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SYSTEMATIC REVIEW AND META-ANALYSIS CONFIRM THE MODERATE EFFICACY OF HIGH-FREQUENCY R-TMS IN ALZHEIMER'S DISEASE: MEDIATING EFFECTS OF ANHEDONIA-APATHY AND ADD-ON MOTOR-COGNITIVE EXCERSIZES

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SUMMARY

***Objectives**: Alzheimer's disease (AD) presents a major global health issue of significant socio-economic impact. Pharmacological treatments for AD have limited efficacy, prompting the exploration of alternative therapies, such as repetitive transcranial magnetic stimulation (rTMS), a promising non-invasive technique to enhance cognitive function in AD patients. Our systematic review and meta-analysis aim to evaluate the efficacy of rTMS in relation to cognitive function in AD patients, identify optimal rTMS stimulation parameters, and understand the underlying neural mechanisms.*

***Methods**: We conducted a comprehensive literature search in PubMed using predefined search terms to identify original research articles investigating the effects of rTMS on cognitive function in AD patients. We selected only randomized controlled trials (RCTs) with sufficient quantitative data for comparing active rTMS to the sham-coil treatment, and then performed a random effects meta-analysis using standardized mean differences (SMDs) to synthesize the effects across studies.*

***Results**: The systematic review included 22 studies, among which 14 RCTs met our criteria for meta-analysis. High-frequency rTMS, particularly targeting the dorsolateral prefrontal cortex (DLPFC), evoked significant cognitive improvements in AD patients, with a moderate positive effect size of rTMS on cognitive function (Hedges' $g=0.580$, 95% CI [0.268, 0.892], $p<0.001$), albeit with substantial heterogeneity ($I^2=59\%$). Funnel plot asymmetry and Egger's test suggested a potential publication bias, but fail-safe N analysis indicated a robust finding. Moreover, anhedonia-apathy symptoms and motor-cognitive exercises mediated the efficacy of tTMS in ameliorating cognitive functioning across several studies.*

***Conclusion**: rTMS demonstrates moderate efficacy in improving cognitive function in AD-patients, most distinctly with high-frequency rTMS stimulation protocols targeting the DLPFC area. The meta-analysis support rTMS as a viable therapeutic intervention for cognitive enhancement in AD. Future promising research should focus on personalized treatment strategies targeting mediating factors, baseline connectivity patterns, and TMS-induced neuroplasticity in AD.*

***Key words:** anhedonia – apathy - Alzheimer's disease - cognitive function – connectivity - meta-analysis – motor activities - rTMS - systematic review - transcranial magnetic stimulation*

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INTRODUCTION

Alzheimer's disease (AD) poses a significant global health challenge due to its devastating impact on cognitive function of afflicted individuals, and the substantial economic burden that their care places on societies. The limited efficacy of current pharmacological interventions for AD (including immunotherapy targeting beta-amyloid) has spurred extensive research into alternative therapeutic approaches, with repetitive transcranial magnetic stimulation (rTMS) emerging as a notably promising candidate. Indeed, there is an abundance of studies exploring the potential of rTMS to enhance cognitive function in individuals with AD. Such approaches range from investigations targeting specific brain regions like the dorsolateral prefrontal cortex (DLPFC) (Guo et al. 2021, Chen et al. 2023, Millet et al. 2023) to those examining the pro-cognitive effects of rTMS administered in conjunction with cognitive training and psychopharmacology (Qin et al. 2024, Viotti et al. 2023).

This growing body of research has yielded encouraging results, consistently demonstrating an ability of rTMS to promote neuroplasticity, modulate brain connectivity, and improve cognitive deficits associated with AD (Guo et al. 2021, Miller et al. 2023, Xie et al. 2021). Studies employing high-frequency rTMS targeting the DLPFC have shown significant improvements in cognitive function in AD patients and its prodromal mild cognitive impairment (MCI) (Chen et al. 2023, Miller et al. 2023). Furthermore, research has highlighted the potential neuroprotective effects of rTMS, suggesting that it can mitigate against neuronal damage associated with oxidative stress, which a key factor in the pathogenesis of diverse neurological disorders (Kim et al. 2023).

Meta-analyses and systematic reviews have further reinforced the generally positive findings of individual studies, thus providing compelling evidence for the efficacy of rTMS in improving cognitive function in patients with AD (Jiang et al. 2021, Miller et al. 2023, Millet et al. 2023, Wei et al. 2023). These analyses have not only confirmed the cognitive benefits of rTMS but have also explored the optimal stimulation parameters, such as frequency, duration, and target brain regions, to maximize its therapeutic effects (Millet et al. 2023, Wei et al. 2023). Furthermore, there has been consideration of the possible neural mechanisms underlying these benefits, further exemplifying the potential of rTMS to modulate neural connectivity and network function (Qin et al. 2023).

Spurned by these the encouraging findings, there is a rapid evolution in the application of rTMS for amelioration of AD symptoms, with new studies continually adding to the existing knowledge base. This highlights the need for regular updates of previous meta-analyses to incorporate the latest findings and provide a comprehensive overview of the current state of research. Therefore, we undertook a systematic review of the existing literature and conducted a meta-analysis to assess the efficacy of repetitive transcranial magnetic stimulation (rTMS) on cognitive function in AD patients. By synthesizing the data from multiple studies, we sought to quantify the impact of rTMS on cognitive outcomes and evaluate the consistency of these effects across different assessment tools. Additionally, we aimed to identify the most efficient rTMS protocols with respect to optimal modalities and target brain regions, for enhancing cognitive function in AD patients. This study thus expands upon previous reviews and meta-analyses, providing an updated and more comprehensive current understanding of the efficacy of rTMS in ameliorating cognitive impairments in AD.

METHODS

Literature Search and Study Selection

We conducted a systematic literature search in PubMed using the following search string:

("transcranial magnetic stimulation"[MeSH Terms] OR "TMS"[Title/Abstract] OR "repetitive transcranial magnetic stimulation"[Title/Abstract]) AND ("Alzheimer's disease"[MeSH Terms] OR "Alzheimer disease"[Title/Abstract] OR "Alzheimer's"[Title/Abstract] OR "dementia, Alzheimer's"[Title/Abstract]) AND ("efficacy"[Title/Abstract] OR "effectiveness"[Title/Abstract] OR "treatment outcome"[Title/Abstract]).

We supplemented this search by examining the references of identified articles for additional relevant sources.

In our study selection process, we applied specific criteria to identify relevant research both for the systematic review and for the meta-analysis. For the systematic review, we included original research articles published in English that investigated the effects of rTMS on AD patients and reported cognitive function or other treatment outcomes. We excluded reviews, meta-analyses, and case reports. The meta-analysis employed more stringent criteria, focusing on randomized controlled trials comparing active rTMS to sham treatment. We selected only data that addressed direct effects of rTMS for meta-analysis. This means that we compared either rTMS vs. sham, or rTMS + other treatment modalities vs. other treatment modalities + sham. We also excluded from analysis the only instance of a low-frequency arm. When there were several time points reported in a single study, we selected only those time points that were indicated as being primary outcomes. These studies needed to provide sufficient quantitative data on pre- and post-intervention means and standard deviations of cognitive outcomes as assessed using standardized assessment tools like MMSE, MoCA, or ADAS-Cog. This allowed for the calculation of standardized mean differences (SMDs), enabling a quantitative synthesis of the treatment effects across studies. Also, we included in the meta-analysis only papers that contai-

ned either pre- and post-intervention means and standard deviations or equivalent statistics enabling a comparison of changes in active rTMS and control groups. Studies that met the systematic review criteria but lacked sufficient quantitative data for effect size calculation were included only in the qualitative synthesis, ensuring a comprehensive review of the available literature, while maintaining rigorous standards for the quantitative analysis.

