographic and clinical characteristics of the MCI studies.

	Study	participants	Gender(F/M)	Age(Y)	Education(Y)	disease	Design
1	Yuan(2021)	rTMS=12	6/6	65.8	11.83	aMCI	Parallel
		Sham=12	5/7	64.67	11.33		
2	Esposito(2022)	rTMS=11	14/13	67.85	13	MCI	Parallel
		Sham=16			11		
3	Yuan(2023)	rTMS=11	NR	NR	NR	aMCI	Parallel
		Sham=11					

Abbreviations: MCI, mild cognitive impairment; aMCI, amnestic mild cognitive impairment; F, female; M, male; NR, not reported; Y, year.

In the case of the AD group, rTMS was applied to specific brain regions, including the left dorsolateral prefrontal cortex, lateral parietal region, bilateral cerebellum, angular gyrus, and left lateral temporal lobe. As for rTMS, 5–40 Hz stimulation coils were placed on the scalp in a tangential position with intensity varying from 40% to 100% resting motor threshold. The treatment duration spanned from 4 weeks to 3 months. For an overview of the intervention parameters and cognitive assessments, please refer to Table 3.

Table 3. The characteristics of intervention parameters and cognitive assessments of AD studies

	Study	Intervention	Stimulation site	Stimulation protocol	Outcome measures	Cognitive domains
1	Wei(2022)	rTMS	Lateral Parietal region	10 Hz, 100% RMT, 10 sessions, 2 weeks	dFC, MMSE	General Cognitive Function
2	Yao(2022)	rTMS	(B) Cerebellum	5 Hz, 90% RMT, 4weeks	FC, MMSE, MoCA	Episodic memory, executive and verbal ability, visuospatial function
3	Qin(2022)	rTMS +COG	(L)DLPFC (L)LTL	10 Hz, 100% RMT, 20 sessions, 4 weeks	FC, ALFF, ADAS-cog	General Cognitive Function
4	Liu(2022)	rTMS	(B) AG	40 Hz, 40% RMT, 12 sessions, 4 weeks	FC, MMSE, MoCA	Executive function
5	Budak(2023)	rTMS	(B) DLPFC	20 Hz, 10 sessions, 2 weeks	NPI, FBI, RSA	Executive function
6	Qin(2023)	rTMS+COG	(L)DLPFC LTL	10 Hz, 100% RMT, 20 sessions, 4 weeks	CBF, ADAS-cog	General Cognitive Function
7	Zhang(2023)	rTMS	(L)DLPFC	10 Hz, 100% RMT, 60 sessions, 3 month	FC, CIBIC-Plus	General Cognitive Function

Abbreviations: ADAS-cog, Alzheimer's disease assessment scale-cognitive subscale; ALFF, amplitude of low-frequency fluctuation; CBF, cerebral blood flow; B, bilateral; CIBIC-Plus, Clinician's Interview-Based Impression of Change plus caregiver input; COG, cognitive training; dFC, dynamic functional connectivity; DLPFC, dorsolateral prefrontal cortex; FBI, Frontal Behavioral Inventory; FC, functional connectivity; L, left; MMSE, mini-mental state examination; MoCA, Montreal cognitive assessment; NPI, Neuropsychiatric Inventory Questionnaire; RSA, resting-state activity; RSN, resting-state networks.

The stimulation target sites of rTMS in the MCI group included the left dorsolateral prefrontal cortex and precuneus. As for rTMS, 10 Hz stimulation coils were placed on the scalp in a tangential position with intensity varying from 80% to 120% resting motor threshold. Similarly, the treatment time lasted 4 weeks. The intervention parameters and cognitive assessments of the MCI studies are presented in Table 4.

Table 4. The characteristics of intervention parameters and cognitive assessments of MCI studies

	Study	Intervention	Stimulation site	Stimulation protocol	Outcome measures	Cognitive domains
1	Yuan(2021)	rTMS	(L)DLPFC	10 Hz, 80% RMT, 20 sessions, 4 weeks	ALFF, MoCA	General Cognitive Function
2	Esposito(2022)	rTMS	(B)DLPFC	10 Hz, 80% RMT, 20 sessions, 4 weeks	FC, RBANS	Semantic fluency, visuospatial performance
3	Yuan(2023)	rTMS	Precuneus	10 Hz, 80-120% RMT, 20 sessions, 4 weeks	FC, EM, EF	episodic memory, executive function,

Abbreviations: ALFF, amplitude of low-frequency fluctuation; B, bilateral; DLPFC, dorsolateral prefrontal cortex; FC, functional connectivity; L, left; MoCA, Montreal cognitive assessment; RBANS, repeatable battery for the assessment of neuropsychological status; EM, episodic memory; EF, executive function.

