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REVIEW

Efficacy and safety of transcranial magnetic stimulation on cognition in mild cognitive impairment, Alzheimer's disease, Alzheimer's disease-related dementias, and other cognitive disorders: a systematic review and meta-analysis

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ABSTRACT

Objective: We aim to analyze the efficacy and safety of TMS on cognition in mild cognitive impairment (MCI), Alzheimer's disease (AD), AD-related dementias, and nondementia conditions with comorbid cognitive impairment.

Design: Systematic review, Meta-Analysis

Setting: We searched MEDLINE, Embase, Cochrane database, APA PsycINFO, Web of Science, and Scopus from January 1, 2000, to February 9, 2023.

Participants and interventions: RCTs, open-label, and case series studies reporting cognitive outcomes following TMS intervention were included.

Measurement: Cognitive and safety outcomes were measured. Cochrane Risk of Bias for RCTs and MINORS (Methodological Index for Non-Randomized Studies) criteria were used to evaluate study quality. This study was registered with PROSPERO (CRD42022326423).

Results: The systematic review included 143 studies ($n = 5{,}800$ participants) worldwide, encompassing 94 RCTs, 43 open-label prospective, 3 open-label retrospective, and 3 case series. The meta-analysis included 25 RCTs in MCI and AD. Collectively, these studies provide evidence of improved global and specific cognitive measures with TMS across diagnostic groups. Only 2 studies (among 143) reported 4 adverse events of seizures: 3 were deemed TMS unrelated and another resolved with coil repositioning. Meta-analysis showed large effect sizes on global cognition (Mini-Mental State Examination (SMD = 0.80 [0.26, 1.33], $p = 0.003$), Montreal Cognitive Assessment (SMD = 0.85 [0.26, 1.44], $p = 0.005$), Alzheimer's Disease Assessment Scale–Cognitive Subscale (SMD = −0.96 [−1.32, −0.60], $p < 0.001$)) in MCI and AD, although with significant heterogeneity.

Conclusion: The reviewed studies provide favorable evidence of improved cognition with TMS across all groups with cognitive impairment. TMS was safe and well tolerated with infrequent serious adverse events.

Key words: cognition, dementia, meta-analysis, MCI, mild cognitive impairment, systematic review, TMS, transcranial magnetic stimulation

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Introduction

Dementia is a global challenge due to its profound negative psychosocial impact on individuals with dementia, their caregivers, and society at large. More than 55 million people live with dementia worldwide, and prevalence is expected to increase to 78 million by end of 2030 (Gauthier *et al.*, 2021). Mild cognitive impairment (MCI) has a prevalence of 12% to 18% in people who are 60 years and older (Gaugler *et al.*, 2021). Individuals with MCI have a higher risk of developing dementia, with dementia progression rates at 10% to 15% in the clinical setting and 8% to 18% per year in the community (Petersen *et al.*, 2018). Currently, medications approved by the US Food and Drug Administration (FDA) for Alzheimer's disease (AD) only temporarily treat cognitive and behavioral symptoms, although the latest approved drugs aducanumab and lecanemab may delay disease progression (Esang and Gupta 2021; van Dyck *et al.*, 2022). Nonpharmacologic interventions such as risk reduction, cognitive training, psychosocial therapies, and nutraceuticals require further studies (Arvanitakis *et al.*, 2019). More research is needed on novel therapies to improve cognitive impairments or delay progression in MCI or dementia.

Previously published clinical trials and systematic reviews with meta-analyses on the efficacy and safety of transcranial magnetic stimulation (TMS) are limited to focused groups as MCI, dementia due to AD, and AD-related dementias (Birba *et al.*, 2017; Cheng *et al.*, 2018; Dong *et al.*, 2018; Nardone *et al.*, 2014). These investigations suggest that TMS holds promise for enhancing cognitive functions. Much of the extant literature is confounded by methodological inconsistency despite such encouraging findings. For instance, treatment protocols vary considerably between investigations, with location, intensity, and frequency of magnetic stimulation differing across clinical trials. Additionally, outcome variables vary between studies, with some focusing on global cognition, while others measuring specific functions. Consequently, it is difficult to delineate clear and coherent conclusions from these disparate investigations, and a thorough systematic review may clarify matters.

To address these challenges, we conducted a systematic review to examine the efficacy and safety of TMS on cognitive functions in dementia and MCI and in populations with cognitive impairment not due to neurodegenerative disorders. In addition, we conducted a meta-analysis to assess the efficacy of randomized clinical trials (RCTs) of TMS compared to sham stimulation in MCI and AD populations.

Methods

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Moher *et al.*, 2009) and registered with PROSPERO (CRD42022326423).

Search strategy and selection criteria

We conducted a comprehensive search of several databases from January 1, 2000, to May 26, 2021, limited to the English language and excluding animal studies. The search was updated on February 9, 2023. Databases searched were Ovid MEDLINE, Ovid Embase, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews (2005+), Ovid APA PsycINFO, and Scopus via Elsevier. The search strategy was designed and conducted by a medical librarian (L.C.H.) with investigators input. Controlled vocabulary supplemented with keywords was used to search for studies describing TMS in AD and related disorders. The actual strategy listing all search terms used and how they are combined is available in Supplemental Table 1.

Included studies met the following criteria: (1) study population with cognitive impairment or dementia regardless of underlying cause, or healthy older adults (HOAs); (2) TMS as an intervention; (3) cognitive functions as outcomes; (4) study design: controlled or uncontrolled studies, including RCTs, open-label trials, case-control studies, or case series; and (5) English language. Studies on HOAs were included if TMS was used as an intervention to improve cognition. Single case studies, preclinical studies, abstracts only, and clinical trial registries without results were excluded.

Four reviewers (M.I.L., S.R.P., R.K., and L.C.H.) worked independently in pairs to identify and screen titles and abstracts using a standardized protocol. Subsequently, the full texts were reviewed separately by two reviewers (S.R.P., R.K.) Excluded articles and reasons for exclusion were logged (Supplemental Table 2). Disagreements were resolved through consensus. If there were multiple studies from the same cohort, only the study with a larger sample size was included.

Data collection and quality assessment

Data were extracted by two reviewers for each article (S.R.P. and R.K.) and discrepancies adjudicated by a third reviewer (M.I.L.). To check for reliability, 10% of the data extracted was randomly selected and verified for accuracy by three other reviewers (P.E.C., S.K., B.N.L.). Information extracted

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includes authors, year, country, study design (RCT, open-label, case series), study population (diagnosis), sample size, demographic characteristics of study participants, inclusion and exclusion criteria, TMS protocols and treatment parameters, cognitive outcome measures, adverse events, and study funding.

Studies were divided into six diagnostic groups – (1) dementia due to AD, (2) MCI and dementia due to AD (studies that included patients with AD and MCI), (3) MCI, (4) dementia due to non-AD, (5) other nondementia conditions with comorbid cognitive impairment, and (6) HOAs (including subjective cognitive decline). Studies that included more than one type of study population are each represented only once in our data set. Studies with combined patient population of MCI and dementia due to AD were grouped as "MCI and dementia due to AD." The group of "other nondementia conditions with comorbid cognitive impairment" included psychiatric disorders such as schizophrenia, depression, bipolar disorder, and other brain disorders.

Two reviewers (S.R.P. and R.K.) independently assessed the quality of RCTs using the Cochrane risk of bias tool (Schünemann *et al.*, 2019) and the Methodological Index for Non-Randomized Studies (MINORS) criteria (Slim *et al.*, 2003) for nonrandomized studies.

Meta-analysis

Given heterogeneity in study designs, repetitive TMS (rTMS) protocols, and cognitive outcome measures, including all of the studies in meta-analysis was not feasible. We therefore only analyzed RCTs with common global cognitive outcomes (Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog)) in MCI and AD compared to sham stimulation. In instances of studies with multiple treatment groups, each treatment group was treated as an individual study. Change from baseline means and SDs was calculated for studies which only provided pre- and post-treatment means and SDs following standard formulas (Supplemental Table 3) (Higgins, 2011).

Overall heterogeneity was assessed using the Cochrane Q test and I^2 statistic, and two-tailed P values reported (Cooper *et al.*, 2009). Cochrane Q test P values of <0.1 and $I^2 > 50\%$ were deemed thresholds of study heterogeneity. Fixed-effect models were fit when study heterogeneity was absent, and random-effect models were fit when study heterogeneity was observed (Riley *et al.*, 2011). Data analyses were performed in R version 4.2.2 (RStudio Team 2021, Boston, Massachusetts).

Results

Search results

A total of 1,199 abstracts were screened, of which 327 articles were selected for full-text review eligibility, and 143 studies met inclusion criteria for systematic review. Twenty-five studies met inclusion criteria for meta-analysis as shown in the PRISMA flow diagram (Figure 1). Inter-reviewer agreement during both phases of study selection was excellent (>95%).

Characteristics of included studies: diagnostic groups and study design

A composite sample size of 5,800 participants emerged from the 143 included studies (Table 1) worldwide, which comprised of 94 RCTs, 43 open-label prospective, 3 open-label retrospective, and 3 case series. Diagnostic groups included non-dementia conditions with comorbid cognitive impairment (2,337 [40.3%]), dementia due to AD (1,827 [31.5%]), MCI and dementia due to AD (271 [4.7%]), dementia due to non-AD (720 [12.4%]), MCI (522 [9%]), and HOA (123 [2.1%]). Sex was reported in only 133 studies, of which 2 studies included only men, and there were 2,439 (45.6%) women. Mean ages ranged from 60 to 74 years for MCI, dementia due to AD, and non-AD; 38 to 47 years for nondementia conditions with comorbid cognitive impairment; and a mean age of 63.4 years for HOA.

Characteristics of included studies: Efficacy, safety, and TMS protocols

Table 2 outlines author, publication year, country, study design, study population, sample size, TMS protocols, cognitive outcomes, and adverse events. Studies are listed by diagnosis and study type: dementia due to AD ($n = 56$), combined MCI and dementia due to AD ($n = 6$), MCI ($n = 16$), dementia due to non-AD ($n = 26$), nondementia conditions with comorbid cognitive impairment ($n = 34$), and HOA ($n = 5$). Detailed inclusion and exclusion criteria, mean ages, and financial support for the studies are listed in Supplemental Table 4. More than half the included studies reported were from China ($n = 48$), Italy ($n = 16$), and USA ($n = 13$) with 25 other countries reporting 1 to 6 studies each (Supplemental Table 5) representing different population types and global work.

TMS efficacy across diagnostic groups

The studies in each diagnostic group are further classified by the study design type and report the number of patients and mean age (Table 1). The

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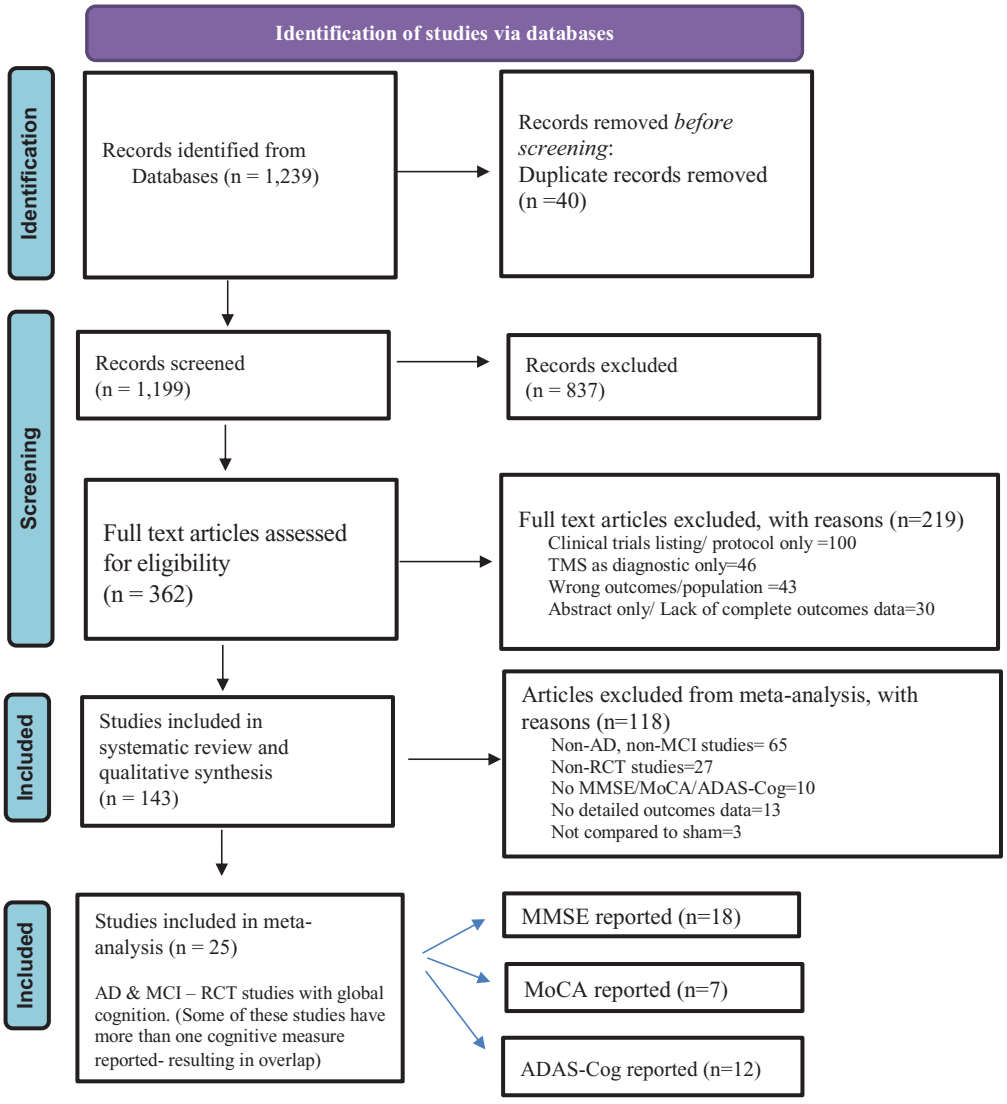

AD indicates Alzheimer disease; ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive Subscale; MCI, mild cognitive impairment; MMSE, Mini-Mental Status Examination; MoCA, Montreal Cognitive Assessment; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; RCT, randomized clinical trial; TMS, transcranial magnetic stimulation.

Figure 1. PRISMA flow diagram.

TMS protocol parameters are reported in Supplemental Figure 1. High-frequency (HF) stimulation is defined as 5 Hz or greater, while all stimulation frequencies less than 5 Hz is labeled as low frequency (LF).