Data Extraction and Analysis

From each included study, we extracted data on sample sizes, pre- and post-intervention mean scores for scales assessing overall cognitive functioning (e.g., MMSE, MoCA, ADAS-Cog), and standard deviations (SD) or standard errors (SE) for both active and sham groups or between-group difference and 95% confidence interval (CI 95%). We then used different transformation formulae to compute non-reported values for each study based on the results provided[1].

The JASP 0.18.3 software served to conduct a random effects meta-analysis. We chose this approach to account for the expected heterogeneity due to differences in rTMS protocols, patient characteristics, and outcome measures. We calculated standardized mean differences (SMDs) as our effect size measure (Hedges' g), which allowed us to compare results across studies using different assessment tools for cognitive functioning.

Due to differences in scoring between scales (e.g., for MMSE and MoCA, higher scores indicate better functioning, whereas for ADAS-Cog, it's the opposite), we ensured consistent interpretation across different cognitive scales by reverting the sign of SMDs for studies using ADAS-Cog as an outcome. This enabled a uniform interpretation where positive SMDs consistently indicate improvement in cognitive function. We adhered to a standard interpretation of effect sizes: small (0.2-0.5), medium (0.5-0.8), or large (>0.8).

[1] Mean Difference Calculation: Mean Difference = Mean_After - Mean_Before
Standard Deviation (SD) of Mean Difference: SD = sqrt(SD_before^2 + SD_after^2 - 2 * r * SD_before * SD_after) Where r is the correlation between before and after measurements, assumed to be 0.5.
Conversion of Standard Error (SE) to SD: SD = SE * sqrt(N) Where N is the sample size.
Standardized Mean Difference (SMD) using Cohen's d: SMD = (Mean_active - Mean_sham) / SD_pooled Where SD_pooled = sqrt((SD_active^2 + SD_sham^2) / 2)
Standard Error (SE) of SMD: SE = sqrt((n_active + n_sham) / (n_active * n_sham) + SMD^2 / (2 * (n_active + n_sham)))
SD_pooled ≈ (UCL95% - LCL95%) / (2 * 1.96) Where UCL95% and LCL95% are the upper and lower bounds of the 95% confidence interval. b. Calculating SMD: SMD = Unstandardized MD / SD_pooled c. Calculating SE of SMD: SE of SMD = (UCL95% - LCL95%) / (2 * 1.96 * sqrt(n_active + n_sham))

The risk assessment for the included studies followed guidelines from the Cochrane Handbook, evaluating five key domains of bias: selection bias, performance bias, detection bias, attrition bias, and reporting bias. (1) We assessed Selection Bias through random sequence generation and allocation concealment. Reliable randomization methods (e.g., random number table) and proper allocation concealment (e.g., sealed envelopes) indicated low risk. If these were not described or inadequate, we deemed the risk as high. (2) Performance Bias examined whether participants and personnel were blind to the interventions. Adequate blinding indicated low risk; lack of description or blinding indicated high risk. (3) Detection Bias considers if outcome assessors were blind to the interventions. Adequate blinding indicated low risk, while lack of description or absent blinding indicated high risk. (3) Attrition Bias considers the handling of incomplete outcome data. Proper handling and valid reasons for attrition indicated low risk, while improper handling or lack of description or indicated high risk. (4) Reporting Bias evaluated the reporting of prespecified outcomes. Comprehensive reporting indicated low risk, while selective reporting indicated high risk. (5) Assessment Process involved reviewing each study to apply specific criteria for each domain. If one domain had a high risk, the overall risk was marked as moderate. If more than one domain had a high risk, the overall risk was marked as high.

The meta-analysis was conducted using the restricted maximum likelihood (REML) method to estimate the between-study variance. We included an intercept in our model to account for the baseline level of cognitive function. To assess the overall effect of TMS, we examined the pooled SMD and its 95% confidence interval, and evaluated the significance using a Z-test. Heterogeneity among studies was assessed using Cochran's Q test and the I^2 statistic.

To evaluate potential publication bias, we generated funnel plots and conducted the Egger's regression test for funnel plot asymmetry. Additionally, we performed a trim and fill analysis to assess and adjust for potential publication bias. This method involves removing the most extreme small studies from the positive side of the funnel plot, re-computing the effect size at each iteration until the funnel plot is symmetric about the new effect size. Then, the original studies are replaced along with their "missing" counterparts around the adjusted effect size. This analysis provides an estimate of the number of missing studies and an adjusted effect size that takes into account the potential publication bias.

We also calculated the fail-safe N to determine the number of null studies that would be needed to nullify our significant results.

For all statistical tests, we used a significance level (alpha) of 5%.

RESULTS

The study selection process as illustrated in Figure 1. Of the 28 identified publications, 22 studies were included in the systematic review and 14 studies were included in the meta-analysis after applying exclusion criteria.

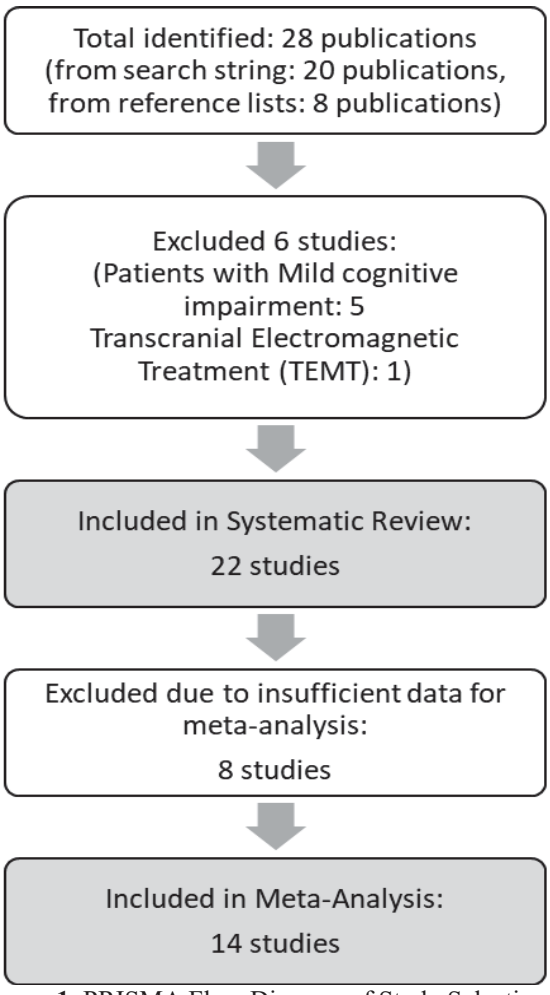

Figure 1. PRISMA Flow Diagram of Study Selection Process

Table 1 also presents a thorough review of the results for the 22 studies included in this systematic review of TMS efficacy in AD. The most commonly employed TMS modality was high-frequency repetitive rTMS, being used in 16 of 22 studies; 72.7%). High-frequency rTMS showed the most promising results, with 14 of 16 studies (87.5%) reporting significant improvements in cognitive scores for the various instruments. Additionally, five of the 16 studies (31.3%) reported enhanced functional connectivity to functional magnetic resonance imaging (fMRI), particularly within the default mode detwork (DMN). Four studies (25%) noted improvements in behavioral and psychiatric symptoms.