3.2. Convergence of neuroimaging findings in Alzheimer's and MCI

Upon conducting meta-analyses to assess significant convergence across all eligible neuroimaging experiments involving Alzheimer's patients compared to the sham group, no significant clusters of convergence were observed. A similar outcome was observed when conducting meta-analyses of the MCI group.

3.3. FC in patients with MCI

Based on the collective descriptions in the literature of rTMS, the seed-based region of interest (ROI) was placed on left frontoparietal networks (L.FPN) (Esposito et al.,2022), and precuneus (Yuan et al.,2023), respectively. In the case of the former, rTMS resulted in heightened FC within the left supramarginal gyrus, middle frontal gyrus, superior temporal gyrus, and parahippocampal gyrus. Conversely, a separate study focusing on individuals with aMCI revealed increased FC within the right posterior cerebellar lobes (CPL) subsequent to rTMS. Importantly, rTMS-induced

improvements in episodic memory function among aMCI patients correlated closely with the observed FC alterations within CPL (Yuan et al., 2023).

3.4. FC in patients with AD

Five distinct randomized controlled trials (RCTs) have contributed insights into alterations in FC following rTMS in individuals with AD. Wei et al. (2022) highlighted a significant elevation in dynamic FC magnitude within the DMN among patients undergoing rTMS treatment, underscoring its potential for cognitive enhancement. Notably, Li et al. (2023) revealed that rTMS interventions facilitated cognitive improvements through the restructured inter-network connectivity of the cerebellum and augmented intra-network connectivity of frontal-parietal regions. Similarly, Liu and colleagues showcased elevated local functional integration in the bilateral angular gyrus, heightened long-distance functional connections involving the left angular gyrus, superior frontal gyrus, and right inferior frontal gyrus, as well as reinforced information transmission from the left posterior temporoparietal region to frontal areas. These enhanced integrations were closely linked to improved clinical symptoms encompassing executive function and memory (Liu et al., 2022). In the study by Yao et al. (2022), rTMS fostered heightened functional connectivity between the left cerebellum and the right dorsolateral prefrontal cortex, bilateral medial frontal cortex, and bilateral cingulate cortex. Furthermore, another investigation indicated the predictive potential of baseline multivariate FC, specifically involving the right hippocampus/posterior parahippocampal gyrus and cortical clusters, for individual treatment outcomes (Zhang et al., 2023).

3.5. Resting-state activity differences in patients with AD

Incorporating two pertinent trials into the analysis, investigations delved into the impact of rTMS on the modulation of resting-state activity disparities among patients with AD. One of the studies unveiled that following High-frequency rTMS, there was a noteworthy elevation in resting-state activation within the DMN, encompassing the middle temporal gyrus, central opercular cortex, intracalcarine, superior parietal lobule, and paracingulate cortex (Budak et al., 2023). In parallel, a distinct study showcased significant increases in resting-state activation within the right

cerebellum, left lingual/cuneus, and left cingulate gyrus, while concurrently observing a decrease in the left middle frontal gyrus (Qin et al., 2022).

3.6 FC changes in DMN after rTMS

The investigation of FC changes within DMN has yielded significant insights, particularly in two distinct studies focusing on distinct stimulation sites and targets. In the first study, activation of the inferior parietal lobule and left lateral parietal region were observed, regions that are presumed to play integral roles within the DMN (Wie et al.,2022). Similarly, the second study conducted by Chen and colleagues targeted the left angular cortex, a region also implicated in DMN function. They indicate that intra-DMN functional connectivity is potentially a neuroimaging target for the therapeutic effectiveness of rTMS during recovery of cognitive impairment in this group of patients(Chen et al.,2023).