Dementia due to AD

Among all AD studies, the most used cognitive outcomes were measures of global cognition such as the MMSE ($n = 30$), ADAS-Cog ($n = 26$), and MoCA ($n = 15$). Thirty-four of the 37 RCT studies compared TMS to sham stimulation, among which 31 (91%) showed significant improvement in cognitive measures. Three other studies (8%) reported the following: no overall efficacy (Saitoh *et al.*, 2022), no statistically significant improvement (Vecchio *et al.*, 2021), and low improvement rates in ADAS-Cog scores noted in only 13 of 27 patients with AD (Lithgow *et al.*, 2021). Among AD open-label studies, 18 of 19 studies (95%) showed improvement in global cognition (MMSE, MoCA, ADAS-Cog) and other specific cognitive functions measured (memory, learning, naming, executive function). Teti Mayer *et al.*, noted no impact on MMSE, but improved semantic and visual memory (Teti Mayer *et al.*, 2021). Overall, a majority of AD studies report improvement in different cognitive measures with TMS.

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Table 1. Characteristics of 143 studies in the systematic review by diagnostic groups ($N = 5,800$)[a]

DIAGNOSIS	STUDY DESIGN (N)	SAMPLE SIZE	FEMALE (%)[a]	MEAN AGE[a] (Y)
Dementia due to AD ($n = 1,827$)	RCT (37)	1,492	815 (55)[b]	72[c]
	OLP (19)	335	147 (53.3)[d]	71.2[c]
MCI and dementia due to AD ($n = 271$)	RCT (2)	60	25 (41.7)	73.7
	OLP (3)	158	87 (55)	62.3
	Case Series (1)	53	NR	74
MCI ($n = 522$)	RCT (12)	335	166 (49.6)	66.2
	OLP (4)	187	124 (66.3)	67.8
Dementia due to non-AD ($n = 720$)	RCT (20)	652	226 (34.7)	62.2
	OLP (5)	66	38 (57.6)	59.7
	Case Series (1)	2	0 (0)	70.5
Nondementia conditions with comorbid cognitive impairment ($n = 2,337$)	RCT (20)	1,069	241 (26.1)[d]	43.7[c]
	OLP (10)	939	302 (54.3)[b]	47.0[c]
	OLR (3)	306	188 (61.4)	46.6
	Case Series (1)	23	13 (57.0)	38.2
Healthy older adults ($n = 123$)	RCT (3)	85	47 (68.1)[b]	60.4
	OLP (2)	38	20 (52.6)	70.0

Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment; NR, not reported; OLP, open-label prospective; OLR, open-label retrospective; RCT, randomized clinical trial.
[a]Studies not reporting mean age or sex were excluded from the analysis.
[b]One study did not report sex.
[c]One study did not report mean age.
[d]Three studies did not report sex.

MCI and dementia due to AD

Two of the six studies were RCTs. Five of the six studies (83%) reported improved memory, executive function, and global cognition with TMS. One study analyzing the TMS impact on AD progression, using continuous theta burst stimulation (TBS) and intermittent TBS (iTBS), found that AD progression was faster in patients with cerebrospinal fluid–positive AD (positive CSF biomarkers and presence of dementia) or prodromal AD (positive CSF biomarker and absence of dementia) than MCI (negative CSF biomarker and absence of dementia) patients, as measured by MMSE over 36 months (Di Lorenzo *et al.*, 2020).

Mild cognitive impairment

There were 16 MCI studies, comprised of 12 RCTs and 4 open-label prospective studies. Diagnoses included MCI ($n = 12$), vascular MCI ($n = 3$), and MCI-Parkinson disease (PD) ($n = 1$). Of the 12 RCTs, 11 studies (92%) reported improved cognitive outcomes, while 1 study (Sedlackova *et al.*, 2008) in vascular MCI participants reported no change. All open-label studies reported improvement in MMSE and recognition memory with TMS.

Dementia due to non-AD

Diagnoses for dementia due to non-AD included stroke ($n = 10$), frontotemporal dementia ($n = 7$) (including primary progressive aphasia and progressive nonfluent aphasia), PD ($n = 6$), multiple sclerosis ($n = 1$), Huntington disease ($n = 1$), and corticobasal degeneration ($n = 1$). Five of nine RCTs in stroke patients used LF (1 Hz) stimulation. HF stimulation was used in four studies, which included two iTBS protocols (Chu *et al.*, 2022; Tsai *et al.*, 2020). All nine RCT studies in stroke patients showed improvement in cognitive function. Among PD studies, all studies demonstrated cognitive improvement with TMS except for 1 study that only applied a single iTBS session to the L-DLPFC (Hill *et al.*, 2020). In progressive nonfluent aphasia, LF stimulation (1 Hz) on the right Broca's area showed significant improvement in cognition compared to HF stimulation (10 Hz) (Hu *et al.*, 2018). One study in Huntington disease did not show significant cognitive improvement with a single session, M1 motor area stimulation utilizing 200 pulses (Groiss *et al.*, 2012). Overall, a majority of non-AD studies (24 out of 26 studies) demonstrate that TMS has a positive impact on cognitive functions.

Nondementia conditions with comorbid cognitive impairment

Of the 20 RCTs, conditions with comorbid cognitive impairment included psychiatric (schizophrenia [$n = 9$], major depressive disorder [MDD] [$n = 9$], generalized anxiety disorder [$n = 1$]), and nonpsychiatric (traumatic brain injury, $n = 1$) diagnoses. In schizophrenia, there was no benefit in cognitive function when 10 Hz was applied to the L-DLPFC (Guse *et al.*, 2013; Hasan *et al.*, 2016;

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Table 2. Summary of rTMS studies across diagnostic groups (N=143)

AUTHOR, YEAR, COUNTRY	DIAGNOSIS, SAMPLE SIZE (% FEMALE), STUDY SAMPLE: TMS (NO.), CONTROL (NO.)	TMS MACHINE COIL	SITE OF STIMULATION	FREQUENCY INTENSITY	MOTOR THRESHOLD, %	TREATMENT DURATION	COGNITIVE OUTCOMES	ADVERSE EVENTS
AD RCT (n = 37)								
Ahmed *et al.*, 2012, Egypt	AD 45 (64%) 15/15, 15	Magstim Figure 8. Coil	DLPFC – Bilateral Sham: Coil angled away from head	HF: 20 Hz LF: 1 Hz 2,000 pulses	90	5 sessions	Improved MMSE, Independent activities of daily living, Geriatric depression score with HF-rTMS compared to LF and sham.	None
Alcala-Lozano *et al.*, 2018, Mexico	AD 19 (58%) 10, 9	MagPro Figure 8. Coil	Protocol 1: DLPFC – Left Protocol 2: 6 sites – right and left DLPFC, Broca's area, Wernicke's area, right and left PSAC	Protocol 1: 5 Hz 1,500 pulses Protocol 2: 5 Hz 1,500 pulses	100	15 sessions	Improved ADAS-Cog ($p < 0.001$) and MMSE ($p < 0.001$) with both protocols. Effects maintained at 4 weeks.	Headache
Budak *et al.*, 2023, Turkey	AD 27 (63%) 10, 17	PowerMag Figure 8. Coil	DLPFC – Bilateral	Group 1: 20 Hz 3,000 pulses Group 2: Aerobic exercise Group 3: Control	NR	10 sessions	Improved executive function, behavior, quality of life with rTMS group; balance, mobility with aerobic exercise; visual memory, behavior in controls ($p < 0.05$).	NR
Brem *et al.*, 2020, USA	AD 47 (57%) 16, 31 (10/8/13)	Magstim Figure 8. Coil NeuroAD	6 sites – right and left DLPFC, Broca's area, Wernicke's area, right and left inferior parietal lobe	10 Hz NR	120	30 sessions	Improved ADAS-Cog with combined TMS and cognitive training compared to sham. Further ADAS-Cog improvement 4–6 weeks after rTMS.	None

Table 2. Continued

AUTHOR, YEAR, COUNTRY	DIAGNOSIS, SAMPLE SIZE (% FEMALE), STUDY SAMPLE: TMS (NO.), CONTROL (NO.)	TMS MACHINE COIL	SITE OF STIMULATION	FREQUENCY INTENSITY	MOTOR THRESHOLD, %	TREATMENT DURATION	COGNITIVE OUTCOMES	ADVERSE EVENTS
Cheng *et al.*, 2021, USA	AD 26 (4%) 13, 13	Mag Venture Pro R30 Stimulator Cool-B65 AP Coil	DLPFC – Left	10 Hz 4,000 stimuli	120	20 sessions	Improved auditory-verbal memory at end of treatment and 4-month follow-up with rTMS compared to sham.	Seizures ($n = 3$, 6–12 mos. after TMS), headache
Cotelli *et al.*, 2011, Italy	AD - Probable 10 (NR) 5, 5	Magstim Figure 8. Coil	DLPFC – Left	20 Hz 2,000 pulses	100	20 sessions	Improved auditory sentence comprehension – Battery for the Analysis of Aphasic Deficits subtest with rTMS compared to placebo. Effect seen at 12 weeks. No difference in MMSE.	None
Hu *et al.*, 2022, China	AD 84 (55%) 21 rTMS, tDCS, 21 rTMS, 21 tDCS, 21 sham	Tianjin Figure 8. Coil	Angular gyrus – Bilateral Sham: Sham coil	40 Hz 3,000 pulses	90	12 sessions	Improved NPI, MMSE at weeks 4 and 12 with rTMS and tDCS compared to rTMS or tDCS alone and sham.	Headache, scalp burns, scalp numbness
Jia *et al.*, 2021, China	AD 69 (70%) 35, 34	Magstim Figure 8. Coil	Lateral parietal cortex - Left Sham: Coil rotated 45° away	10 Hz 800 pulses	100–110	10 sessions	Improved MMSE ($p = 0.002$), time orientation ($p = 0.026$), recall ($p = 0.026$), Philadelphia Verbal Learning Test ($p = 0.039$) with rTMS compared to sham.	Scalp discomfort, fatigue
Jiang *et al.*, 2021, China	AD 32 (50%) 16, 16	MagPro R30 Figure 8. Coil	DLPFC – Bilateral	HF: 10 Hz LF: 2 Hz NR	80	40 sessions	Improved MMSE, Behavioral Pathology in Alzheimer's Disease Rating Scale, ADL at 2 and 4 weeks with HF-rTMS compared to LF rTMS.	Headache, rash

Table 2. Continued

AUTHOR, YEAR, COUNTRY	DIAGNOSIS, SAMPLE SIZE (% FEMALE), STUDY SAMPLE: TMS (NO.), CONTROL (NO.)	TMS MACHINE COIL	SITE OF STIMULATION	FREQUENCY INTENSITY	MOTOR THRESHOLD, %	TREATMENT DURATION	COGNITIVE OUTCOMES	ADVERSE EVENTS
Koch *et al.*, 2018, Italy	AD - Prodromal 14 (50%) 14, 0	Magstim Figure 8. Coil	Precuneus Sham: Sham Coil	20 Hz 1,600 pulses	100	10 sessions	Improved Rey Auditory Verbal Learning Test delayed recall ($p = 0.029$) with rTMS compared to sham. No effects on executive function, attention, global cognition.	NR
Koch *et al.*, 2022, Italy	AD 50 (52%) 25, 25	Magstim Figure 8. Coil	Precuneus	20 Hz 1,600 stimuli	NR	32 sessions	Improved ADAS-Cog ($p = 0.035$), MMSE ($p = 0.041$) with rTMS compared to sham-SB stable with rTMS, worse with sham.	Headache, scalp discomfort, neck pain, fatigue
Kumar *et al.*, 2020, Canada	AD 32 (50%) 16, 16	Magstim Figure 8. Coil	DLPFC – Left	0.1 Hz, 180 pulses (Repetitive Paired Associative Stimulation); NR for TMS	NR	10 sessions	No differences between active and control Repetitive Paired Associative Stimulation on DLPFC plasticity or working memory.	Sleep problems, transient blurry vision, transient muscle weakness
Leblhuber *et al.*, 2022, Austria	AD 28 (57%) 18, 10	TAMAS® apparatus	Frontopolar cortex	68 Hz 2,400 stimuli	NR	10 sessions	Improved MMSE ($p < 0.01$), repeat address phrase test ($p < 0.01$) with rTMS compared to sham.	None
Lee *et al.*, 2016, Korea	AD - Probable 26 (58%) 18, 8	NeuroAD Figure 8. Coil	6 sites - right and left DLPFC, Broca's area, Wernicke's area, right and left PSAC Sham: Same sounds, no magnetic stimulation	10 Hz 1,200 pulses	90 – Broca's, DLPFC 110 - Wernicke's, PSAC	30 sessions	Improved ADAS-Cog, MMSE, Clinical Global Impression of Change with rTMS compared to sham.	Headache, fatigue

Table 2. Continued

AUTHOR, YEAR, COUNTRY	DIAGNOSIS, SAMPLE SIZE (% FEMALE), STUDY SAMPLE: TMS (NO.), CONTROL (NO.)	TMS MACHINE COIL	SITE OF STIMULATION	FREQUENCY INTENSITY	MOTOR THRESHOLD, %	TREATMENT DURATION	COGNITIVE OUTCOMES	ADVERSE EVENTS
Lee *et al.*, 2020, Korea	AD 44 (36%) 30, 14	NeuroAD Figure 8. Coil Cognitive training	6 sites - right and left DLPFC, Broca's area, Wernicke's area, right and left PSAC Sham: Same sounds, no magnetic stimulation	10 Hz 1,200 pulses	90 – Broca's, DLPFC 110 – Wernicke's, PSAC	30 sessions	Improved ADAS-Cog, MMSE, Clinical Dementia Rating with rTMS-cognitive training compared to sham.	Pain sensation, fatigue
Leocani *et al.*, 2020, Italy	AD - Probable 28 (46%) 16, 12	Magstim Figure 8. Coil	Bilateral frontal-parietal-temporal regions Sham: Electric field <30% of active coil, similar acoustic artifact, and scalp sensations	10 Hz 840 pulses	120	16 sessions	Improved ADAS-Cog ($p < 0.04$) but not MMSE with rTMS compared to sham. Trend not evident after 2 months.	Headache
X. Li *et al.*, 2021, China	AD 75 (41%) 37, 38	Magstim Figure 8. Coil	DLPFC – Left Sham: pseudo-stimulus coil	20 Hz 2,000 pulses	100	30 sessions	Improved MMSE ($p < 0.001$), ADAS-Cog ($p < 0.001$) with rTMS compared to sham.	NR
Lithgow *et al.*, 2021, Canada	AD 43 (47%) 13/14, 16	NR	DLPFC – Bilateral	Protocol 1: 20 Hz, 1,500 pulses Protocol 2: 20 Hz, 4,000 pulses	NR	Protocol 1: 10 or 20 sessions Protocol 2: 13 sessions	In 27 patients with AD with significant cerebrovascular symptomatology, 13 improved with rTMS, but 14 did not improve. AD severity affects rTMS efficacy.	NR