Three studies (13.6%) using low-frequency rTMS, showing mixed results, with two studies (66.7%) reporting cognitive improvements in selective domains, although these were generally less pronounced compared to those with high-frequency rTMS. One study (4.5%) used theta burst stimulation (TBS) and a combination of rTMS and one study used transcranial direct current stimulation (tDCS). The TBS study did not report significant improvements, while the combined rTMS and tDCS study showed promising results with greater improvement in neuropsychiatric symptoms and cognitive scores compared to single-modality treatments.

The most frequent stimulation target was DLPFC, targeted in 11 of 22 studies (50%). Nine of these 11 studies (81.8%) reported significant improvements in cognitive function, with three studies (27.3%) also noting improvements in behavioral symptoms. The lateral parietal cortex or angular gyrus was the focus in five studies (22.7%), among which four (80%) reported significant improvements in cognitive scores, and three (60%) also reporting enhanced functional connectivity to fMRI, particularly within the DMN. Three of 22 studies (13.6%) targeted multiple cortical regions simultaneously, all reporting significant improvements in cognitive function, with two of these studies also noting enhanced functional connectivity across multiple brain networks. The precuneus was the target in two studies (9.1%), both reporting stabilization of cognitive decline compared to sham treatment, with one study also reporting enhanced local gamma oscillations. The motor cortex was the target in one study (4.5% each), in which the primary endpoint was altered cortical plasticity in AD rather than cognitive outcomes. The cerebellum Crus II was the target in one study, reporting enhanced functional connectivity between cerebellar nodes and various cortical regions, which occurred in association with multi-domain cognitive improvements.

The duration of TMS interventions varied widely, ranging from single-session experiments to long-term treatments spanning several months. Most studies fell into the medium-term category, typically involving 20-30 sessions over 4-6 weeks.

Five studies (22.7%) reported that improvements were maintained for several months post-treatment, suggesting potential long-term benefits of TMS. Four studies (18.2%) using fMRI found that baseline connectivity patterns or TMS-induced neuroplasticity could predict treatment response, pointing towards the possibility of personalized treatment approaches. Furthermore, six studies (27.3%) combined TMS with cognitive training, all reporting positive outcomes, suggesting a potential synergistic effect between brain stimulation and cognitive exercises.

Table 1. Summary on the studies of rTMS Interventions in Alzheimer's Disease

Study	Design	Participants	Type of the coil	Sample Size	Interventions	Duration	Primary Outcome	Secondary Outcome	Main Results
Ahmed et al. 2012	Randomized, Sham-controlled	Patients with a probable Alzheimer's Disease (AD), 60-82 y o	A Magstim Super Rapid (Magstim Company Ltd.) with an air-cooled figure-eight coil, 70 mm diameter	45 (15 per group)	*Group 1:* High-frequency rTMS (20 Hz, 5s, 20 trains, 25s interstimulus interval, 2000 pulses/day at 90% RMT, 10 min for each hemisphere) over DLPFC bilaterally (right then left) *Group 2:* Low-frequency rTMS (1 Hz, 1000 pulses, 2 trains, 30 s interstimulus interval, 2000 pulses/day at 100% RMT, 33 min) over DLPFC bilaterally (right then left) *Group 3:* Sham stimulation (20 Hz, 5s, 20 trains, 25s interstimulus interval, 2000 pulses/day at 90% RMT, 10 min for each hemisphere) over DLPFC bilaterally (right then left) with a coil angled away from the head	5 sessions (5 consecutive days)	MMSE, IADL, GDS	Cortical excitability (rMT, aMT, TI)	High-frequency rTMS significantly improved MMSE, IADL, and GDS scores compared to low-frequency and sham groups. Improvement was maintained for 3 months. High-frequency rTMS reduced TI duration.
Brem et al. 2020	Randomized, sham-controlled, multicenter	Patients with mild-moderate AD, 55-90 y o	handheld figure-of-eight focal coil (SuperRapid stimulator, Magstim Co.)	34 (16 real/real, 8 sham/sham, 10 real/sham)	*Real/Real:* 10 Hz rTMS to 6 cortical regions - left dlPFC, right dlPFC, left IPL, right IPL, left IFG, left STG (3 areas of 6 per day, in total each area is stimulated about 15 times. 4000 pulses/day, 2 sec trains, 20 trains of 50 pulses each with 120% of the patient's RMT, 1 h session) + 20-40 sec computerized cognitive training *Sham/Sham:* Sham rTMS + sham cognitive training *Real/Sham:* Sham rTMS + real cognitive training	30 sessions (6 weeks)	ADAS-Cog	MMSE, ADCS-ADL, ADCS-CGIC, TMS measures rMT, aMT, SICI, ICF, LICI, plasticity	Real/real group showed significant improvement in cognition compared to sham/sham group. Baseline TMS-induced plasticity predicted post-intervention cognitive change.
Chen et al. 2023	Sham-controlled, cross-sectional and longitudinal	Subjects with cognitive impairment (HC, aMCI, AD), 58-75 y o	no information about the coil type	113 (26 HC, 30 aMCI, 23 AD, 24 rTMS, 10 sham)	*rTMS:* Left angular gyrus-navigated rTMS (20 Hz, 2s trains, 28s inter-interval, 20-min sessions, 1600 pulses/day with 100 % of the patient's RMT) *Sham:* Sham stimulation at the same target	20 sessions (4 weeks)	MoCA-BJ, MMSE, CDR	fMRI (seed-based and network-based analysis), CPM (predicting rTMS response using baseline connectivity)	rTMS significantly improved cognition in AD. Improved cognition correlated with DMN subsystems. Baseline DMN connectivity patterns predicted Δ language and memory cognition after rTMS.
Hu et al. 2022	Randomized, sham-controlled	Patients with moderate AD, 60-90 y o	figure-of-eight coil Electromagnetic Stimulator	84 (21 per group)	*rTMSetDCS:* Simultaneous rTMS and tDCS over bilateral AG (40 Hz rTMS, 2 mA tDCS, 15 min per hemisphere with 90% of the patient's RMT, 2-sec trains and 58-sec intertrain interval, 30 trains, 15 min, 1200 pulses/day) *Single-rTMS:* Active rTMS + sham tDCS over bilateral AG *Sham:* Sham rTMS + sham tDCS over bilateral AG *Single-tDCS:* Active tDCS + sham rTMS over bilateral AG	12 sessions (4 weeks)	NPI	MMSE, ADAS-cog, PSQI, Adverse Events	rTMSetDCS showed greater improvement in NPI scores compared to single-tDCS and sham. rTMSetDCS improved MMSE scores and PSQI compared to other groups. rTMSetDCS-induced improvements in NPI/PSQI were associated with MMSE/ADAS-cog improvement.