4. Discussion

It has been suggested that the diverse and often conflicting findings regarding brain structure and function in a variety of disorders may be ameliorated by a more finely-tuned understanding of which structures in networks are most implicated (Celle et al.,2016; Eickhoff et al., 2020). In this vein, in our study, we have undertaken to gain a greater understanding of the effectiveness of rTMS in activity alteration in patients with AD and MCI across the published literature by using the ALE meta-analysis of currently available functional imaging studies.

rTMS could alleviate neurological deficits and improve cognitive performance in patients with MCI and AD. The improvements in neuropsychological scores have been discussed in some previous meta-analysis studies (Chou et al.,2023; Wang et al.,2021; Inagawa et al.,2019) so we will not discuss them further here. In this paper, we mainly focus on changes in rsfMRI after rTMS intervention. In our study, the combined ALE quantitative analyses on group contrasts between Alzheimer's patients and the sham group showed no significant clusters of convergence. A similar null finding was observed when conducting meta-analyses of the MCI group. It is crucial to acknowledge that the absence of significant findings in our meta-analysis can be attributed, in

part, to the limited statistical power resulting from the relatively small number of studies included in the meta-analysis.

In our case, the restricted pool of eligible studies may have hindered our ability to detect meaningful clusters of convergence. Future research in this area may benefit from a larger and more comprehensive dataset to enhance statistical power and improve the precision of our findings.

4.1. Efficacy of rTMS in Angular Gyrus

An rTMS-fMRI study conducted by Wang et al. (2014) employed a multi-session rTMS protocol focused on the left angular cortex, leveraging its connectivity within the cortical hippocampal network. This intervention led to a noteworthy enhancement in memory performance, attributed to the modulation of synaptic plasticity. Similarly, Nilakantan et al. (2019) examined older adults and found that targeted stimulation of the left angular cortex effectively altered age-related recollection impairments.

Building upon these findings, Chen et al. (2023) extended the research to patients with AD, showcasing the potential therapeutic value of targeting the left angular cortex. The authors identified the left angular cortex as a viable candidate due to its weakest functional connectivity with the left hippocampus in individuals with AD. Notably, their study substantiated the effectiveness of rTMS in ameliorating cognitive deficits in AD patients when applied to the left angular cortex.

Chen et al. (2023) delved into the mechanisms underlying the cognitive improvements brought about by rTMS. They discovered that rTMS intervention influenced the intricate relationships between different subsystems of the DMN and the broader functional networks associated with the DMN. This dynamic regulation was particularly pertinent to the interactions both within and between the DMN subsystems. Notably, the study hinted at the potential for baseline intra- and inter-DMN dynamics to serve as predictive markers for favorable responses to rTMS.

4.1. rTMS affects Precuneus functional connectivity

Prior investigations have consistently demonstrated that rTMS can induce neuroplastic effects not only within the directly stimulated cortical regions but also in distal brain areas connected functionally to the site of stimulation. In a recent study by Koch and colleagues (2022), the posterior brain area known as the precuneus, implicated in the progression of neurodegeneration, was specifically targeted. The rationale behind this approach was the observed decline in functional connectivity and damage to various components of the DMN in this region. Notably, their findings highlighted the substantial impact of rTMS on cortical activity in patients who underwent rTMS treatment. Particularly, they observed that cortical excitability, which displayed stabilization at the baseline level, remained consistent even after a span of 24 weeks. In stark contrast, the sham-rTMS group experienced a significant reduction in cortical excitability over the same period. In a related study conducted by the same research group, a combination of rTMS and electroencephalogram techniques yielded intriguing results. This investigation revealed that rTMS targeted at the precuneus yielded improvements in long-term memory among individuals with prodromal AD. Further, local gamma-band oscillations were boosted only in patients who received real rTMS. This improvement was attributed to the modulation of neural activity within the precuneus itself and its connections with other regions, such as medial parietal and frontal areas within the DMN (Koch et al., 2018).

Furthermore, recent advancements have extended the understanding of rTMS effects. Cui et al. (2019) employed functional magnetic resonance imaging (fMRI) to investigate rTMS-induced changes in functional connectivity within the DMN. Remarkably, these connectivity alterations were associated with significant cognitive improvements in individuals with aMCI. Notably, the application of rTMS with the precuneus as the target not only modulated the functional connectivity of the posterior cerebellar network in patients with aMCI but also effectively enhanced their cognitive status (Yuan et al., 2023).