Table 2. Continued

AUTHOR, YEAR, COUNTRY	DIAGNOSIS, SAMPLE SIZE (% FEMALE), STUDY SAMPLE: TMS (NO.), CONTROL (NO.)	TMS MACHINE COIL	SITE OF STIMULATION	FREQUENCY INTENSITY	MOTOR THRESHOLD, %	TREATMENT DURATION	COGNITIVE OUTCOMES	ADVERSE EVENTS
C. Liu *et al.*, 2021, China	AD - Probable 37 (57%) 25, 12	Magstim Figure 8. Coil	Angular gyrus, dorsal – Bilateral Sham: Same sounds, no magnetic stimulation	40 Hz 2,400 pulses	40 maximal output intensity	12 sessions	Improved MMSE, MoCA, ADAS-Cog (all $p < 0.01$) with rTMS compared to sham. Effects seen at 8 weeks.	None
Lu *et al.*, 2022, China	AD/Non-AD 55 (69%) 27, 28	Magstim Figure 8. Coil	DLPFC – Left Sham: Sham Coil	10 Hz 1,500 pulses	120	15 sessions	Higher score change in Hong Kong version MoCA from baseline to T1 with rTMS compared to sham. Improvements of global cognitive function and mood persisted for 8 weeks in both groups.	None
Padala *et al.*, 2020, USA	AD 20 (10%) 9, 11	NeuroStar XPLOR Figure 8. Coil	DLPFC – Left Sham: Same sounds, no magnetic stimulation	10 Hz 3,000 pulses	120	20 sessions	Improved modified MMSE ($p = 0.012$) with rTMS group compared to sham at 4 weeks. Effects seen at 12 weeks.	Headache, pain, discomfort, eye twitching
Qin *et al.*, 2022, China	AD 17 (71%) 9, 8	Mag Venture Figure 8. Coil	DLPFC – Left, then lateral temporal lobe – Left Sham: Coil rotated 90° away	10 Hz 1,000 pulses	100	20 sessions	Improved ADAS-Cog ($p = 0.028$), NPI ($p = 0.011$) with rTMS compared to sham. Improved ACE-III, ADL for both rTMS and sham ($p < 0.05$).	NR
Rabey *et al.*, 2013, Israel	AD 15 (33%) 7, 8	NeuroAD Figure 8 coil	6 sites - right and left DLPFC, Broca's area, Wernicke's area, right and left PSAC	10 Hz 1,300 pulses	90 – Broca's, DLPFC 110 – Wernicke's, PSAC	30 sessions, followed by 12 sessions (weekly)	Improved ADAS-Cog with rTMS compared to placebo. Effect seen at 4.5 months.	None

Table 2. Continued

AUTHOR, YEAR, COUNTRY	DIAGNOSIS, SAMPLE SIZE (% FEMALE), STUDY SAMPLE: TMS (NO.), CONTROL (NO.)	TMS MACHINE COIL	SITE OF STIMULATION	FREQUENCY INTENSITY	MOTOR THRESHOLD, %	TREATMENT DURATION	COGNITIVE OUTCOMES	ADVERSE EVENTS
Rutherford *et al.*, 2015, Canada	AD 11 (64%) 11	NR	DLPFC – Bilateral	20 Hz 2,000 pulses to each side/session	90–100	13 sessions	Improved MoCA, word image association with rTMS compared to sham. ADAS-Cog improved but not significant.	Headache
Sabbagh *et al.*, 2020, USA	AD 109 (54%) 59, 50	NeuroAD Figure 8 Coil	6 sites - right and left DLPFC, Broca's area, Wernicke's area, right and left PSAC Sham: Same sounds, no magnetic stimulation	10 Hz 1,300 pulses	110	30 sessions	Improved ADAS-Cog ($p <$ .05) with rTMS compared to sham; greater effect when baseline ADAS-Cog <30 (85% of study population).	Headache, scalp discomfort, neck pain, fatigue
Saitoh *et al.*, 2022, Japan	AD 42 (63%) 15/14, 13	TEN-P11 Figure 8. Coil	DLPFC – Bilateral Sham: Sham coil	10 Hz 1,200 pulses	90 120	8 sessions	No efficacy. Post hoc – improved MMSE (if ≥ 15) with rTMS 120% compared to sham; responders had improved ADAS-Japanese Cog ($p = 0.045$) with rTMS compared to sham. Effects not evident at 20 weeks.	Scalp tenderness
Tao *et al.*, 2022, China	AD 46 (54%) 23, 23	Yiruide	DLPFC – Left Sham: identical coil with no magnetic stimulation	20 Hz 1,760 pulses	100	30 sessions	Improved MoCA, MMSE, Modified Barthel Index, ADAS-Cog ($p < 0.05$) with rTMS compared to sham.	NR

Table 2. Continued

AUTHOR, YEAR, COUNTRY	DIAGNOSIS, SAMPLE SIZE (% FEMALE), STUDY SAMPLE: TMS (NO.), CONTROL (NO.)	TMS MACHINE COIL	SITE OF STIMULATION	FREQUENCY INTENSITY	MOTOR THRESHOLD, %	TREATMENT DURATION	COGNITIVE OUTCOMES	ADVERSE EVENTS
Turriziani *et al.*, 2019, Italy	AD 38 (63%) 38	Magstim Figure 8. Coil	Experiment 1: DLPFC – Right or Left, then cross-over to opposite side Experiment 2: DLPFC – Right vs sham	1 Hz 600 pulses	90	Experiment 1: 4 sessions Experiment 2: 10 sessions	Experiment 1: Improved memory with rTMS on the right but not left DLPFC. Experiment 2: Improved cognition with rTMS on right DLPFC compared to sham.	NR
Vecchio *et al.*, 2021, Italy	AD 63 (54%) 30, 17, 16	NeuroAD Figure 8. Coil Cognitive training	6 sites - right and left DLPFC, Broca's area, Wernicke's area, right and left PSAC	10 Hz 1,200 – 1,400 pulses	90 – Broca's, DLPFC 110 – Wernicke's, PSAC	42 sessions	Improved cognition with rTMS compared to cognitive training alone, though not statistically significant.	NR
Wei *et al.*, 2022, China	AD 86 (47%) 29, 27	Magstim Figure 8. Coil	Lateral parietal cortex – Left Sham: Coil rotated 45° away	10 Hz 800 pulses	100–110	10 sessions	Improved MMSE ($p = 0.004$), Philadelphia Verbal Learning Test ($p < 0.001$) with rTMS compared to sham. No improvement at 12 weeks.	Scalp pain, fatigue
Wu *et al.*, 2015, China	AD 52 (60%) 26, 26	MagPro R30 Figure 8. Coil	DLPFC – Left Sham: Coil turned 180°	20 Hz 1,200 pulses	80	20 sessions	Greater improvement on Behavioral Pathology in Alzheimer's Disease Rating Scale ($p < 0.001$), ADAS-Cog ($p < 0.001$) with rTMS compared to controls.	Headache, mild extrapyramidal reactions

Table 2. Continued

AUTHOR, YEAR, COUNTRY	DIAGNOSIS, SAMPLE SIZE (% FEMALE), STUDY SAMPLE: TMS (NO.), CONTROL (NO.)	TMS MACHINE COIL	SITE OF STIMULATION	FREQUENCY INTENSITY	MOTOR THRESHOLD, %	TREATMENT DURATION	COGNITIVE OUTCOMES	ADVERSE EVENTS
Wu *et al.*, 2022, China	AD 47 (55%) 24, 23	Magstim Figure 8. Coil	DLPFC – Left	50 Hz 1,800 pulses (Accelerated iTBS - 3/day, 15 minutes apart)	70	14 days	Improved MoCA ($p < 0.001$), MMSE ($p < 0.001$), associative memory ($p = 0.012$) with rTMS compared to sham. Similar findings observed at week 10.	Painful scalp sensation, eyelid twitching, tinnitus (in sham)
Yao *et al.*, 2022, China	AD 27 (48%) 15, 12	Mag Venture Figure 8. Coil MagPro X100 Figure 8 coil	Cerebellum - Bilateral	5 Hz 2,000 pulses	90	20 sessions	Higher MoCA, MMSE, ADAS-Cog ($p < 0.001$) with rTMS compared to sham at 4 and 12 weeks.	None
Zhang *et al.*, 2019, China	AD 28 (79%) 15, 13	Mag Venture Figure 8. Coil	DLPFC – Left, then Lateral temporal lobe – Left Sham: Front edge touching scalp at 90°	10 Hz 1,000 pulses	100	20 sessions	Improved ADAS-Cog, MMSE, ACE-III, NPI with rTMS compared to sham, immediately and at 4 weeks.	Anxiety, scalp tingling
S. Zhang *et al.*, 2022, China	AD 35 (40%) 19, 18	Magstim2 Figure 8. Coil	DLPFC – Left	10 Hz 2,400 pulses	100	60 sessions	Improved severe impairment battery ($p = 0.049$), NPI ($p < 0.001$), Clinician's Interview-Based Impression of Change Plus caregiver input ($p < 0.001$) with rTMS compared to sham. No effect on MoCA, MMSE, ADL.	None
Zhao *et al.*, 2017, China	AD 30 (57%) 17, 13	NR	Parietal P3/P4 Posterior Temporal T5/T6	20 Hz NR	NR	30 sessions	Improved ADAS-Cog, MMSE, AVLT with rTMS compared to sham. Increased seen at 6 weeks. Effect on memory and language superior on mild AD than moderate AD.	Headache, fatigue

Table 2. Continued

AUTHOR, YEAR, COUNTRY	DIAGNOSIS, SAMPLE SIZE (% FEMALE), STUDY SAMPLE: TMS (NO.), CONTROL (NO.)	TMS MACHINE COIL	SITE OF STIMULATION	FREQUENCY INTENSITY	MOTOR THRESHOLD, %	TREATMENT DURATION	COGNITIVE OUTCOMES	ADVERSE EVENTS
Zhou *et al.*, 2022, China	AD 65 (68%) 33, 32	YRD CCY NR	DLPFC – Bilateral Sham: Coil with special insulation	Left DLPFC: 10 Hz Right DLPFC: 1 Hz 1,500 pulses	120	20 sessions	Improved ADAS-Cog (4 weeks: $p = 0.048$, 8 weeks: $p = 0.038$) with rTMS compared to sham. Effect lasted 4 weeks.	Headache, scalp and skin discomfort, eye twitching
AD Open label (n = 19)								
Avirame *et al.*, 2016, Israel	AD 11 (45%) 11	Magstim H-Coil	PFC – Bilateral	10 Hz NR	100–120	20 sessions	Improved Mind streams, ACE with deep TMS though not significant. Improved ACE ($p = 0.001$) with deep TMS in more progressed stage patients (6).	Headache, fatigue
Bentwich *et al.*, 2011, Israel	AD - Probable 7 (14%) 7	Neuronix Figure 8. Coil	6 sites – right and left DLPFC, Broca's area, Wernicke's area, right and left PSAC	10 Hz 1,200 pulses	90 – Broca's, Wernicke's, DLPFC-Left 110 – DLPFC-Right, PSAC	54 sessions	Improved ADAS-Cog, Clinical Global Impression of Change, MMSE with rTMS. Effects seen at 6 weeks, but not 4.5 months.	None
Cotelli *et al.*, 2006, Italy	AD 15 (NR) 15	NR Figure 8. Coil	DLPFC – Left DLPFC – Right Sham: Vertex, coil positioned perpendicular to scalp	20 Hz 10 pulses/train	90	1 session	Improved action naming with rTMS compared to sham.	None
Cotelli *et al.*, 2008, Italy	AD - Probable 24 (NR) 12-mild /12-moderate to severe	NR Figure 8. Coil	DLPFC – Left DLPFC – Right Sham: Vertex	20 Hz NR	90	1 session	Improved action naming with rTMS in both mild and moderate to severe dementia compared to sham. Improved object naming with rTMS in moderate to severe dementia only.	None

Table 2. Continued

AUTHOR, YEAR, COUNTRY	DIAGNOSIS, SAMPLE SIZE (% FEMALE), STUDY SAMPLE: TMS (NO.), CONTROL (NO.)	TMS MACHINE COIL	SITE OF STIMULATION	FREQUENCY INTENSITY	MOTOR THRESHOLD, %	TREATMENT DURATION	COGNITIVE OUTCOMES	ADVERSE EVENTS
Devi *et al.*, 2014, USA	AD 12 (42%) 12	Magstim2 Figure 8. Coil	DLPFC – Bilateral	First 6: 10 Hz, 1,000 pulses Second 6: 15 Hz, 1,500 pulses	90	4 sessions	Improved Boston diagnostic aphasia examination verbal and non-verbal agility immediately and 4 weeks post-treatment ($p < 0.05$) with rTMS. Effects seen at 1 month. No change in MMSE, COWAT.	None
Gandelman-Marton *et al.*, 2017, Israel	AD 8 (13%) 8	Magstim Figure 8. Coil COG	6 sites - right and left DLPFC, Broca's area, Wernicke's area, right and left PSAC	10 Hz 1,200 pulses	90	54 sessions	MMSE improved after 30 sessions ($p = 0.049$) but decreased after 54 sessions. ADAS-Cog improved after 30 and 54 rTMS-COG sessions ($p = 0.015$). Long-term changes in electroencephalogram.	None
Golaszewski *et al.*, 2021, Italy	AD – Probable, HC 20 (50%) 10, 10	Magstim Figure 8. Coil	F3, F4, T3, T4, TP3, TP4, P3, P4	50 Hz 600 pulses	80	8 sessions	Clock drawing test improved with iTBS over right temporo-parietal and parietal regions; reduced with iTBS over left temporo-parietal and parietal regions.	NR
Guo *et al.*, 2021, China	AD, HC 34 (68%) 23, 11	MagPro Figure 8. Coil	DLPFC – Left	10 Hz 1,600 pulses	100	20 sessions	Improved MoCA with TMS in mild and moderate AD ($p = 0.01$).	None
Hanoglu *et al.*, 2022, Turkey	AD/PD 39 (46%) 18 AD, 8 PD, 13 HC	PowerMag Figure 8 Coil	AD: Lateral parietal cortex – Left PD: Pre-supplemental motor area – Left	AD: 20 Hz, 1,640 pulses PD: 5 Hz, 1,000 pulses	NR	10 sessions	AD: Improved clock drawing ($p = 0.031$), visual memory recognition ($p = 0.048$). PD: Improved Unified PD Rating Scale-III ($p < 0.05$).	NR