Table 1. Continues

Study	Design	Participants	Type of the coil	Sample Size	Interventions	Duration	Primary Outcome	Secondary Outcome	Main Results
Inghilleri et al. 2006	Age-matched control	Patients with Alzheimer's Disease (AD) and healthy controls, 55-82 y o	A Magstim Super Rapid (Magstim Company Ltd.) with an air-cooled figure-eight coil, 70 mm diameter	40 (20 AD, 20 HC)	*AD & HC:* 5 Hz rTMS (10 trains of 10 stimuli at 120% RMT, 2 min tntertrain-interval) over left motor cortex (single session) *AD & HC:* 1 Hz rTMS (10 trains of 10 stimuli at 120% rMT) over left motor cortex	Single session	MEP size and CSP duration	rMT	5 Hz rTMS failed to elicit MEP facilitation in AD patients, unlike healthy controls. 1 Hz rTMS produced similar responses in both groups. This suggests altered cortical plasticity in AD.
Jung et al. 2024	Rando-mized, sham-con-trolled	Patients with AD, 50-85 y o	70-mm diameter figure-of-eight coil (Magstim Rapid)	30 (18 rTMS, 12 sham)	*rTMS:* Personalized hippocampal network-targeted rTMS (20 Hz, 40 pulses/train, Amplitude 40% of the patient's RMT. 2-sec trains, 1600 pulses/day) targeted at left lateral parietal cortex *Sham:* Sham stimulation at the same target	20 sessions (4 weeks)	ADAS-Cog	ADAS-Cog, COWAT, TMT, MMSE, CDR-SOB, S-IADL, MOCA-K, CANTAB, fMRI	rTMS improved ADAS-Cog, CDR-SOB, and S-IADL scores compared to sham. rTMS increased functional connectivity between hippocampus and precuneus, which correlated with ADAS-Cog improvement.
Koch et al. 2022	Rando-mized, sham-con-trolled	Patients with mild-to-moderate AD, 50-85 y o	?	50 (25 per group)	*PC-rTMS:* Precuneus rTMS (20 Hz, 40 trains of 2sec, 28s inter-interval, amplitude 100% of the patient's RMT, time of session (min) - 20 min, pulses/day 1600.) *Sham-rTMS:* Sham stimulation at the same target	32 sessions (24 weeks - 2 weeks intensive, 22 weeks maintenan-ce)	CDR-SB	ADAS-Cog, MMSE, ADCS-ADL, FAB, NPI, TMS-EEG (TEPs, TRSP)	PC-rTMS patients showed stable CDR-SB scores while sham group worsened. PC-rTMS improved secondary outcomes compared to sham. PC-rTMS stabilized precuneus cortical excitability while sham reduced it. PC-rTMS enhanced local gamma oscillations.
Liu et al. 2021	Randomize d, double-blind, sham controlled, crossover pilot study	Patients with probable AD, 50–85 y o	A wind-coo-led figure-eight coil (70 mm diame-ter) (Mag-stim)	37 (ratio rTMS: sham = 2:1)	*rTMS* targeted at bilateral angular gyrus (40 Hz, amplitude 40% of the patient's RMT. 2-sec trains and 58-sec intertrain interval, 30 trains, 30 min, 2400 pulses/day) *Sham:* Sham stimulation at the same target	12 sessions (3 weeks)	ADAS-Cog	MMSE, MoCA, CDR	rTMS significantly improved MMSE and MoCA scores and decreased ADAS-Cog scores in the active group. Improved clinical symptoms remained at the 8-week follow-up. Sham group showed no significant changes in this scales.
Moussavi et al. 2024	Randomize d, sham-controlled, multicenter	Patients with mild to moderate AD, >55 y o	70-mm diameter figure-of-eight coil (Magstim Rapid)	156 (52 R2, 53 R4, 51 S4)	*R2:* active rTMS over bilateral DLPFC (20 Hz, 30 pulses/train, 25 trains, 1,5-sec trains, 10-s intertrain interval, amplitude 40% of the patient's RMT, 1500 pulses/day) *R4:* active rTMS over bilateral DLPFC (20 Hz, 30 pulses/train, 25 trains, 1.5-sec trains, 10-s intertrain interval, amplitude 40% of the patient's RMT, 1500 pulses/day) *S4:* sham rTMS over bilateral DLPFC	10 sessions (2 weeks) 20 sessions (4 weeks) 20 sessions (4 weeks)	ADAS-Cog	NPI, ADCS-ADL	Active rTMS showed similar improvements in cognitive function compared to sham treatment, which persisted up to 2 months post-treatment. This suggests a potential benefit of sham rTMS, possibly due to induced electric fields.
Qin et al. 2022	Randomize d, Sham-controlled	Patients with mild or mode-rate AD, >50 y o	a Butterfly focal coil (MCF-B65 coil)	17 (9 real, 8 sham)	*rTMS:* Left DLPFC and left lateral TL rTMS (10 Hz, 1000 pulses/day) + cognitive training for 4 weeks *Sham:* Sham stimulation at the same target + cognitive training	20 sessions (4 weeks)	ADAS-cog, rsfMRI (fALFF, FC)	ACE-III, ADL, NPI	rTMS combined with cognitive trai-ning increased fALFF in regions associated with cognition. Increa-sed fALFF in specific regions corre-lated with cognitive improvement.