4.2. rTMS affects the modulation of DMN connectivity

Several research studies have provided evidence supporting the effectiveness of rTMS in regulating connectivity within the DMN and enhancing episodic memory in individuals with early AD (Koch et al., 2018; Nilakantan et al., 2019). The DMN holds a significant role as the initial brain network associated with amyloid deposition during the early stages of AD. Amyloid protein accumulation disrupts FC between DMN regions and other brain areas (Pereira et al., 2018).

Although the DMN plays a crucial role in the aging process and the pathological trajectory of cognitive function, its changes over time are indicative of shifts in interconnectivity that correspond to distinct stages of FC alterations (Bai et al., 2008; Uddin et al., 2009). The decline in FC within the DMN is often regarded as a biomarker of functional deterioration in AD. However, the varying interpretations of bidirectional connectivity changes observed across different studies involving patients with MCI, particularly the heightened interactions with the posterior cingulate gyrus (PCG), have yielded diverse explanations (Cui et al., 2019).

One plausible explanation for the observed increase in FC is that it could reflect a "compensatory process" within the brain, aiming to counteract hypoactivation in specific brain regions. Consequently, it is a valid proposition that both increased and decreased FC might manifest after rTMS treatment. However, substantiating these arguments requires further validation through extensive clinical trials.

4.3. rTMS modulates hippocampal connectivity

The hippocampus, another vulnerable brain region in patients with MCI and AD, is an important brain structure connecting the anterior temporal and posterior medial regions of the medial temporal system (Zhuo et al.,2016). A noteworthy characteristic of AD patients is the marked reduction in resting-state FC between the hippocampus and the medial prefrontal cortex. The hippocampus exerts a significant influence as a driving force on brain functional activity, while the medial prefrontal cortex functions as a vital hub for integrating converging information (Li et al., 2020). The interaction between these two regions plays an instrumental role in processes such as memory, learning, and other intricate cognitive functions (Preston and Eichenbaum, 2013).

Pathological examinations of AD have consistently demonstrated the initial emergence of neurofibrillary tangles within the structures of the medial temporal lobe, with the hippocampus being among the earliest affected brain regions (Braak and Braak, 1991). In a preceding study, a combination of established techniques, namely fMRI and rTMS, was employed to unravel the causal relationship between neuroimaging-based functional changes in the hippocampus and episodic memory deficits in MCI patients. The outcomes revealed that rTMS exerted a positive impact on ameliorating episodic memory impairments in MCI by directly modulating the circuit encompassing the precuneus, hippocampus, and middle temporal gyrus (Chen et al., 2022). Furthermore, the dynamic changes occurring within the hippocampus functional activity hold the potential as a valuable target for monitoring the cognitive progression of AD patients over time.

5. Limitations

According to our current findings, there are several important factors that require attention. Firstly, it is worth noting that our analyses may have been influenced by a relatively limited number of placebo-controlled trials and the often restricted pool of study participants. To elaborate this issue further, our initial literature search revealed only 10 studies where patients with AD and MCI were subjected to rTMS treatment. Secondly, we observed that the studies included in our meta-analysis had rather small sample sizes. This is evident from the fact that three out of the ten studies considered had a sample size of less than or equal to 20 participants. This limited sample size may have hindered our ability to conduct comprehensive and robust statistical analyses. Thirdly, it is important to acknowledge that our use of Ginger ALE was based on coordinates obtained from published studies rather than raw data. This approach introduced potential limitations in terms of accuracy. Lastly, it is worth mentioning that our current analysis could not determine whether MCI would progress to AD following rTMS intervention. To address this gap in knowledge, future longitudinal studies should investigate the effect size of rTMS interventions and their impact on the progression from MCI to AD.

6. Conclusions

Despite the current meta-analysis did not show significant results, our systematic review suggested that rTMS intervention appeared to be an effective and safe treatment for patients with MCI and AD. The improvement may be attributed to the positive modulation of rTMS on the spontaneous neural activity and cognitive network. fMRI evaluations could be added to target-specific rTMS treatment to evaluate the contribution to the therapeutic effectiveness of rTMS. These findings provide new insights into the neuroimaging mechanisms underlying the efficacy of rTMS. Further, the findings indicate that DMN functional connectivity is potentially a neuroimaging target for the therapeutic effectiveness of rTMS during recovery from cognitive impairment in this group of patients.

This has so far been difficult to implement, but future careful experimental designs might help with this issue. Finally, it is hoped that the findings presented here may offer a tentative first step toward this task and provide an initial theoretical framework for interpreting the aberrant activity within these network nodes.

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