Table 2. Continued

AUTHOR, YEAR, COUNTRY	DIAGNOSIS, SAMPLE SIZE (% FEMALE), STUDY SAMPLE: TMS (NO.), CONTROL (NO.)	TMS MACHINE COIL	SITE OF STIMULATION	FREQUENCY INTENSITY	MOTOR THRESHOLD, %	TREATMENT DURATION	COGNITIVE OUTCOMES	ADVERSE EVENTS
Kayasandik *et al.*, 2022, Turkey	AD 14 (64%) 14	PowerMag Figure 8 Coil	Posterior parietal cortex – Left	20 Hz 1,640 pulses	100	10 sessions	Improved MMSE ($p < 0.05$) with rTMS.	NR
Mano 2022, Japan	AD 16 (75%) 16	MagPro X100 Figure 8 Coil	DLPFC – Bilateral	10 Hz 600 pulses	120	10 sessions	Improved MoCA-Japanese with rTMS. Effect not seen at 1 month.	Scalp pain, neck pain
Nguyen *et al.*, 2017, France	AD 10 (50%) 10	Neuronix Figure 8. Coil	Six sites – right and left DLPFC, Broca's area, Wernicke's area, right and left PSAC	10 Hz 1,300 pulses, additional 100 pulses daily over left or right DLPFC	100	25 sessions	Improved ADAS-Cog with rTMS, although returned to baseline at 6 months.	Fatigue
Rabey and Dobronevsky 2016, Israel	AD 30 (43%) 30	NeuroAD Figure 8 Coil	6 sites - right and left DLPFC, Broca's area, Wernicke's area, right and left PSAC	10 Hz 1,300 pulses	90 – Broca's, DLPFC 110 – Wernicke's, PSAC	42 sessions	Improved ADAS-Cog, MMSE (all $p < 0.001$) with rTMS-COG. Effects seen up to 1 year.	None
Suarez Moreno *et al.*, 2022, France	AD 30 (50%) 30	Neuro AD NR	Six sites - right and left DLPFC, right and left parietal cortex, left IFG, left superior temporal gyrus	10 Hz NR	NR	30 sessions	Improved ADAS-Cog ($p = 0.003$) with rTMS, but no change in MMSE. Both measures deteriorated at year 1.	None

Table 2. Continued

AUTHOR, YEAR, COUNTRY	DIAGNOSIS, SAMPLE SIZE (% FEMALE), STUDY SAMPLE: TMS (NO.), CONTROL (NO.)	TMS MACHINE COIL	SITE OF STIMULATION	FREQUENCY INTENSITY	MOTOR THRESHOLD, %	TREATMENT DURATION	COGNITIVE OUTCOMES	ADVERSE EVENTS
Teti Mayer *et al.*, 2021, France	AD 12 (75%) 12	Magstim2 Figure 8. Coil	DLPFC – Left	10 Hz 2,000 pulses	110	10 sessions	No impact on primary outcomes MMSE, Mattis dementia rating scale with rTMS. Improved semantic memory ($p = 0.01$) and visual recognition memory ($p = 0.04$).	None
Traikapi *et al.*, 2022, Cyprus	AD 5 (40%) 5	Magstim Figure 8. Coil	Precuneus – Bilateral (alternating side/day)	40 Hz 1,000 pulses	90	10 sessions	Improved ADAS-Cog with rTMS, effect seen at 3 months. 1 patient withdrew from study.	None
Velioglu *et al.*, 2021, Turkey	AD 15 (67%) 15	Brain Voyage Figure 8. Coil	Lateral parietal cortex - Left	20 Hz 1,640 pulses	100	2 weeks	Improved Weschler Memory Scale – Visual Reproduction Test Recognition ($p = 0.017$) with rTMS.	NR
Wu *et al.*, 2020, China	AD 13 (69%) 13	Magstim2 Figure 8 Coil	DLPFC - Left	50 Hz 1,800 pulses	70	14 sessions	Improved memory (free recall, $p = 0.008$; recognition $p < 0.001$) with iTBS.	None
Xiao *et al.*, 2022, China	AD 20 (NR) 20	Magstim2 Figure 8 Coil	DLPFC – Left	50 Hz 1,800 pulses	NR	14 sessions	Improved MoCA, MMSE, CAVLT-immediate and delay (all $p < 0.001$), CAVLT-recognition ($p = 0.004$), BNT ($p = 0.002$) with iTBS.	NR
AD and MCI (RCT & Non-RCT) (n = 6)								
Bagattini *et al.*, 2020, Italy	AD, MCI 50 (42%) 27, 23 (RCT)	DuoMAG XT-100 Figure 8. Coil Sham: 3cm wood between coil and scalp	DLPFC – Left	20 Hz 2,000 pulses	100	20 sessions	Improved face-name associative memory ($p < 0.001$) with rTMS and cognitive training compared to sham. No effect on MMSE.	None

Table 2. Continued

AUTHOR, YEAR, COUNTRY	DIAGNOSIS, SAMPLE SIZE (% FEMALE), STUDY SAMPLE: TMS (NO.), CONTROL (NO.)	TMS MACHINE COIL	SITE OF STIMULATION	FREQUENCY INTENSITY	MOTOR THRESHOLD, %	TREATMENT DURATION	COGNITIVE OUTCOMES	ADVERSE EVENTS
Eliasova *et al.*, 2014, Czech Republic	AD, aMCI 10 (40%) 10 – Crossover (RCT)	Magstim Figure 8. Coil	IFG & superior temporal gyrus - Right Control: Vertex	10 Hz 2,250 pulses	90	2 sessions	Improved Trail making test A ($p = 0.037$) and B ($p = 0.049$) with rTMS compared to control at vertex.	Scalp pain
Di Lorenzo *et al.*, 2020, Italy	ADD, PROAD, MCI, Healthy subjects 105 (50%) 28, 24, 21, 32	Magstim Figure 8. Coil	NR	cTBS, iTBS, Short Intracortical Inhibition, Short-latency Afferent Inhibition protocols	120	3 sessions	MMSE decreased for AD with manifest dementia (ADD), PROAD at 12 months; for MCI at 36 months. Progression in ADD, PROAD was faster than MCI.	None
Lv *et al.*, 2023, China	AD 31 (68%) 15/16	CCY-IV Figure 8. Coil	Angular gyrus – Left	20 Hz 1,600 pulses	100	20 sessions	Improved MMSE, MoCA, episodic memory, encoding/language function (all $p < 0.05$) with rTMS for both low- and high-connectivity groups compared to baseline.	NR
Tumasian and Devi 2021, USA	AD, aMCI 53 (NR) 48 AD, 5 aMCI (Case series)	Magstim Figure 8. Coil	Right and left DLPFC, Broca's area, right and left parietal	10–15 Hz 504–4,350 pulses	90	≥ 5 sessions over 12 months	Less decline in COWAT ($p = 0.02$), BNT ($p = 0.002$) with rTMS compared to controls.	Seizure, site discomfort, supraorbital nerve pain, hair loss, essential tremor worsening
Yang *et al.*, 2022, China	AD, MCI 6 AD, 16 MCI (59%) 16, 6	CCY-IV Figure 8. Coil	Angular gyrus - Left	20 Hz 1,600 pulses	100	20 sessions	After rTMS, improved MoCA-Beijing version ($p < 0.05$) in aMCI and AD; improved episodic memory, language ($p < 0.05$) in aMCI only.	NR

Table 2. Continued

AUTHOR, YEAR, COUNTRY	DIAGNOSIS, SAMPLE SIZE (% FEMALE), STUDY SAMPLE: TMS (NO.), CONTROL (NO.)	TMS MACHINE COIL	SITE OF STIMULATION	FREQUENCY INTENSITY	MOTOR THRESHOLD, %	TREATMENT DURATION	COGNITIVE OUTCOMES	ADVERSE EVENTS
MCI RCT (n = 12)								
Chen *et al.*, 2021, China	aMCI 12 (75%) 8, 4	Magstim Figure 8. Coil	Precuneus Sham: Coil angled away	10 HZ 1,000 stimuli	100	25 sessions	Improved episodic memory (AVLT) with rTMS ($p < 0.001$) compared to sham ($p > 0.05$).	None
Cui *et al.*, 2019, China	aMCI 21 (62%) 11 10	MagPro R30 Figure 8. Coil	DLPFC – Right Sham: coil 90° to skull	10 Hz 1,500 pulses	90	10 sessions	Improved AVLT with rTMS compared to sham: Immediate free recall ($p = 0.002$), 5 min delayed free recall ($p < 0.001$), 20 min delayed free recall ($p = 0.004$).	None
Drumond Marra *et al.*, 2015, Brazil	MCI 34 (65%) 15, 19	MagPro X100 Figure 8 Coil Sham coil: Placebo coil	DLPFC – Left	10 Hz 2,000 pulses	110	10 sessions	Improved Rivermead behavioral memory test (T0 × T1, $p = 0.042$; T0 × T2, $p = 0.029$), delayed logical memory (T0 × T1, $p = 0.033$; T0 × T2, $p = 0.002$) with rTMS compared to sham. Improvement sustained for 1 month.	Headache, scalp pain
Esmaeili *et al.*, 2020, Iran	MCI 16 (31%) 8, 8	Medtronic Figure 8. Coil	DLPFC – Left Sham: Same but wires disconnected	5 Hz 60 pulses	NR	16 sessions, crossover after 8 sessions	Improved MoCA with rTMS compared to baseline ($p = 0.01$) and to sham at 9 weeks ($p < 0.001$).	None
Esposito *et al.*, 2022, Italy	MCI 40 (53%) 27, 13 HC	Magstim2 Figure 8 Coil	DLPFC – Bilateral	10 Hz 2,000 pulses	80	20 sessions	Improved RBANS Form B: line orientation ($p = 0.014$), semantic fluency ($p = 0.026$) with rTMS compared to controls.	NR

Table 2. Continued

AUTHOR, YEAR, COUNTRY	DIAGNOSIS, SAMPLE SIZE (% FEMALE), STUDY SAMPLE: TMS (NO.), CONTROL (NO.)	TMS MACHINE COIL	SITE OF STIMULATION	FREQUENCY INTENSITY	MOTOR THRESHOLD, %	TREATMENT DURATION	COGNITIVE OUTCOMES	ADVERSE EVENTS
Gy *et al.*, 2021, Mexico	MCI 24 (58%) 12, 12	Mag Venture Pro R30 Figure 8. Coil	DLPFC – Left Sham: Small electrical pulses same frequency as active rTMS through electrodes connected to coil system	5 Hz 1,500 pulses	100	Phase 1: 30 sessions Washout 4 weeks, then crossover. Phase 2: 30 sessions	Improved MoCA with rTMS compared to sham. Effect size on MoCA larger in active rTMS phase.	Headache
He *et al.*, 2021, Taiwan	MCI-PD 35 (34%) 20, 15	Magstim Figure 8. Coil	DLPFC - Left	Standard iTBS protocol	100	10 sessions	Improved total RBANS and MoCA with iTBS ($p < 0.001$) immediately after and at 3 mos.	None
Padala *et al.*, 2018, USA	MCI 9 (11%) 4, 5	NeuroStar XPLOR Figure 8. Coil	DLPFC – Left	10 Hz 3,000 pulses	120	10 sessions Washout 4 weeks, then crossover. 10 sessions	Improved Modified Mini-Mental State exam (5.2, $p = 0.021$), MMSE (3.4, $p = 0.002$), Trail Making Test-A (– 4.6, $p = 0.041$), and Clinical Global Impression – Improvement (– 2.5, $p = 0.005$) with rTMS compared to the sham.	Neck discomfort, wrist pain, discomfort at treatment site, shock sensation at treatment site or eye, facial twitching, insomnia, dizziness
Pan *et al.*, 2020, China	Vascular Cognitive Impairment nondementia 106 (49%) 53, 53	CCYI Figure 8. Coil	Left frontal lobe – lateral area	10 Hz 3,000 pulses	100	20 sessions	Higher space and executive function, attention, delayed recall, and directional scores ($p < 0.05$) than control group.	Headache, nausea, facial muscle numbness, scalp numbness
Rektorova *et al.*, 2005, Czech Republic	MCI-Vascular 7 (29%) 7	Magstim Figure 8. Coil	Active: DLPFC – Left Control: Left Motor Cortex	10 Hz 450 pulses	Not reported	2 sessions	Improved Stroop interference with rTMS over left DLPFC compared to control. Digit Span Test improvement regardless of stimulation site.	NR

Table 2. Continued

AUTHOR, YEAR, COUNTRY	DIAGNOSIS, SAMPLE SIZE (% FEMALE), STUDY SAMPLE: TMS (NO.), CONTROL (NO.)	TMS MACHINE COIL	SITE OF STIMULATION	FREQUENCY INTENSITY	MOTOR THRESHOLD, %	TREATMENT DURATION	COGNITIVE OUTCOMES	ADVERSE EVENTS
Sedlackova *et al.*, 2008, Czech Republic	MCI-Vascular 7 (29%) 7	Magstim Figure 8. Coil	DLPFC – Left Left Motor Cortex	HF: 10 Hz, 450 pulses LF: 1 Hz, 1,800 pulses	100	HF: 1 session LF: 1 session	No positive or negative significant effect of one session of either HF or LF rTMS applied over left DLPFC or motor cortex.	None
Yuan *et al.*, 2021, China	aMCI 24 (54%) 12, 12	CCYIA Figure 8. Coil	DLPFC – Left Sham: Coil tilted 90° relative to the skull	10 Hz 400 pulses	80	20 sessions	Improved MoCA end of treatment and 1 month ($p < 0.05$) compared to sham.	Headache
MCI Open label (n = 4)								
Y-C Chen *et al.*, 2022, USA	MCI 9 (60%) 9, 0	MagPro X100 Figure 8. Coil	Superior lateral occipital cortex (6) Superior parietal lobule (2) Precuneus – left (1)	50 Hz 600 pulses iTBS, cTBS	70	6 sessions	Increased associative memory with iTBS compared to cTBS. Increased resting state functional connectivity with iTBS compared to sham.	NR
Trebbastoni *et al.*, 2016, Italy	aMCI, HC 55 (44%) 20, 20	Magstim Figure 8. Coil	M1 - dominant hemisphere	5 Hz NR	120	1 session	Mean yearly conversion rate to AD was 15% aMCI, 12.5% aMCIsd (single domain), 18.3% aMCImd (multi-domain). Alterations in synaptic plasticity and cortical excitability significantly correlated with the time of conversion to AD.	None
Turriziani *et al.*, 2012, Italy	MCI, HC 108 (74%) 8-MCI, 40/40/20	Magstim Figure 8. Coil	DLPFC - Left and/or Right	Inhibitory: 1 Hz, 600 pulses Excitatory: 50 Hz, 600 pulses	1 Hz: 90 50 Hz: 80	2 sessions	Inhibitory rTMS of right DLPFC enhanced recognition memory in MCI, HC. iTBS left DLPFC in HC had no effect on recognition memory.	NR