Table 1. Continues

Study	Design	Participants	Type of the coil	Sample Size	Interventions	Duration	Primary Outcome	Secondary Outcome	Main Results
Rabey et al. 2013	Randomized, sham-controlled	Patients with AD, no information about the age	a 47–86 mm diameter figure of eight magnetic coil (the NeuroAD system)	15 (7 active, 8 sham)	*Active:* rTMS to six cortical regions (Broca, right DLPFC, left DLPFC, Wernicke, right pSAC, left pSAC) + cognitive training for 6 weeks (5 sessions/week) followed by 3 months of biweekly sessions. Parametres - Frequency 10 Hz. Amplitude 90 % of the patient's RMT for the first 3 regions and 110% for the last 3 regions. 2-sec trains and no informationabout intertrain interval, 20 trains (for 2 regions) and 25 for the 3rd, 1300-1500 pulses/day. *Sham:* Sham stimulation at the same target + cognitive training	30 sessions (6 weeks (intensive) + 3 months (maintenance))	ADAS-Cog	CGIC, NPI	rTMS combined with cognitive training improved ADAS-Cog and CGIC scores compared to sham, suggesting an effective therapy for AD.
Rutherford et al. 2015	Randomize, crossover design, sham-controlled at stage 1 and open-label at stage 2	Patients with probable AD (57-87 y o)	figure-of-eight coil	10 (5 active, 5 sham)	*Active:* Stage 1: №13 sessions (5 times per a week – 2 weeks + 3 times per a 2 next weeks).Frequency 20 Hz. Amplitude 90-100% of the patient's RMT. 2-sec trains and 5-sec IP. 40 pulses in train. PPS 2000. Stage 2: the same, but :№13 sessions (5 times per a week – 2 weeks, repeated every 3 months) *Sham:* Sham stimulation at the same target	Stage 1: 13 sessions (4 weeks) Stage 2: 10 sessions (2 weeks, repeated every 3 months)	MoCa, MMSE, ADAS-Cog	RMBC, spatial awareness, word-image association, associative memory	Changes in MOCA scores were statistically significant, with particularly stable results in the six patients who were in the early stages of the AD. Long-term trends observed in the second phase of the study also showed generally less deterioration than would be expected for their condition.
Sabbagh et al. 2020	Randomized, sham-controlled, multicenter	Patients with mild to moderate AD, 60-90 y o	figure-of-eight coil (The neuroAD Therapy System)	109 (59 active, 50 sham)	*Active:* rTMS to six cortical regions (left IFG, left STG; left and right DLPFC; left and right IPL. During each daily session, 3 of these 6 regions are targeted) + cognitive training. Parametres - Frequency 10 Hz. Amplitude 110 % of the patient's RMT, no informationabout trains lasting and intertrain interval, 20 trains, 1300 pulses/day. *Sham:* Sham stimulation at the same target	30 sessions (6 weeks)	ADAS-Cog, ADSC-CGI-C		Study showed significant improvement ADAS-Cog and ADSC-CGI-C in the active treatment group, but not in the sham group.
Traikapi et al. 2023	Concurrent multiple baseline, randomized	Patients with probable AD, no information about the age	a figure-of-eight coil (Magstim Super Rapid Plus Therapy System)	5 (4 completed)	*rTMS* targeted at precuneus bilaterally, 40 Hz. amplitude 90 % of the patient's RMT, 1-sec trains and 29-sec intertrain interval, 25 trains, 1000 pulses/day	10 sessions (2 weeks)	Word learning tasks (immediate recall, delayed recall, recognition)	ADAS-cog, Semantic association, Naming, Corsi block tasks, Trail Making Test A & B	Gamma TMS improved immediate word recall in 3 out of 4 patients. Significant improvement in attention in 2 patients. No effect on semantic or visual memory, or executive function. ADAS-cog showed improvement for all patients and persisted for 3 months post-treatment.
Padala et al. 2020	Randomized, sham-controlled	Patients with AD and apathy, >55 y.o.	A standart coil (The NeuroStar® TMS Therapy)	20 (9 rTMS, 11 sham)	*Active:* Left DLPFC rTMS (10 Hz, amplitude 120% of the patient's RMT, 4-sec trains and 26-sec intertrain interval, 75 trains, 3000 pulses/ day) *Sham:* Sham stimulation at the same target	20 sessions (4 weeks)	AES-C	MMSE, 3MS, EXIT-25, ZBS, IADL, CGI-S, CGI-I, TMT A & B	rTMS significantly improved apathy scores (AES-C) compared to sham treatment at 4 weeks. rTMS also significantly improved 3MS, IADL, CGI-S, and CGI-I scores. Effects were durable at 12 weeks.

Table 1. Continues

Study	Design	Participants	Type of the coil	Sample Size	Interventions	Duration	Primary Outcome	Secondary Outcome	Main Results
Vecchio et al. 2022	Randomized, sham-controlled	Patients with Alzheimer's Disease (AD), aged 60–85 years	Figure-eight coil (Magstim Company)	45 (30 active, 15 sham)	*Active rTMS:* 10 Hz rTMS over left dorsolateral prefrontal cortex (DLPFC) with 2-second trains, 20 trains, 25-second intertrain interval, 1200 pulses/day, amplitude 100% of the patient's resting motor threshold (RMT) *Sham:* Sham stimulation at the same target with the same parameters	20 sessions (4 weeks)	ADAS-Cog	MMSE, NPI, ADCS-ADL	Active rTMS group showed significant improvement in ADAS-Cog and MMSE scores compared to the sham group. There were no significant differences in NPI and ADCS-ADL scores between the groups.
Velioglu et al. 2021	No control group	Patients with AD, 56-84 y o	figure of eight air-cooled coil (PowerMag Research tool of the Mag&More company)	15	Left lateral parietal rTMS (20 Hz, amplitude 100% of the patient's RMT, 2-sec trains and 28-sec intertrain interval, 20-min session, 1640 pulses/day)	10 sessions (2 weeks)	Visual recognition memory, Clock Drawing Test	WMS (immediate recall, delayed recall, recognition), SBST, Boston Naming Test, Judgement of the Line Orientation Test, Benton Facial Recognition Test, Semantic Fluency, Stroop Test, GDS, NPI, fMRI, BDNF, Oxidant status	Left parietal-targeted rTMS significantly improved visual recognition memory and clock drawing scores, associated with increased BDNF levels and decreased oxidant status.
Wei et al. 2022	Randomized, sham-controlled	Patients with mild-to-moderate AD, 50-85 y o	70 mm air-cooled figure eight coil (Magstim Company)	58 (31 active, 27 sham)	*Active:* fMRI-guided left lateral parietal rTMS (10 Hz, amplitude 100-110% of the patient's RMT, 2-sec trains and 28-sec intertrain interval, 800 pulses/day) *Sham:* Sham stimulation at the same target	10 sessions (2 weeks)	MMSE, PVLT (immediate recall, short delay recall)	fMRI (dFC of DMN), ADL, CDR, PHQ-9, PVLT (long delay recall)	Active rTMS improved MMSE, PVLT-Immediate recall, and PVLT-Short Delay recall scores compared to sham. Active rTMS increased dFC magnitude of DMN, which correlated with MMSE improvement.
Wu et al. 2015	Randomized, sham-controlled	Patients with AD and BPSD, 60-80 y o	figure-of-eight coil (MagproR30)	54 (27 active, 27 sham)	*Active:* Low-dose risperidone + left DLPFC rTMS (20 Hz, amplitude 80% of the patient's RMT, no informationabout trains and intertrain interval, 1200 pulses/day) *Sham:* Low-dose risperidone + sham rTMS	20 sessions (4 weeks)	BEHAVE-AD	ADAS-Cog, TESS	rTMS combined with low-dose risperidone significantly improved both BEHAVE-AD and ADAS-Cog scores compared to risperidone alone.
Yao et al. 2022	Randomized, sham-controlled	Patients with AD, 60-80 y o	a figure-of-eight coil with a 70-mm diameter (Magventure Denmark)	27 (13 real, 14 sham)	*Real:* 5 Hz rTMS over bilateral cerebellum crus II in short bursts of 20 pulses. Amplitude 90 % of the patient's RMT, no informationabout trains and intertrain interval, 2000 pulses/day . *Sham:* Sham stimulation at the same target	20 sessions (4 weeks)	N/A (primary outcome focused on functional connectivity)	MMSE, MoCA, CDR, ADAS-Cog, RAVLT, CDT, BNT, VFT, TMT A&B, SDMT, DST, HAMD, HAMA, PSQI, ADL, CSF biomarkers	Cerebellum rTMS significantly enhanced functional connectivity between cerebellum nodes and DLPFC, medial frontal cortex, and cingulate cortex in the real group. This was associated with multi-domain cognitive improvements. Sham showed no effect.