Table 2. Continued

AUTHOR, YEAR, COUNTRY	DIAGNOSIS, SAMPLE SIZE (% FEMALE), STUDY SAMPLE: TMS (NO.), CONTROL (NO.)	TMS MACHINE COIL	SITE OF STIMULATION	FREQUENCY INTENSITY	MOTOR THRESHOLD, %	TREATMENT DURATION	COGNITIVE OUTCOMES	ADVERSE EVENTS
X. Zhang *et al.*, 2022, China	MCI 30 (50%) 15, 15	MagPro X100 Figure 8. Coil	DLPFC – Left, then Precuneus	DLPFC – Left: 10 Hz, 1200 pulses Precuneus: 10 Hz, 800 pulses	120	20 sessions	Improved overall cognition (MoCA, $p < 0.001$), memory (CAVLT-immediate, $p < 0.01$; 5 min, $p < 0.05$; 20 min, $p < 0.01$), executive function (connected test A, $p < 0.05$; B $p < 0.01$; digital breadth backward, $p < 0.05$).	NR
Non-AD RCT (n = 20)								
Barwood *et al.*, 2013, Australia	CVA – Aphasia 12 (25%) 6, 6	Magstim Figure 8. Coil	Anterior portion of homologue to pars triangularis (Brodmann area 45) in Broca's area (right hemisphere)	1 Hz 1,200 pulses	90	10 sessions	Improved naming, expressive language, auditory comprehension with rTMS compared to placebo. Changes were observed up to 12 months poststimulation compared to placebo.	NR
T-C. Cheng *et al.*, 2021, Taiwan	PD 48 (33%) 13/16, 11	Magstim Figure 8. Coil	DLPFC – Left	50 Hz 600pulses Sham: <5% of magnetic output	90	10 sessions	Increased RBANS total ($p = 0.005$), immediate memory ($p = 0.016$), language ($p = 0.038$), delayed memory ($p = 0.018$); MoCA total ($p = 0.005$), language ($p = 0.02$), delayed recall ($p = 0.011$) in rTMS-Virtual Reality group compared to rTMS group. RBANS changes remained at 3 months.	Dull skull pain
Chu *et al.*,	PSCI	CCYI	DLPFC – Left	50 Hz	70	30 sessions	Improved Loewenstein Oc-	None

Table 2. Continued

AUTHOR, YEAR, COUNTRY	DIAGNOSIS, SAMPLE SIZE (% FEMALE), STUDY SAMPLE: TMS (NO.), CONTROL (NO.)	TMS MACHINE COIL	SITE OF STIMULATION	FREQUENCY INTENSITY	MOTOR THRESHOLD, %	TREATMENT DURATION	COGNITIVE OUTCOMES	ADVERSE EVENTS
2022, China	60 (25%) 21 iTBS/19 tDCS, 20 Cognitive training	Figure 8. Coil		600 pulses			cupational Therapy Cognitive Assessment with cognitive training combined with iTBS ($p = 0.003$) and tDCS ($p = 0.006$). Cognitive function improved in all three groups (including cognitive training alone) at 6 weeks.	
Groiss *et al.*, 2012, Germany	Huntington's Disease 8 (50%) 8, 0	Magstim Figure 8. Coil	M1 - Left	HF: 10 Hz LF: 1Hz Sham: 5Hz 200 pulses	90	1 session	No effect on Nine Hole Peg Test, Digit Span Test, Huntington's Disease ADL score. With 10 Hz, prolonged simple RT in contralateral hand but no effect on ipsilateral hand; shortened choice RT in ipsilateral hand.	NR
Hill *et al.*, 2020, Australia	PD 14 (29%) 14, 0	MagPro Figure 8. Coil	DLPFC – Left	50 Hz 600 pulses	80	1 session	No effect on executive function and working memory.	None
Hu *et al.*, 2018, China	PNFA 40 (40%) 10/10/10, 10	Magstim Figure 8. Coil	Mirror area within right hemispheric Broca's area Sham: Coil oriented vertically to skull	HF: 10 Hz LF: 1 Hz 600 pulses	80	10 sessions	Improved spontaneous speech, auditory comprehension, aphasia quotients with HF-rTMS immediately and 2 months post-treatment ($p < 0.05$).	Dizziness
Huang *et al.*, 2023, China	FTD-PPA 40 (53%) 20, 20	Magstim Figure 8. Coil	DLPFC – Left (right-handed) DLPFC – Right (left-handed)	10 Hz 1,000 pulses	120	20 sessions	Improved BNT, Western Aphasia Battery, language with rTMS compared to sham. Changes observed at 6-month follow-up.	NR

Table 2. Continued

AUTHOR, YEAR, COUNTRY	DIAGNOSIS, SAMPLE SIZE (% FEMALE), STUDY SAMPLE: TMS (NO.), CONTROL (NO.)	TMS MACHINE COIL	SITE OF STIMULATION	FREQUENCY INTENSITY	MOTOR THRESHOLD, %	TREATMENT DURATION	COGNITIVE OUTCOMES	ADVERSE EVENTS
Khedr *et al.*, 2020, Egypt	PD 33 (27%) 18, 15	Magstim Figure 8. Coil	M1 Sham: Coil rotated 90° away	20 Hz 2,000 pulses	90	10 sessions 5 booster sessions	Improved motor function with rTMS compared to sham, but only minor effect on MMSE and MoCA, and no effect on Clinical Dementia Rating and Memory Executive Screening.	Headache, insomnia
Ko *et al.*, 2014, Taiwan	CVA - Nonfluent aphasia 56 (27%) 33, 23	Magstim Figure 8. Coil	Contralesional pars triangularis	1Hz 600 pulses Sham: <5% of magnetic output	90	10 sessions	Improved overall Concise Chinese aphasia test ($p <$ .001) and subcategories (conversation, p = .032; description, p = .024; expression, p = .002); repetition, p = .023) with rTMS compared to sham. Effects sustained at 3 months.	None
Li *et al.*, 2020, China	PSCI 30 (47%) 15, 15	Magstim Figure 8. Coil	DLPFC – Left Sham: Coil perpendicular to skull	5 Hz 40 pulses	100	15 sessions	More significant improvements in cognition (MoCA, MMSE, $p < 0.05$) with rTMS compared to controls.	Headache, dizziness
H. Li *et al.*, 2021, China	CVA with Cognitive Impairment 65 (38%) 33, 32	M100 Ultimate Stimulator Figure 8 Coil	DLPFC – Contralateral F3, F4	1 Hz 1,000 pulses	90	20 sessions	Improved MoCA with rTMS ($p < 0.001$) compared to controls.	NR
Margolis *et al.*, 2019, Netherlands	FTD-PPA 8 (25%) 8, 0	Neurostar NR	DLPFC – Left or Right (randomized)	20 Hz 3,360 pulses	90	2 sessions (sham followed by either left or right DLPFC)	Improved action naming ($p = 0.036$) with left DLPFC compared to right. Improved global cognition (MoCA) with both left ($p = 0.029$) and right ($p = 0.015$) DLPFC.	Headache, fatigue, temporary decreased hearing, anxiety, trouble sleeping, temporary decrease in mental clarity

Table 2. Continued

AUTHOR, YEAR, COUNTRY	DIAGNOSIS, SAMPLE SIZE (% FEMALE), STUDY SAMPLE: TMS (NO.), CONTROL (NO.)	TMS MACHINE COIL	SITE OF STIMULATION	FREQUENCY INTENSITY	MOTOR THRESHOLD, %	TREATMENT DURATION	COGNITIVE OUTCOMES	ADVERSE EVENTS
Medina *et al.*, 2012, UK	Left Middle Cerebral Artery stroke - chronic nonfluent aphasia 10 (30%) 5, 5	Magstim Figure 8. Coil	IFG – Right Sham: Coil perpendicular to skull	1 Hz 1,200 pulses	90	10 sessions	Increased discourse productivity with rTMS compared to sham (use of closed-class words, $p = 0.036$), but not sentence productivity or grammatical accuracy.	None
Pytel *et al.*, 2021, Spain	FTD-PPA 27 (59%) 20, 7	Magstim Figure 8. Coil	Variable: IFG-Left, Superior frontal gyrus-Left, IFG-Right, DLPFC-Left, Anterior temporal lobe-Left, Right, Supplementary motor area, Anterior cingulate, Vertex	Excitatory: 20 Hz 1,500 pulses Inhibitory: 1 Hz 600 pulses	100	15 sessions	Improved spontaneous speech, other language tasks, patient and caregiver global impression of change, apathy, and depression with TMS compared to controls. Improved language, apathy, depression, but not global cognition with HF-rTMS with personalized targeting.	Headache
Srovnalova *et al.*, 2012, Czech Republic	PD 10 (40%) 10, 0	Magstim Figure 8. Coil	DLPFC – Left or Right (randomized)	25 Hz 600 pulses	80	4 sessions	Enhanced problem-solving ($p = 0.037$) with rTMS on DLPFC-Right. No effects seen with DLPFC-Left or sham.	Headache
Trung *et al.*, 2019, Canada	PD 28 (32%) 14, 14	Magstim Figure 8. Coil	DLPFC – Left	50 Hz 600 pulses	NR	6 sessions	Improved overall cognition ($p = 0.011$) and visuospatial domain ($p = 0.008$) with iTBS compared to sham. Effect seen at one month. Attention improved in both iTBS and sham.	NR

Table 2. Continued

AUTHOR, YEAR, COUNTRY	DIAGNOSIS, SAMPLE SIZE (% FEMALE), STUDY SAMPLE: TMS (NO.), CONTROL (NO.)	TMS MACHINE COIL	SITE OF STIMULATION	FREQUENCY INTENSITY	MOTOR THRESHOLD, %	TREATMENT DURATION	COGNITIVE OUTCOMES	ADVERSE EVENTS
Tsai *et al.*, 2020, Taiwan	PSCI 41 (20%) 15/11, 15	Magstim Figure 8. Coil	DLPFC – Left	50 Hz 5 Hz 600 pulses Sham: <5% of magnetic output	80	10 sessions	Improved global cognition, attention, memory function with both 5 Hz and 50 Hz rTMS compared to baseline. (5 Hz: increased total RBANS ($p = 0.003$), delayed memory ($p = 0.007$), attention ($p = 0.005$); iTBS: increased total RBANS ($p = 0.001$), immediate memory ($p = 0.006$), language ($p = 0.005$), delayed memory (p= 0.008)).	None
Wei *et al.*, 2021, China	PD 60 (45%) 30, 30	Yingchi Figure 8. Coil	DLPFC – Left Sham: Coil held at inverted orientation	5 Hz 1,200 pulses	110	20 sessions	Improved WCST ($p = 0.002$), Stroop interference effect ($p < 0.001$) with rTMS compared to sham.	NR
Yin *et al.*, 2020, China	PSCI 34 (12%) 16, 18	MagPro Figure 8. Coil	DLPFC – Left	10 Hz 2,000 pulses	80	20 sessions	Improved MoCA, ADLs with rTMS compared to control ($p < 0.001$). MoCA increased after 2 and 4 weeks for rTMS group ($p = 0.03$).	NR
Yingli *et al.*, 2022, China	PSCI 36 (31%) 18, 18	Magstim Figure 8. Coil	DLPFC – unaffected side Sham: Coil perpendicular to skull	1 Hz 20 pulses	80	40 sessions	Improved Loewenstein Occupational Therapy Cognitive Assessment with rTMS than control ($p < 0.05$).	None
Non-AD Open label and Case series (n = 6)								
Antczak *et al.*, 2018, Poland	FTD 11 (64%) 11 (OLP)	Magstim Figure 8. Coil	DLPFC – Bilateral	10 Hz 3,000 pulses	90	10 sessions	Improved MoCA ($p = 0.036$), Letter cancelation test ($p = 0.021$), Stroop test with rTMS.	Headache, scalp pain

Table 2. Continued

AUTHOR, YEAR, COUNTRY	DIAGNOSIS, SAMPLE SIZE (% FEMALE), STUDY SAMPLE: TMS (NO.), CONTROL (NO.)	TMS MACHINE COIL	SITE OF STIMULATION	FREQUENCY INTENSITY	MOTOR THRESHOLD, %	TREATMENT DURATION	COGNITIVE OUTCOMES	ADVERSE EVENTS
Cha *et al.*, 2022, South Korea	PSCI 10 (20%) 10 (OLP)	ALTMS R Figure 8. Coil	DLPFC – Left or Right (same side of lesion)	20 Hz 2,000 pulses	100	10 sessions	Improved MoCA, MMSE ($p < 0.05$), Intelligence Quotient Wechsler Adult Intelligence Scale, AVLT, Complex Figure copy Test with rTMS. Improvements sustained at 3 months.	None
Cotelli *et al.*, 2012, Italy	PNFA, Semantic Dementia 14 (64%) 10, 4 (OLP)	NR Figure 8. Coil	DLPFC – Left or Right Left DLPFC Right DLPFC Sham: Vertex	20 Hz NR	90	1 session	Enhanced action naming with left ($p = 0.036$) and right ($p = 0.027$) DLPFC compared to vertex in PNFA. No effects on semantic dementia.	NR
Eydi-Baygi *et al.*, 2022, Iran	Multiple Sclerosis 5 (80%) 5 (OLP)	NR	DLPFC – Left	10 Hz 3000 pulses	110	10 sessions (Start after 3 mindfulness sessions)	Improved information processing and working memory with rTMS combined with mindfulness.	NR
Shehata *et al.*, 2015, Egypt	Corticobasal Degeneration 26 (62%) 26 (OLP)	NR Figure 8. Coil	Motor cortex – contralateral to affected side	1 Hz NR	90	35 sessions	No deterioration in ACE-revised scores over time (84.5–baseline, 83.33–3 months, 81.25–6 months, 80.33–12 months, 78.67–18 months).	NR
Neri *et al.*, 2021, USA	FTD-PPA 2 (0%) 2 (Case series)	NR Figure 8. Coil	Between pars angularis and pars triangularis of IFG-Left	10 Hz 2,000 pulses	100	10 sessions	Improvements with rTMS maintained at follow-up. Patient 1: BNT, sentence reading/repetition, oral description of images, phonemic/semantic fluency. Patient 2: Word repetition, verb naming, grammar understanding, phonemic/semantic fluency.	NR

Table 2. Continued

AUTHOR, YEAR, COUNTRY	DIAGNOSIS, SAMPLE SIZE (% FEMALE), STUDY SAMPLE: TMS (NO.), CONTROL (NO.)	TMS MACHINE COIL	SITE OF STIMULATION	FREQUENCY INTENSITY	MOTOR THRESHOLD, %	TREATMENT DURATION	COGNITIVE OUTCOMES	ADVERSE EVENTS
Nondementia RCT (n = 20)								
Buchholtz *et al.*, 2020, Denmark	MDD 34 (74%) 17, 17	MagPro R30 Figure 8. Coil	Right prefrontal rTMS (ECT-rTMS vs ECT-placebo)	1 Hz 2,000 pulses	110	ECT-rTMS: ECT avg. 9 sessions; rTMS avg. 6 sessions (on non-ECT days)	Less impaired cognition in ECT-rTMS compared to ECT-placebo. High dropout rate.	Headache, discomfort, confusion
Cheng *et al.*, 2016, Taiwan	MDD 60 (NR) 15/15/15, 15	Magstim2 Figure 8 Coil Sham: Coil turned 90°	A: DLPFC – Right B: DLPFC – Left	50 Hz – A: cTBS 1,800 pulses; B: iTBS 1,800 pulses; C: cTBS + iTBS, 1,800 pulses; D: sham	80	10 sessions	Improved executive function (WCST) in B group, but not in other groups.	NR
Du *et al.*, 2022, China	Schizophrenia 47 (51%) 25, 22	MagPro R30 Figure 8. Coil	DLPFC - Left	10 Hz 1,500 pulses	110	20 sessions	Higher pattern recognition memory with rTMS compared to sham at week 8 ($p < 0.001$), but not week 4.	NR
Guan *et al.*, 2020, China	Schizophrenia 41 (NR) 21, 20	Magstim Figure 8. Coil Sham: False coil	DLPFC - Left	20 Hz 64,000 pulses	110	40 sessions	Improved immediate memory ($p = 0.009$) with rTMS compared to sham.	NR
Guse *et al.*, 2013, Germany	Schizophrenia 47 (26%) 24, 23	MagPro X100 Figure 8 Coil Sham: coil 45° to skull	DLPFC - Left	10 Hz 1000 pulses	100	15 sessions	No change in working memory with rTMS in schizophrenia or healthy controls.	NR
Hasan *et al.*, 2016, Germany	Schizophrenia 156 (21%) 77, 79	MagPro X100 Figure 8. Coil	DLPFC - Left	10 Hz 1,000 pulses	110	15 sessions	No significant group differences were found. Improved cognition with rTMS not superior to sham.	NR

Table 2. Continued

AUTHOR, YEAR, COUNTRY	DIAGNOSIS, SAMPLE SIZE (% FEMALE), STUDY SAMPLE: TMS (NO.), CONTROL (NO.)	TMS MACHINE COIL	SITE OF STIMULATION	FREQUENCY INTENSITY	MOTOR THRESHOLD, %	TREATMENT DURATION	COGNITIVE OUTCOMES	ADVERSE EVENTS
Hausmann *et al.*, 2004, USA	MDD, Bipolar I 38 (61%) 12/13, 13	Magstim200 Rapid Figure 8. Coil	A1: HF to L-DLPFC, then sham to R-DLPFC A2: HF to L-DLPFC, then LF to R-DLPFC C: Sham HF to L-DLPFC, then sham LF to R-DLPFC	HF: 20 Hz, 2,000 pulses LF: 1 Hz, 2,600 pulses	HF: 100 LF: 120	10 sessions	Improved Stroop (2, p = .008; 3, p = .001) with rTMS (A1, A2) compared to sham.	Headache, mania
Holczer *et al.*, 2021, Hungary	MDD 20 (75%) 10, 10	Magstim2 Figure 8 Coil	DLPFC – Bilateral	50 Hz, 600 pulses cTBS, iTBS	30 maximal output	10 sessions	No effect on executive function, attention, working memory with theta burst stimulation.	None
Hou *et al.*, 2022, China	MDD 92 (30%) 32 HF, 29 LF	Medtronic MagPro Figure 8. Coil	HF: Left DLPFC LF: Right DLPFC	HF: 10 Hz NR LF: 1 Hz NR	80	40 sessions	RBANS higher after rTMS for both HF and LF.	Headache, scalp numbness
Hoy *et al.*, 2019, Australia	Traumatic brain Injury 21 (52%) 11, 10	Mag Venture Magpro30 Figure 8 Coil	DLPFC – Bilateral	DLPFC – Right: 1 Hz, 900 pulses DLPFC - Left: 10 Hz, 1,500 pulses	110	20 sessions	Improved working memory (p = 0.021), executive function (p = 0.029) with rTMS compared to sham.	Headache, site discomfort
Jagawat *et al.*, 2022, India	MDD 20 (40%) 10, 10	NR Figure 8. Coil	DLPFC - Left	10 Hz 3,000 pulses	100	10 sessions	Improved visuomotor coordination, attention, information processing speed with rTMS (p = 0.023) compared to sham.	NR
Mittrach *et al.*, 2010, Germany	Schizophrenia 32 (22%) 18, 14	MagPro X100 Figure 8. Coil	DLPFC – Left Sham: no magnetic field	10 Hz 1,000 pulses	110	10 sessions	No significant group differences were found. No evidence of cognitive deterioration.	Headache

Table 2. Continued

AUTHOR, YEAR, COUNTRY	DIAGNOSIS, SAMPLE SIZE (% FEMALE), STUDY SAMPLE: TMS (NO.), CONTROL (NO.)	TMS MACHINE COIL	SITE OF STIMULATION	FREQUENCY INTENSITY	MOTOR THRESHOLD, %	TREATMENT DURATION	COGNITIVE OUTCOMES	ADVERSE EVENTS
Myczkowski *et al.*, 2018, Brazil	MDD Bipolar I/II 43 (77%) 20, 23	BrainsWay H1-coil	DLPFC – Left Sham: mimicked the scalp sensations, acoustics	18 Hz 1,980 pulses	120	20 sessions	Improved cognition in all domains (attention and processing speed, working memory and executive function, inhibitory control, language, immediate verbal memory, long-term verbal memory; all $p < 0.001$) with both rTMS and sham. No cognitive side effects.	NR
Nadeau *et al.*, 2014, USA	MDD 48 (60%) 34-rTMS (16 right, 18 left) 14-Sham (7 right, 7 left)	Magstim Figure 8. Coil	DLPFC – Left or Right	5 Hz 2,000 pulses	100	10 sessions	Greater gains in language, visuospatial function, verbal episodic memory with right rTMS compared to left rTMS and sham. Improvement not related to depression reduction.	NR
Wen *et al.*, 2021, China	Schizophrenia 52 (44%) 26, 26	YRD CCY-I Figure 8. Coil	DLPFC – Left Sham: Coil perpendicular to scalp	10 Hz 1,600 pulses	110	20 sessions	Improved recall (immediate, $p = 0.016$; delayed $p = 0.047$) and negative symptoms ($p = 0.002$) with rTMS compared to sham.	Headache, reduced sleep
Wolwer *et al.*, 2014, Germany	Schizophrenia 32 (22%) 18, 14	MagPro X100 Figure 8. Coil	DLPFC - Left	10 Hz 1,000 pulses	110	10 sessions	No improvement in neurocognitive performance with rTMS or sham. Improved facial affect recognition with rTMS ($p < 0.001$) compared to sham.	NR

Table 2. Continued

AUTHOR, YEAR, COUNTRY	DIAGNOSIS, SAMPLE SIZE (% FEMALE), STUDY SAMPLE: TMS (NO.), CONTROL (NO.)	TMS MACHINE COIL	SITE OF STIMULATION	FREQUENCY INTENSITY	MOTOR THRESHOLD, %	TREATMENT DURATION	COGNITIVE OUTCOMES	ADVERSE EVENTS
Xiu *et al.*, 2020, China	Schizophrenia 120 (0%) 40–10 Hz/40–20 Hz, 40-Sham	Magstim2 Figure 8. Coil	DLPFC – Left Sham: Same vibration, no magnetic field	20 Hz, 64,000 pulses 10 Hz, 48,000 pulses	110	40 sessions	Improved immediate memory at week 8 with 20 Hz rTMS, but not 10 Hz, associated with Positive and negative syndrome scale positive score reduction. Improved RBANS at 6 months with both 20 Hz and 10 Hz rTMS.	Dizziness, scalp pain, insomnia
Yu *et al.*, 2022, China	MDD 44 (NR) 23, 21	Magstim2 Figure 8 Coil	DLPFC - Left	10 Hz 3,000 pulses	100	15 sessions	Improved stop-signal response time ($p = 0.045$) and Hamilton Depression Scale ($p = 0.003$) with rTMS compared to sham.	NR
Zeng *et al.*, 2022, China	General Anxiety Disorder 62 (58%) 31, 31	KF-10 Loop coil	Whole brain (Inflow-frequency TMS) Sham: Sham coil	1 mHz NR	NR	10 sessions	No differences on Hamilton Depression Scale, CGI, neurocognitive test (all $p > 0.05$).	Constipation, dizziness
Zhuo *et al.*, 2019, China	Schizophrenia 60 (32%) 33, 27	MagPro X100 Figure 8. Coil	DLPFC – Left Sham: coil flipped 180°	20 Hz 2,000 pulses	90	20 sessions	No cognitive improvement with rTMS. Improved scale for assessment of negative symptoms ($p = 0.021$), Positive and negative syndrome scale negative ($p = 0.006$), CGI-S ($p = 0.040$) with rTMS.	Headache, dizziness
Nondementia Open label and case series (n = 14)								
Abo Aoun *et al.*, 2019, Canada	MDD 25 (44%) 12/13 (OLP)	Magstim Figure 8. Coil	DLPFC – Left	10 Hz 3,000 pulses	120	30 sessions	Faster RT and decreased 3-Back omission errors in remitted MDD with rTMS compared to non-remitters.	NR

Table 2. Continued

AUTHOR, YEAR, COUNTRY	DIAGNOSIS, SAMPLE SIZE (% FEMALE), STUDY SAMPLE: TMS (NO.), CONTROL (NO.)	TMS MACHINE COIL	SITE OF STIMULATION	FREQUENCY INTENSITY	MOTOR THRESHOLD, %	TREATMENT DURATION	COGNITIVE OUTCOMES	ADVERSE EVENTS
X. Chen *et al.*, 2022, China	MDD 116 (68%) 45-TMS, 23-ECT + TMS, 22-ECT 26 control (OLR)	CCY-I Circular coil	DLPFC – Left	10 Hz 1,150 pulses	NR	NR	MoCA improved with rTMS but deteriorated with ECT.	NR
Demiroz *et al.*, 2022, Turkey	MDD 66 (65%) 33, 33 (OLP)	Neuro-MS Figure 8. Coil	DLPFC – Left	20 Hz 1,000 pulses	100	20 sessions	Improved Stroop with rTMS.	NR
Furtado *et al.*, 2013, Australia	MDD 29 (62%) 29, 0 (OLP)	Medtronic MagPro Figure 8. Coil	DLPFC – Left DLPFC – Bilateral	Left: 10 Hz, NR Bilateral: 1 Hz, NR	120	30 sessions	Improved Brief visuospatial memory test – Revised total learning and delayed recall, Rey Auditory Verbal Learning Test total learning with rTMS.	NR
Galletly *et al.*, 2016, Australia	MDD 63 (62%) 63, 0 (OLP)	MagPro R30 Figure 8. Coil	DLPFC – Bilateral	10 Hz, 1,500 pulses to left, then 1 Hz, 900 pulses to right	110	18–20 sessions	Improved cognitive functioning with rTMS accounted for by reduction in depression.	NR
Hopman *et al.*, 2021, China	MDD 22 (23%) 10 /12, 0 (OLP)	Magstim Figure 8. Coil	DLPFC – Left	10 Hz 3,000 pulses	120	20 sessions	Improved executive function, sustained attention with rTMS.	None
Hoy *et al.*, 2012, Australia	MDD, Bipolar 137 (55%) 27/25/40, 45 (OLR)	Medtronic MagPro Figure 8. Coil	Study 1: DLPFC - Right or Left Study 2: DLPFC – Left Study 3: Sequential DLPFC – Bilateral Study 4: Sequential bilateral or left DLPFC	Right: 1 Hz Left: 10 Hz 720–1,500 pulses	100-110	NR	Improved Digit span backward, COWAT with rTMS.	NR

Table 2. Continued

AUTHOR, YEAR, COUNTRY	DIAGNOSIS, SAMPLE SIZE (% FEMALE), STUDY SAMPLE: TMS (NO.), CONTROL (NO.)	TMS MACHINE COIL	SITE OF STIMULATION	FREQUENCY INTENSITY	MOTOR THRESHOLD, %	TREATMENT DURATION	COGNITIVE OUTCOMES	ADVERSE EVENTS
Iznak *et al.*, 2015, Russia	MDD 20 (100%) 20, 0 (OLP)	Neuro-MS Figure 8. Coil	DLPFC – Left	20 Hz 1,600 pulses	60–80	10 sessions	Improved WCST and perseverative errors ($p < 0.01$) with rTMS.	NR
Noda *et al.*, 2022, Japan	Long COVID 23 (57%) 23, 0 (Case Series)	MagPro R30 Figure 8. Coil	DLPFC – Left Lateral orbitofrontal cortex - Right	iTBS: 50Hz, 1,200 pulses for left DLPFC, then 1 Hz, 600 pulses for right Lateral orbitofrontal cortex	70–120	20 sessions	Improved cognitive function (Perceived Deficits Questionnaire–Depression 5-item) with rTMS.	Scalp pain
Rostami *et al.*, 2022, Iran	MDD 135 (53%) 120, 0 (OLP)	Neuro-MS Figure 8. Coil	DLPFC – Bilateral	Left: 10 Hz, 3,750 pulses Right: 1 Hz, 1,500 pulses	Left: 110 Right: 120	20 sessions	Improved general cognitive functioning, sustained attention, working memory, executive function with bilateral rTMS.	Headache
Schaffer *et al.*, 2020, USA	MDD 53 (64%) 17, 36 (OLR)	NR Figure 8. Coil	Right DLPFC Supplementary motor area	1 Hz 1,200 pulses	100–110	30 sessions	Improved neurocognitive performance with rTMS beyond changes related to improvements in depressive or anxious symptoms.	NR
Schulze-Rauschenbach *et al.*, 2005, Germany	MDD 45 (47%) 16/14, 15 (OLP)	Magstim Figure 8 Coil	DLPFC – Left	10 Hz NR	100	10 sessions	Constant or improved cognitive performance with rTMS compared to ECT.	NR
Zhou *et al.*, 2021, China	Traumatic brain injury 166 (44%) 83, 83 (OLP)	NR Figure 8. Coil	Healthy Prefrontal area	1 Hz 750 pulses	80	60 sessions	Greater improvement in MMSE with rTMS compared to control.	NR
Zhuo *et al.*, 2022, China	Schizophrenia 383 (NR) 9 group combinations (tDCS, rTMS, Lithium) (OLP)	NR	Left occipital lobe Prefrontal cortex	10 Hz 1,600 pulses	110	72 sessions	Improved cognition with rTMS with adjunct lithium.	Headache, dizziness, nausea