Table 1. Continues

Study	Design	Participants	Type of the coil	Sample Size	Interventions	Duration	Primary Outcome	Secondary Outcome	Main Results
Zhang et al. 2019	Randomized, sham-controlled	Patients with mild or moderate AD, 60-77 y o	MCF-B65 Butterfly coil, outer diameter, 75 mm (Magventure stimulator, Denmark and Localite TMS navigator, Germany)	30 (15 real, 15 sham)	*Real:* 10 Hz rTMS over left DLPFC and left LTL, amplitude 100 % of the patient's RMT, 5-sec trains and 25-sec intertrain interval, 10-min session, 20 trains, 1000 pulses/day. *Sham:* Sham stimulation at the same target	20 sessions (4 weeks)	ADAS-Cog	MMSE, ACE-III, NPI, ADL, 1H-MRS (NAA/Cr, Cho/Cr, mI/Cr)	rTMS combined with cognitive training significantly improved cognitive function and behavior in the real group compared to sham. rTMS increased NAA/Cr ratio in the left DLPFC and was negatively correlated with changes in ADAS-Cog.
Zhang et al. 2022	Randomized, sham-controlled	Patients with moderate-to-severe AD, 60–90 y o	A Magstim Super Rapid (Magstim Company Ltd.) with an air-cooled figure-eight coil	37 (18 real, 19 sham)	*Real:* 10 Hz rTMS over left DLPFC (Amplitude 100% of the patient's RMT. 4-sec trains and 16-sec intertrain interval, 20 min sessions, 2400 pulses/day) + cognitive training *Sham:* Sham stimulation at the same target + cognitive training	60 sessions (3 months)	SIB	MMSE, MoCA, NPI, CIBIC-Plus, ADL, resting-state fMRI (FC-MVPA)	rTMS significantly improved cognitive performance on SIB, reduced psychiatric symptoms on NPI, and improved CIBIC-Plus scores. Resting-state multivariate FC in the (para)hippocampal region and frontal and occipital clusters were identified as potential neuroimaging markers for predicting individual differences in treatment outcomes.

Note: aMT: Active motor threshold, AD: Alzheimer's Disease, ADAS-Cog: Alzheimer's Disease Assessment Scale - Cognitive Subscale, ADCS-ADL: Alzheimer's Disease Cooperative Study - Activities of Daily Living, AES-C: Apathy Evaluation Scale - Clinical Version, ALFF: Amplitude of Low-Frequency Fluctuations, aMCI: Amnestic Mild Cognitive Impairment, BDNF: Brain-derived neurotrophic factor, BEHAVE-AD: Behavioral Pathology in Alzheimer's Disease Scale, BNT: Boston Naming Test, BPSD: Behavioral and Psychological Symptoms of Dementia, CANTAB: Cambridge Neuropsychological Test Automated Battery, CDR-SB: Clinical Dementia Rating - Sum of Boxes, CGIC: Clinical Global Impression of Change, CGI-I: Clinical Global Impression - Improvement, Cho/Cr: Choline/Creatine Ratio, CIBIC: Clinician's Interview-based Impression of Change Plus Caregiver Input, CSP: Cortical Silent Period, dFC: Dynamic Functional Connectivity, DLPFC: Dorsolateral Prefrontal Cortex, DMN: Default Mode Network, DST: Digit Span Test, FAB: Frontal Assessment Battery, FC: Functional Connectivity, fALFF: Fractional Amplitude of Low-Frequency Fluctuations, fMRI: Functional Magnetic Resonance Imaging, GDS: Geriatric Depression Scale, HAMD: Hamilton Depression Rating Scale, HC: Healthy Control, HAMA: Hamilton Anxiety Rating Scale, IADL: Instrumental Activities of Daily Living, ICF: Intracortical Facilitation, IFG: Inferior frontal gyrus, IPL: Inferior parietal lobule, LICI: Long-Interval Intracortical Inhibition, LM: Logical Memory, LTL: Left Temporal Lobe, MMSE: Mini-Mental State Examination, MoCA: Montreal Cognitive Assessment, MEP: Motor Evoked Potential, NPI: Neuropsychiatric Inventory, PVLT: Philadelphia Verbal Learning Test, rMT: Resting Motor Threshold, rsfMRI: Resting-State Functional Magnetic Resonance Imaging, rTMS: Repetitive Transcranial Magnetic Stimulation, SDMT: Symbol Digit Modalities Test, SICI: Short-Interval Intracortical Inhibition, STG: Superior temporal gyrus, TESS: Treatment Emergent Symptoms Scale, TMS: Transcranial Magnetic Stimulation, TMT: Trail Making Test, VFT: Visual Fluency Test, WMS: Wechsler Memory Scale

Meta-analysis

The meta-analysis revealed a significant overall positive effect of the intervention (SMD = 0.580, 95% CI [0.268, 0.892], p<0.001), indicating a moderate improvement in cognitive function. This effect was consistent across different cognitive assessment scales, as evidenced by the forest plot (Figure 2). However, there was substantial heterogeneity among the studies (I^2=59.0%, 95% CI [19.8%, 85.5%]), suggesting considerable variability in the true effects across different studies. The test for residual heterogeneity was significant (Q=30.585, df=13, p=0.004), further supporting this observation.

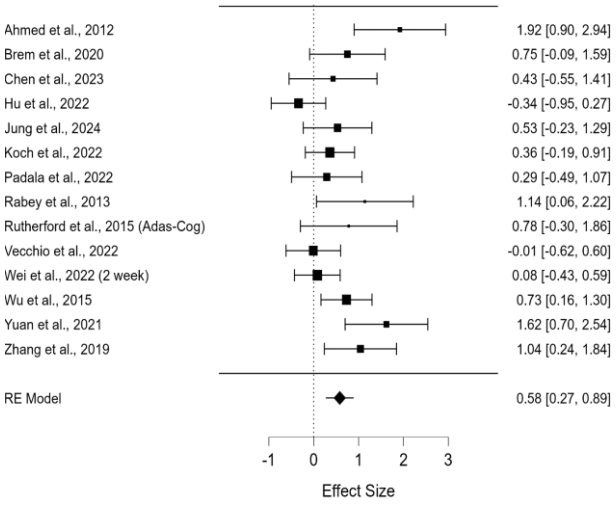

Figure 2. Forest Plot of Effect Sizes for Transcranial Magnetic Stimulation (TMS) in Alzheimer's Disease

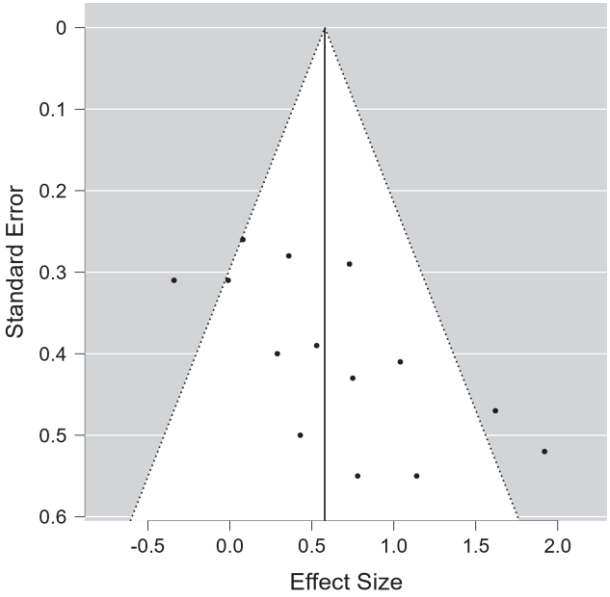

Figure 3. Funnel Plot of Publication Bias in Studies of Transcranial Magnetic Stimulation for Alzheimer's Disease

The funnel plot (Figure 3) and Egger's test for funnel plot asymmetry (z=3.134, p=0.002) indicated potential publication bias. The trim-and-fill analysis (Figure 4) suggested that the overall treatment effect might be somewhat overestimated due to the possible absence of studies with smaller or negative effects. To assess the robustness of the findings, we conducted a fail-safe N analysis. Rosenthal's fail-safe analysis (N=147) suggested that 147 studies with null results would need to be added to the analysis to render the overall effect non-significant, indicating a relatively robust finding.