Table 2. Continued

AUTHOR, YEAR, COUNTRY	DIAGNOSIS, SAMPLE SIZE (% FEMALE), STUDY SAMPLE: TMS (NO.), CONTROL (NO.)	TMS MACHINE COIL	SITE OF STIMULATION	FREQUENCY INTENSITY	MOTOR THRESHOLD, %	TREATMENT DURATION	COGNITIVE OUTCOMES	ADVERSE EVENTS
HOA and SCD (*n* = 5)								
Cotelli *et al.*, 2010, Italy	HOA 13 (69%) 13, 0 (OLP)	NR Figure 8. Coil Sham: 3cm wood between coil and scalp	DLPFC – Left DLPFC – Right	20 Hz NR	NR	1 session	Improved action naming with both left and right rTMS compared to sham.	None
Chen *et al.*, 2020, China	SCD 16 (NR) 8, 8 (RCT)	Magstim Figure 8. Coil Sham: Coil turned 180°	Precuneus	10 Hz 1,000 pulses	100	25 sessions	Improved episodic memory (AVLT) with rTMS compared to sham.	None
Hermiller *et al.*, 2022, USA	HOA 30 (63%) 15/15, 0 (RCT)	MagPro X100 Figure 8. Coil	Parietal location with maximum hippocampal connectivity	Beta: 20 Hz, 600 pulses, 50 Hz, 600 pulses	38–70	2 sessions	Greater swap rate with theta burst compared to beta in younger, but not older adults.	NR
Liu *et al.*, 2021, China	SCD 25 (44%) 25, 0 (OLP)	MagPro X100 Figure 8. Coil	DLPFC – Left	10 Hz 1,500 pulses	100	1 session	Improved RT, attention, ability to suppress irrelevant information, executive function with rTMS when completing visual working memory tasks.	NR
Sole-Padulles *et al.*, 2006, Spain	SCD 39 (72%) 20, 19 (RCT)	Magstim Double cone coil	Left Motor Cortex Sham: Coil placed tangential to scalp	5 Hz NR	80	1 session	Improved associative memory with rTMS compared to sham.	None

Abbreviations: AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive Subscale; aMCI, amnestic mild cognitive impairment; ACE, Addenbrooke Cognitive Examination; ADL, activities of daily living; AVLT, Auditory Verbal Learning Test; BNT, Boston Naming Test; CAVLT, Chinese version of Auditory verbal learning test; COG, Cognition ; COWAT, controlled oral word association test; cTBS, continuous theta burst stimulation; CVA, cerebrovascular accident; DLPFC, dorsolateral prefrontal cortex; ECT, electroconvulsive therapy; FTD, frontotemporal dementia; HC, healthy controls; HF, high frequency; HOA, healthy older adult; IFG, inferior frontal gyrus; iTBS, intermittent theta burst stimulation; LF, low frequency; MCI, mild cognitive impairment; MDD, major depressive disorder; MMSE, Mini-Mental Status Examination; MoCA, Montreal Cognitive Assessment; NPI, neuropsychiatric inventory; NR, not reported; OLP, open-label prospective study; OLR, open-label retrospective study; PANSS, positive and negative syndrome scale; PFC, prefrontal cortex; PD, Parkinson disease; PNFA, progressive nonfluent aphasia; PPA, primary progressive aphasia; PROAD, probable Alzheimer dementia; PSAC, primary somatosensory association cortex; PSCI, post-stroke cognitive impairment; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; RCT, randomized clinical trial; RT, reaction time; rTMS, repetitive transcranial magnetic stimulation; SCD, subjective cognitive decline; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation; WCST, Wisconsin Card Sorting Test.

Wolwer *et al.*, 2014; Xiu *et al.*, 2020), although 1 study (Du *et al.*, 2022) found a higher pattern in recognition memory at week 8 despite no improvement at week 4. Results from using 20 Hz were mixed, with some cognitive benefit in two studies (Xiu *et al.*, 2020; Guan *et al.*, 2020) but none in another study (Zhuo *et al.*, 2019). Stimulation with 10 Hz as a supplement to antipsychotics resulted in improved recall in 1 study (Wen *et al.*, 2021). In MDD, seven studies reported improved cognition (Buchholtz *et al.*, 2020; Cheng *et al.*, 2016; Hou *et al.*, 2022; Jagawat *et al.*, 2022; Myczkowski *et al.*, 2018; Nadeau *et al.*, 2014; Yu *et al.*, 2022), while two studies (Holczer *et al.*, 2021; Hausmann *et al.*, 2004) did not.

Most of the open-label studies involved patients with MDD, except for one study each on schizophrenia (Zhuo *et al.*, 2022), traumatic brain injury (Zhou *et al.*, 2021), and long-COVID (Noda *et al.*, 2022). Patients whose depressive symptoms decreased in response to TMS sustained improvement in cognition (Abo Aoun *et al.*, 2019; Furtado *et al.*, 2013). Only two open-label MDD studies, with stimulation over bilateral DLPFC, noted no improvement in cognition (Galletly *et al.*, 2016; Hoy *et al.*, 2012). Other MDD studies noted cognitive benefit, independent of the improvement in depression.

HOAs and subjective cognitive decline

Three of the five studies are RCTs. All five studies reported improvement in cognition following TMS (Cotelli *et al.*, 2010; Chen *et al.*, 2020; Hermiller *et al.*, 2022; M. Liu *et al.*, 2021; Sole-Padulles *et al.*, 2006).

Meta-analysis: TMS effect on global cognition, compared to sham stimulation in MCI and AD subgroups

Twenty-five RCTs on MCI and AD were included in the meta-analysis. TMS significantly improved cognition in MCI and AD, when compared to sham stimulation, across all three of the most used global cognitive outcome measures. MMSE ($n = 24$, SMD = 0.80 [0.26, 1.33], $p = 0.003$), MoCA ($n = 10$, SMD = 0.85 [0.26, 1.44], $p = 0.005$), and ADAS-Cog ($n = 14$, SMD = − 0.96 [− 1.32, − 0.60], $p < 0.001$) all showed large effects of improvement on global cognition (Figure 2). There was significant heterogeneity in the subgroup analyses (MMSE, $I^2 = 96.68\%$; MoCA, $I^2 = 82.09\%$; ADAS-Cog, $I^2 = 82.09\%$) (Supplemental Table 6a, b, c). Of the 25 studies included in meta-analysis, 10 studies were from China, 4 from Italy, 3 from USA, while other countries namely Iran, Mexico, Taiwan, Japan, Korea, Israel, Egypt, and Turkey had one study each. This represents the diverse regional representation of studies in the meta-analysis. We have not noticed specific differences in results across studies by region.

Safety

Most of the studies demonstrated no major safety concerns (Table 2). Of 143 studies, there were 2 studies that reported 4 serious adverse events as seizures. In 1 RCT, there were 3 instances of seizures that occurred 6 to 12 months after TMS (J. Cheng *et al.*, 2021), with 2 of cases occurring in the sham group, and none were deemed related to rTMS. In another study (Tumasian and Devi, 2021), 1 patient experienced motor movements during parietal rTMS deemed to be focal motor seizures which resolved with coil positioning (Tumasian and Devi, 2021). Two other AD studies reported serious adverse events of acute myocardial infarction (Leocani *et al.*, 2020) and urinary sepsis (Bentwich *et al.*, 2011) all unrelated to TMS. Overall, 47 studies (33%) reported adverse events, most commonly headache, local skin or scalp discomfort, and fatigue. Only 2 patients discontinued the study due to side effect intolerance. Forty (28%) studies reported no adverse events, and 52 (36%) studies did not have information on adverse events.

TMS parameters

TMS parameters are summarized in Supplemental Figure 1, including site of stimulation, frequency, motor threshold, number of treatment sessions, and total pulses per session. Stimulation sites were classified into five different categories based on site of stimulation as L-DLPFC only, bilateral DLPFC, six sites (right DLPFC, left DLPFC, Broca's area, Wernicke's area, right parietal somatosensory association cortices (PSAC), and left PSAC), other sites, and L-DLPFC combined with other sites of stimulation. L-DLPFC is the most common stimulation site across all diagnostic groups. Most of the studies used HF stimulation. Percent motor threshold ranged from 70 to 120%, although 90 to 100% was the most used range. Number of TMS sessions ranged from 1 to 54, with 10 or 20 sessions being the common treatment duration. A total of 19 studies (4-HOA and SCD, 5-non-AD, 4-MCI, 2-AD & MCI, 4-AD) in the systematic review reported 4 or less TMS sessions that they administered in their study. Total number of pulses per session ranged from <600 to 4,000, with 1,000–2,000 per session being the most frequently used.

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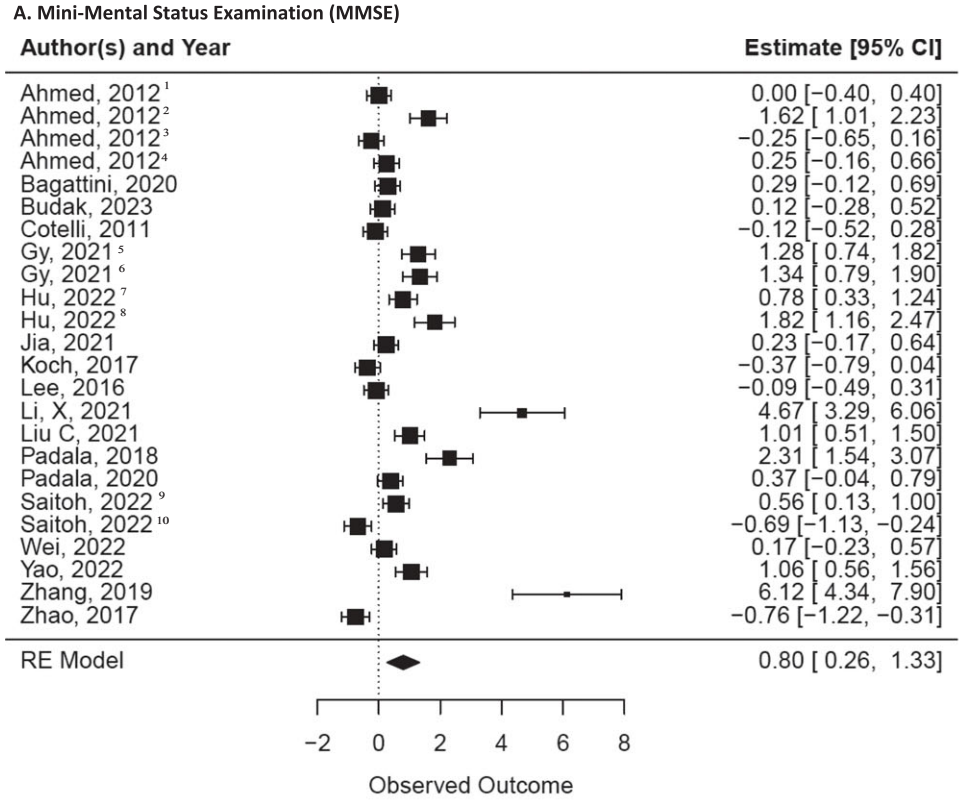
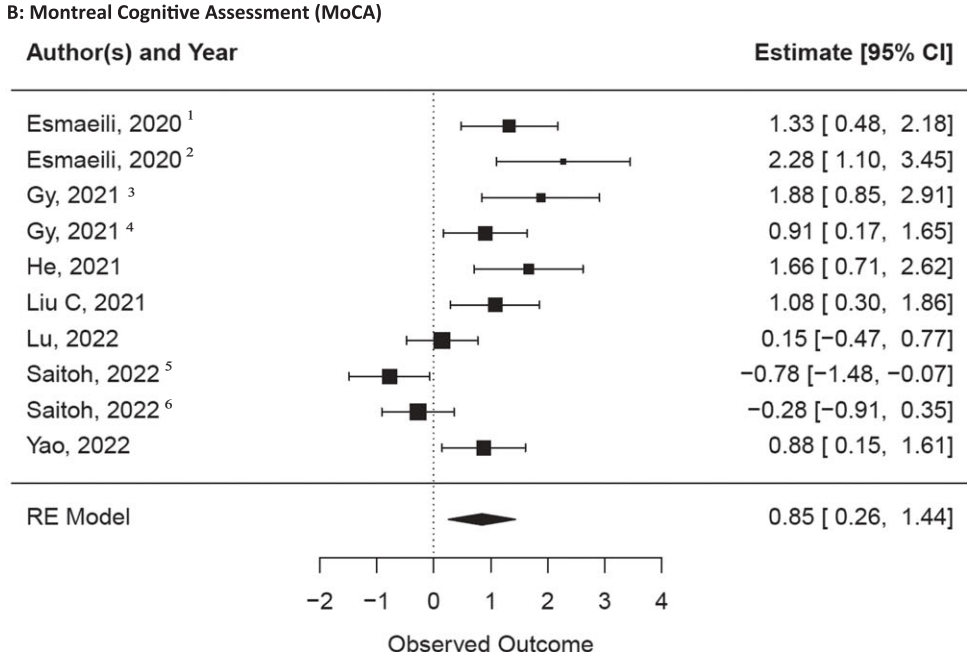


[1]Mild/moderate dementia 1 Hz vs sham
[2]Mild/moderate dementia 20 Hz vs sham
[3]Severe dementia 1 Hz vs sham
[4]Severe dementia 20 Hz vs sham
[5]Active vs sham
[6]Sham vs Active
[7]rTMS-tDCS vs Single tDCS
[8]Single rTMS vs sham
[9]TMS 120% vs sham
[10]TMS 90% vs sham



[1]Active vs sham
[2]Sham vs Active
[3]Active vs sham
[4]Sham vs Active
[5]TMS 120% vs sham
[6]TMS 90% vs sham

Figure 2. Forest plot analysis of different cognitive outcomes. A, Mini-Mental Status Examination (MMSE). B, Montreal Cognitive Assessment (MoCA). C, Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog).

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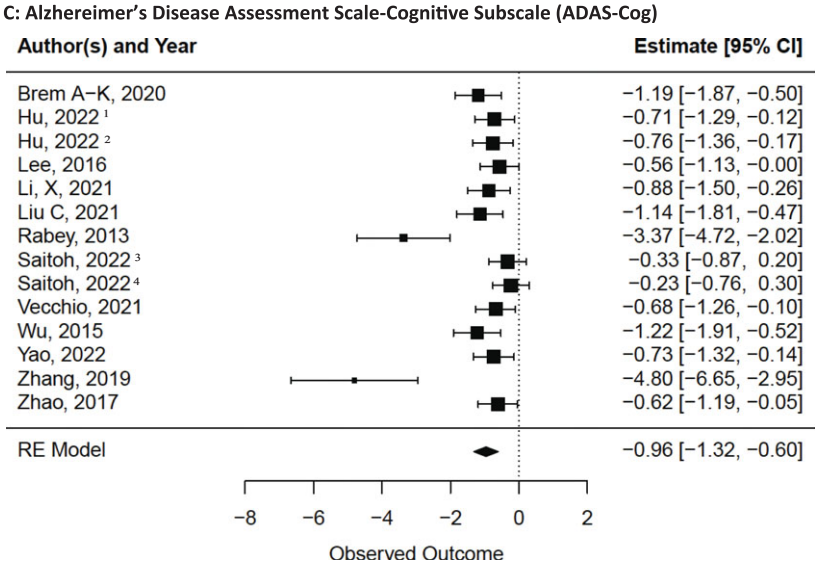

[1]rTMS-tDCS vs Single tDCS
[2]Single rTMS vs sham
[3]TMS 120% vs sham
[4]TMS 90% vs sham

RE, random effects; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation.

Figure 2. (*Continued*)

Quality assessment

The quality assessment is reported in Figures 3A and 3B, with overall quality being modest across the studies. Detailed quality assessments for each study are included in Supplemental Table 7 (Cochrane Risk of Bias) for RCTs and Supplemental Table 8 (MINORS criteria) for non-RCT studies.