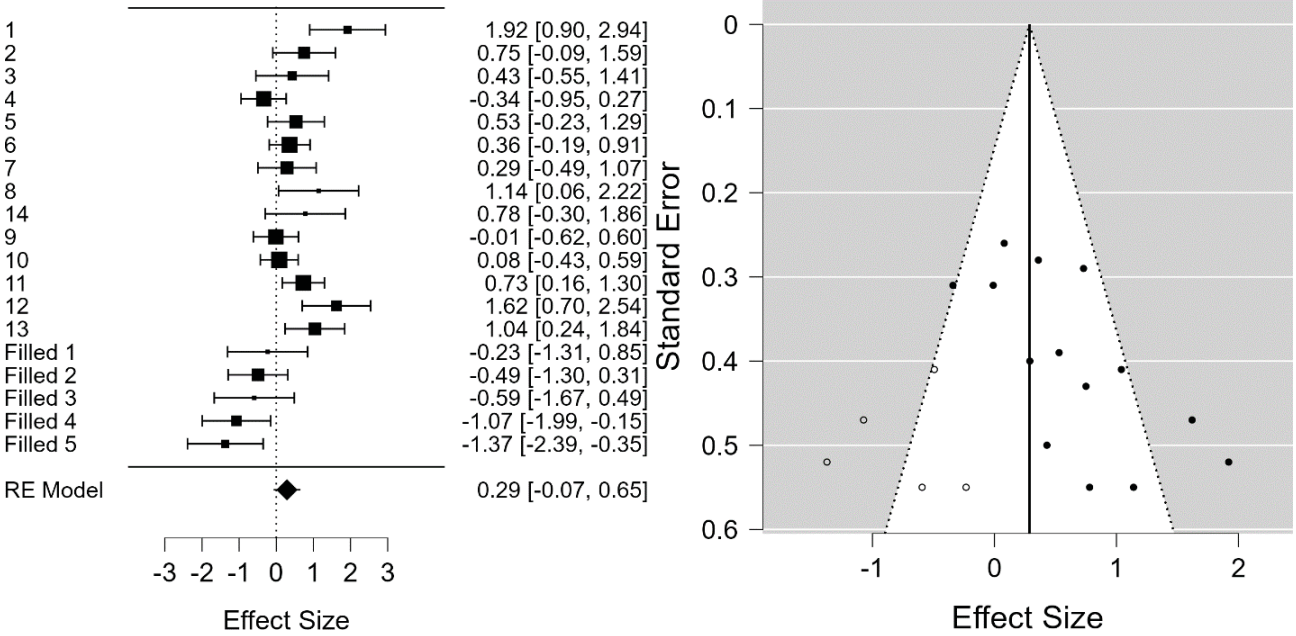

Figure 4. Forest Plot (left) and Funnel Plot (right) of Trim and Fill Analysis for Transcranial Magnetic Stimulation in Alzheimer's Disease studies

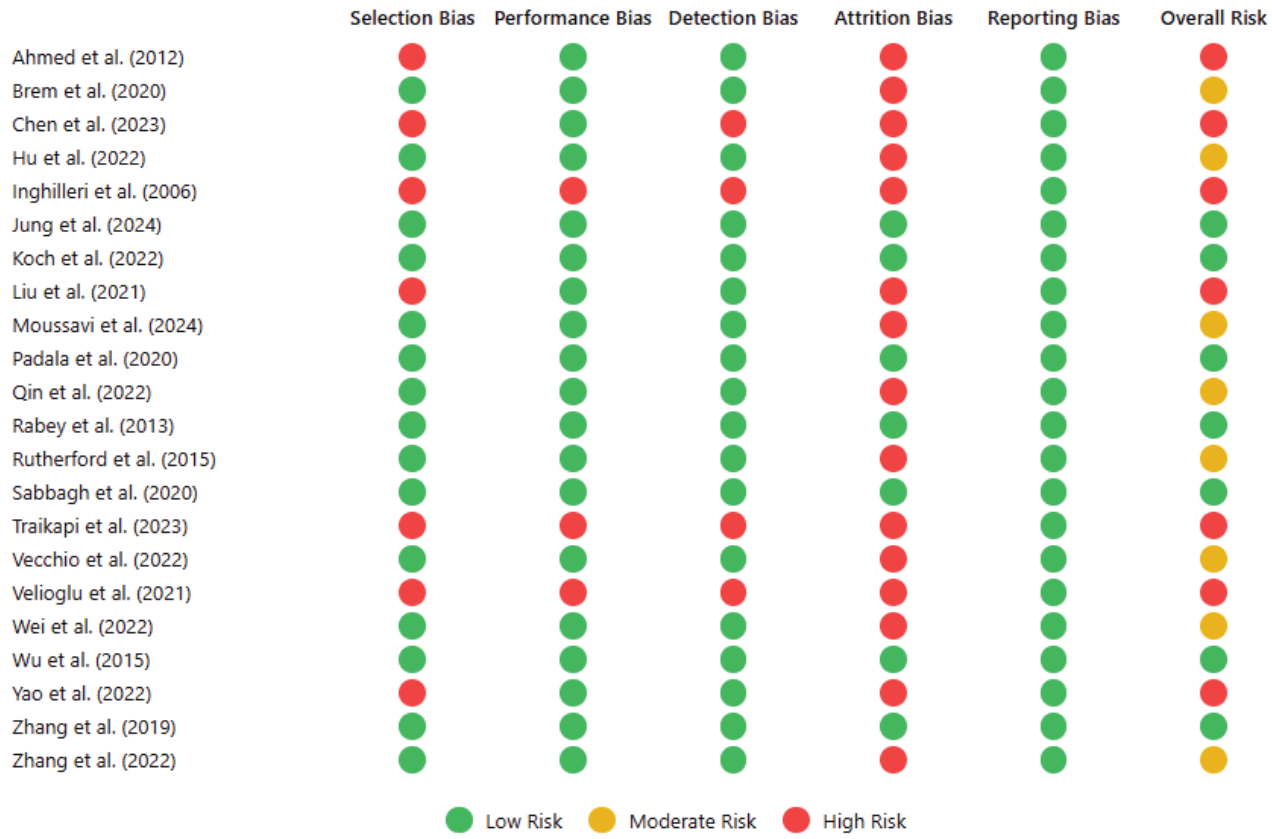

Figure 5. Risk of Bias Assessment for Studies on Transcranial Magnetic Stimulation in Alzheimer's Disease

A comprehensive overview of the risk of bias assessment for all included studies is presented in Figure 5. Attrition bias was the most prevalent issue, affecting 63.6% of the studies. In contrast, reporting bias was well-controlled across all studies. Selection bias was present in 27.3% of studies, while performance and detection biases were less common, occurring in 13.6% and 18.2% of studies, respectively. Despite these individual domain risks, the majority of studies (68.2%) were assessed as having a low overall risk of bias. This result suggests that, while certain methodological challenges persist, particularly regarding the need for better participant retention, the overall quality of the included studies provides a reasonably reliable basis for the meta-analysis results.