Discussion

We have three main findings from this study. First, there is evidence for improvement of global and specific cognitive functions with TMS across all diagnostic groups with cognitive impairment. Second, TMS was safe and well tolerated with minimal serious adverse events generally deemed unrelated to TMS. Third, there was a wide variability across studies, in TMS protocols and cognitive measures which limit the determination of optimal parameters in this population.

Efficacy of rTMS for cognitive impairment

Most of the reviewed studies in our systematic review provide evidence of improved cognitive functions with TMS. Meta-analysis of RCT studies in MCI and AD shows rTMS significantly improved global cognition (MMSE, MoCA, ADAS-Cog) compared to sham stimulation. Improvement in specific domains such as memory, working memory, or executive function was found in different studies, but this may reflect the dearth of studies that addressed such specific domains. Future research might transcend reliance upon general cognitive measures and focus on more sensitive measures of specific cognitive domains. In doing so, those neuropsychologic functions that are most likely to improve may be identified. Furthermore, research may reveal that TMS to specific regions may exert a more potent benefit upon certain cognitive domains. For example, stimulation of frontal regions may yield a more robust benefit of executive function and working memory than new learning. Ultimately, this would allow a more personalized approach, where the TMS intervention might be guided by each patient's symptoms or cognitive disability.

Our study findings are consistent with previously published systematic reviews and meta-analyses reporting a range of effect sizes. A meta-analysis of 12 studies analyzing the effect of rTMS therapy on cognition in AD found a moderate effect size (SMD = 0.60; 95% CI, 0.35–0.85) (Lin *et al.*, 2019). Additionally, multiple sites of stimulation improved cognition more than single-site stimulation, and more rTMS treatments (≥ 5) resulted in

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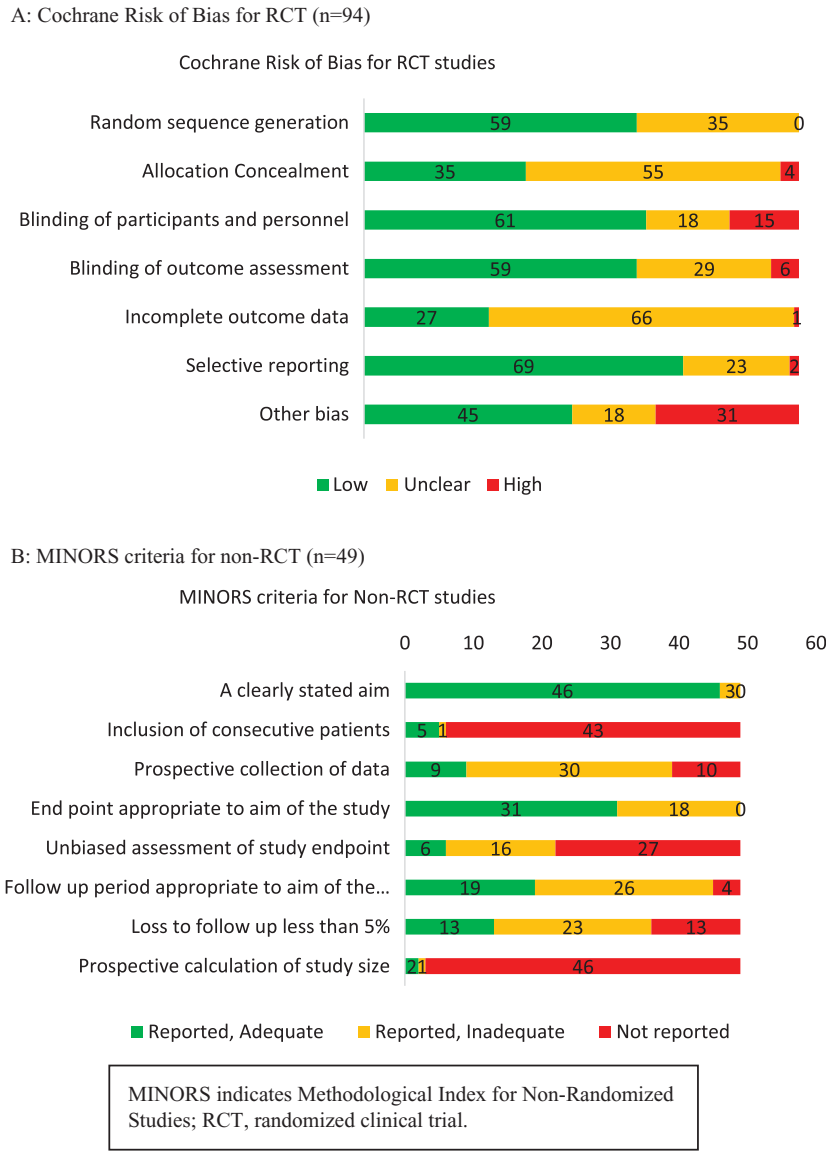

Figure 3. Qualitative assessments. A, Cochrane Risk of Bias for RCT ($n = 94$). B, MINORS criteria for non-RCT ($n = 49$).

better cognitive improvement than less (≤ 3) rTMS treatments (Lin *et al.*, 2019). Another review of 5 RCTs found significant improvement in cognition with high-frequency rTMS when measured by ADAS-Cog (SMD = −3.65; 95% CI, −5.82 to −1.48; $P = 0.001$) but not MMSE (SMD = 0.49; 95% CI, −1.45 to 2.42; $P = 0.62$) (Dong *et al.*, 2018). A meta-analysis investigated the efficacy of two techniques of noninvasive brain stimulation (rTMS and transcranial direct current stimulation [tDCS]) on global cognition and neuropsychiatric symptoms in people with AD and MCI (Teselink *et al.*, 2021). There was significant improvement of global cognition (MMSE, MoCA, ADAS-Cog) with active rTMS but not tDCS (Teselink *et al.*, 2021). Improvement of global cognition was greater in patients with AD and MCI when the site of active stimulation was the L-DLPFC compared to sham stimulation (Teselink *et al.*, 2021). Another review of efficacy of TMS and tDCS on cognitive functioning is similar to our current systematic review in that it included many brain disorders (Begemann *et al.*, 2020). Meta-analysis from 82 studies showed small effect sizes (Hedges' g) of both TMS ($g = 0.17$, $P = 0.015$) and tDCS ($g = 0.17$, $P = 0.021$) on working memory across all brain disorders (Begemann *et al.*, 2020). Another recent meta-analysis by Yan *et al.*, described similar results on the overall cognitive improvement with TMS compared to sham stimulation in patients with MCI and AD both short term (<3 days) and long term (>4 weeks) (Yan *et al.*, 2023). In the study by Yan *et al.*, all the cognitive outcomes namely MMSE, MoCA, ADAS-Cog, and Rivermead Behavioral Memory test have been combined into one Meta-analysis category (Yan *et al.*, 2023). Our study

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analyzed the effect on each cognitive outcome (MMSE, MoCA, and ADAS-Cog) separately. All the RCT TMS studies in AD and MCI populations analyzed in the above different meta-analysis studies were all included in our study along with other new eligible studies.

A clinically relevant change in MMSE scores is an important consideration in both clinical practice and research. While we found large effect sizes on global cognition in our meta-analysis, this does not always translate to clinical meaningfulness. Different studies have provided insights into what constitutes a significant change in MMSE scores or minimum clinically important difference (MCID). In one study of 451 cognitively unimpaired individuals and 292 people with MCI, a change of − 1.5 to − 1.7 points in MMSE was considered as MCID (Borland *et al.*, 2022). Another study that used a distribution-based approach reported a similar range of mean changes in MMSE scores for MCIDs (Watt *et al.*, 2021). One other study indicated that, in repeated assessments with 1.5-year intervals, a change in MMSE of at least 2–4 points indicated a reliable change at the 90% confidence level. However, it was emphasized that small changes in MMSE should be interpreted cautiously due to potential causes like measurement error, regression to the mean, or practice effect (Hensel *et al.*, 2007). In a study of community-dwelling adults, a 3-point change in MMSE scores over a period of 3 years or more has been established as representative of a clinically meaningful decline in cognitive functioning (Pitrou *et al.*, 2022). These studies collectively suggest that a change of 2–4 points in the MMSE score, especially over intervals of 1.5 to 3 years, can be considered clinically significant. However, the interpretation of these changes should be done cautiously, considering the potential for measurement error and individual variations. In our meta-analysis of 25 studies, we observed changes in MMSE scores that were lower than the conventional threshold for clinical significance. However, detecting small changes in MMSE scores even if not clinically significant can be valuable in understanding the subtle effects of TMS on cognitive function in people with MCI and dementia where any degree of cognitive improvement is meaningful.

Safety and tolerability of TMS in cognitively impaired populations

TMS was overall safe and well tolerated, with a low incidence of adverse events that were consistent with known adverse effects of TMS. Although rare, seizures are the most serious adverse event with TMS and the estimated risk is low at less than 1 in 30,000 (Rossi *et al.*, 2021). The more common and expected adverse effects of TMS are transient headaches, scalp discomfort, and muscle twitches during stimulation (Rossi *et al.*, 2021). In people with cognitive impairment, age is an important safety consideration for TMS given age-related physiologic changes, medical and neurologic comorbidities, presence of devices or implants, and polypharmacy, all factors that can affect response to TMS. However, the safety and tolerability of TMS is well-established when proper safety procedures are observed, even in older adults with depression (Iriarte and George, 2018). Following current TMS safety guidelines (Rossi *et al.*, 2021) including proper screening of participants, ensuring stimulation parameters are within safety limits, and using qualified technicians and clinicians can help mitigate seizure risk (Fried *et al.*, 2021; Pandis and Scarmeas, 2012; Targa Dias Anastacio *et al.*, 2022). It is notable that there is significant underreporting as nearly one-third of studies did not report safety or adverse events. Inadequate documentation and disclosure of adverse events can distort the safety profile of TMS and hampers our understanding of the true benefits and risks in this population.

Heterogeneity of TMS treatment parameters

There is a wide variation in the TMS parameters used in each study. The most common site of stimulation is the L-DLPFC, using high-frequency stimulation, i.e. more than 5 Hz frequency, with 1,000–1,500 pulses per session, at 90% to 100% resting motor threshold (RMT), and treatment duration of 10–20 sessions. The current US FDA approval of TMS for MDD uses the L-DLPFC site, with HF 10–20 Hz (1,800–3,000 pulses per session) or iTBS (600 pulses per session), at 120% RMT, and 30 sessions. There are interesting similarities and differences between studies reviewed here and the US FDA-approved parameters in MDD. The similarities are L-DLPFC as the stimulation site and HF stimulation. In contrast to MDD protocols, fewer pulses per session, lower intensity (%RMT), and shorter duration of treatment were noted. In a previous systematic review of 30 studies including patients with psychiatric and neurologic diseases or healthy volunteers, it was reported that TMS was most likely to significantly improve cognitive functions when applied over the L-DLPFC, administered at 10-, 15-, or 20-Hz intensity, dosed at 80% to 110% of motor threshold, and delivered in 10 to 15 successive sessions (Guse *et al.*, 2010). While TMS has received the most attention for depression, its potential use for other conditions is being investigated. There is ongoing debate on the dual identity of TMS as a one-size-fits-all therapeutic intervention and a personalized intervention targeting

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individual substrate and symptom-specific targets. The question of standardized versus personalized approaches remains a crucial area of investigation.

Cognitive impairment and dementia are conditions that are distinct from depression such that different parameters will be needed when TMS treatment is considered. However, it is also possible that improvements in mood could lead to cognitive enhancements in people with dementia and comorbid depression, underscoring the intricate interplay between emotional well-being and cognitive function. Many studies investigating the effects of TMS on cognition target the L-DLPFC but fail to control for potential mood effects. Since L-DLPFC stimulation has known antidepressant effects, any cognitive improvement observed could be directly due to the stimulation of this region or indirectly due to alleviation of depressive symptoms, emphasizing the importance of controlling for depression in these studies to isolate the true cognitive effects of TMS. Cognition is attributed to specific areas of the brain and exploration of sites other than L-DLPFC should be considered. Stimulating at 1 site could affect brain functional connectivity and impact another site (Eshel *et al.*, 2020). HF stimulation is excitatory, which is thought to be needed for depression and dementia, whereas LF (thought to be inhibitory) stimulation has been used for anxiety and depression disorders. Future rTMS studies for dementia could investigate rTMS at 120% of RMT and use higher pulses per session and total number of sessions. Having the knowledge that higher parameters are used for other clinical and research applications of rTMS can help shape future rTMS for dementia research.

The effects of TMS in cognitive impairment or dementia are multifaceted and reflect complex interactions between TMS parameters and targeted brain tissue, therefore resulting in variability of TMS parameters. Varying degrees of brain atrophy can affect the amount of current induced in the brain, necessitating individualized computational modeling of the brain to adjust for optimal therapeutic effects. The slowing of neural oscillatory activity in dementia can influence how the brain responds to TMS, adding another layer of complexity but also offers the opportunity for a more nuanced, individualized and potentially effective approach. Given these diverse anatomical and physiological changes in dementia, there is a critical need for individualized approaches to ensure optimal therapeutic outcomes for each individual.

Strengths and limitations

This study extends findings of previous systematic reviews and meta-analyses to include a broader population with non-AD dementia subtypes and nondementia conditions with cognitive impairment, incorporate newer recently published studies for a more comprehensive review, summarize adverse effects and safety profile in cognitively impaired populations, analyze the extent of heterogeneity in study characteristics that impact generalizability of findings, consolidate existing knowledge, and provide further insights on the impact and potential benefits on TMS in populations with cognitive impairment globally. Limitations include heterogeneity in study designs, variability in stimulation parameters and cognitive outcome measures that limited ability to perform quantitative analysis in other diagnostic groups, and limited long-term data. Despite these limitations, this systematic review and meta-analysis provide valuable insights into the existing literature.

Conclusion

Overall, the reviewed studies provide favorable evidence for improvement of global and specific domains of cognitive functions with rTMS across all diagnostic groups with cognitive impairment. Meta-analysis showed large effect sizes on global cognition in MCI and AD, although with significant heterogeneity. The most common TMS parameters use the left DLPFC as the site for HF stimulation, 1,000–1,500 pulses per session at 90–100% of RMT, and duration of 10–20 sessions. TMS was safe and well tolerated with minimal adverse events, although there may be underreporting of adverse events. Heterogeneity of study design, TMS protocols, and cognitive measures limit the determination of optimal parameters for cognitively impaired populations.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that influenced the work reported in this paper.

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Description of authors' roles

Conceptualization: All authors; Methodology: S.P., R.K., M.L., A.L., L.H.; Data curation: S.P., R.K., M.L., A.L, B.L., S.K., P.C.; Formal analysis: A.L. J.G.; Funding: S.P., M.L.; Writing original draft: S.P., R.K., M.L.; Writing – Review and Editing: All authors reviewed, edited, and approved the final manuscript.

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Supplementary material

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