DISCUSSION

Our meta-analysis revealed a significant positive effect of TMS on cognitive function in AD patients, with a moderate effect size. This finding is in line with previous meta-analytical results (Chen et al. 2023, Miller et al. 2023, Wei et al. 2023), thus lending further support for the potential of TMS as a therapeutic intervention for enhancing cognitive function in AD patients. However, the finding of substantial heterogeneity among studies, together with the the potential publication bias indicated by our funnel plot analysis, call for due caution in making this interpretation.

The high heterogeneity in study outcomes likely reflects the diversity of TMS protocols, patient characteristics, and outcome measures used across studies. Despite this caveat, the fail-safe N analysis indicated robustness of our findings, suggesting that numerous null studies be required to negate the observed effect.

High-frequency rTMS emerged as the most commonly used and most effective modality, with the majority of such studies reporting significant improvements in cognitive scores. The DLPFC and lateral parietal cortex/angular gyrus were the most frequently targeted brain areas, with consistently positive outcomes. This meta-analysis result may constitute an evidence base for future treatment guidelines for targeted rTMS. Nevertheless, isolated findings for other rTMS protocols and target regions require replication, before the selection of optimal parameters.

The several findings that baseline connectivity patterns or TMS-induced plasticity could predict treatment response suggest a potential for personalized treatment procedures (Inghilleri et al. 2006, Rabey et al. 2013). This avenue of research merits further exploration, as it could lead to more effective and appropriately targeted interventions.

The potential of rTMS to improve cognitive function in AD patients, in the short term and potentially over extended periods (Rabey et al. 2013, Sabbagh et al. 2020), raises an intriguing hypothesis about the role of cognitive activity in modulating AD pathogenesis. In this scenario, withdrawal from mental activity and social engagement could be significant factors in the progression of AD, potentially creating a vicious cycle where diminished cognitive activity exacerbates neurodegeneration, which in turn further reduces intellectual engagement. We hypothesize that rTMS may serve in some sense as a surrogate for normal cognitive acitivity, thus breaking the reinforcing cycle of AD progression, though we need further elaboration of this theory.

Several lines of evidence support the hypothesis that intellectual activity plays a crucial role in AD mechanisms and progression. Intellectual demand, as well as educational attainment, may be protective against dementia (Wajman & Bertolucci 2010), and dual language use maintains cognitive function among the elderly (i.e., Downer et al. 2024) in relation to the extent of cognitive reserve. Indeed, non-instrumental behavioral cognitive stimulation therapy has shown promise in improving cognitive function and enhancing the quality of life for AD patients. These interventions target cognitive stimulation and neural network enhancement, addressing the changes in brain function and connectivity associated with cognitive decline in AD (Behfar, 2023). Similarly, motor-cognitive interventions have demonstrated effectiveness in improving cognitive function in older adults with mild cognitive impairment, a condition often preceding AD (Tao 2023).

Anhedonia (in mild forms and at earlier stages of the disorder) or apathy (mostly in severe forms) are common symptoms of AD, which inherently decrease cognitive functioning and are associated with a steadily accelerating cognitive decline in affected patients (Dolphin et al. 2023, Teixeira et al. 2021). A habitual reduction in motor, social, and intellectual mental activities comprise a gestalt of declining volition and disengagement, further restricting the ability of patients to acquire behavioral techniques which might enhance their intellectual engagement in daily life activities. According to this interpretation, behavioral cognitive activation techniques rely on active participation of a patient, but the anhedonia-apathy spectrum of interrelated symptoms presents a significant barrier for adherence to an efficacy of cognitive behavioral therapy for AD patients.

In this context, rTMS emerges as a promising intervention to improve cognitive functioning in AD-patients. Unlike behavioral techniques, rTMS does not require active participation, thereby bypassing the restrictions imposed by anhedonia-apathy spectrum of interrelated symptoms. By directly activating or reingaging neuronal networks, rTMS might stabilize cognitive functions, perhaps evening restoring particular memory deficits in AD-individuals (Clark et al. 2023, Parrotta, 2023, Kesserwani, 2021, Koch et al. 2022). Conjecturally, rTMS may help to circumvent the therapeutic limitations arising from the anhedonia-apathy spectrum of interrelated AD symptoms.

CONCLUSIONS

Results of our meta-analysis and systematic review emphasize the following key findings:

- High-frequency rTMS was moderate efficacy in improving cognitive functioning of AD-patients, with several studies emphasizing the DLPFC as a first-line target for rTMS. However, other studies suggest other brain areas (angular gyrus, precuneus, lateral parietal cortex, medial septal nucleus, and cerebellum Crus II) might also yield beneficial results to enhance overall cognitive functioning in AD-patients;
- The benefits of rTMS stimulation treatment may bear some relation to circumvention of the anhedonia-apathy spectrum of interrelated AD symptoms, which may call for continuous assessments and monitoring in AD-patients;
- Enhancement of functional neural connectivity across brain regions related to basic cognitive processes may explain the efficacy of rTMS treatment in terms of baseline connectivity patterns and/or the induction of neuroplasticity. This raises the possibility that add-on motor-cognitive exercises may act synergistically with rTMS in stabilizing or restoring brain network activity of AD-patients.

Limitations

The present findings of a significant positive effect of rTMS in AD patients suffer from relatively high heterogeneity and potential publication bias. The variability in treatment effects across various studies underscores the necessity for additional research to understand better the factors influencing these differences in efficacy of rTMS efficacy in targeting cognition in AD.

A major limitation in the current body of research lies in the prevalence of small sample sizes and high risk of bias. This highlights the need for larger, well-designed trials to validate and extend these findings. Future research should aim for larger sample sizes, more rigorous methodologies, and longer follow-up periods to assess better the persistence of treatment effects. However, the current state of knowledge is

encouraging for the use of rTMS as a valuable component in a multifaceted approach to managing cognitive decline in aging populations. Moreover, limited evidence emerging from this meta-analysis suggests that rTMS and motor-cognitive or social rehabilitation may work synergistically in reengaging cognitive function in AD.

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Contribution of individual authors:

Oxana Chigareva, Daria Smirnova & Timur Syunyakov elaborated the primary idea and hypothesis.

Oxana Chigareva, Arseny Gayduk & Timur Syunyakov were responsible for literature data collection, systematization, and analysis, and writing the first draft of the manuscript.

Oxana Chigareva & Timur Syunyakov performed the qualitative and quantitative data analysis.

Paul Cumming, Daria Smirnova & Timur Syunyakov provided the key data interpretation.

Darya Astafeva, Kseniya Bikbaeva, Mikhail Sheifer & Daria Smirnova managed the formalization of meta-analysis procedures.

Karina Berezhnaya, Arseny Gayduk, Inara Khairedinova, Alexander Zakharov, Alexander Sack, Theodoros Koutsoumistros, Paul Cumming & Suman Sinha contributed to manuscript editing and provided additional insights and feedback.

All authors reviewed and approved the final manuscript for submission.

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