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RESEARCH ARTICLE

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Does repetitive transcranial magnetic stimulation improve cognitive function in age-related neurodegenerative diseases? A systematic review and meta-analysis

Amy Miller[1] | Richard J. Allen[1] | Alisha A. Juma[1] | Rumana Chowdhury[2] | Melanie Rose Burke[1]

[1]School of Psychology, University of Leeds, Leeds, UK

[2]The Leeds Teaching Hospitals, NHS Trust, Leeds, UK

Correspondence
Amy Miller, School of Psychology, University of Leeds, Leeds LS2 9JT, UK.
Email: ps16am@leeds.ac.uk

Abstract

Objective: High-frequency, repetitive transcranial magnetic stimulation (rTMS) targeted over the dorsolateral prefrontal cortex (DLPFC) is widely used in research to promote neuroplasticity and cognitive enhancement. RTMS is a promising intervention to tackle cognitive decline in people with age-related neurodegenerative diseases. However, there is currently no systematic evidence examining the effects of DLPFC-targeted, high-frequency rTMS on cognitive function in this population. The aim of this systematic review was to evaluate the efficacy and moderators of this treatment intervention.

Methods: A comprehensive literature search of five electronic databases was performed to identify articles published before October, 2022. Following PRISMA guidelines, the identified articles were screened, data was extracted, and the methodological quality was assessed using the Cochrane tool, Risk of Bias 2. Meta-analyses were performed using R Studio (v.4.1.2).

Results: Sixteen studies involving 474 participants met the inclusion criteria, of which 8 studies measured global cognitive function. The results from the random-effects meta-analysis showed rTMS significantly improved global cognitive function relative to control groups shown by a large, significant effect size ($g = 1.39$, 95% CI, 0.34–2.43; $p = 0.017$). No significant effects were found between subgroups or for individual cognitive domains.

Conclusions: High-frequency rTMS, targeted over the DLPFC, appears to improve global cognitive function in people with age-related neurodegenerative diseases. However, these results should be interpreted with caution due to the small number of studies included, and high between-study heterogeneity.

KEYWORDS
ageing, Alzheimer's disease, dementia, dorsolateral prefrontal cortex, MCI, TMS

Key points

- High-frequency repetitive TMS over the dorsolateral prefrontal cortex significantly improved global cognitive function in people with age-related neurodegenerative diseases, compared to control/sham stimulation.

1 | INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS) is a well-tolerated and painless form of non-invasive brain stimulation, recommended as a treatment for various neurological and psychiatric disorders according to the updated reporting guidelines on the therapeutic use of rTMS.[1] RTMS is widely used in research for promoting cognitive enhancement[2] is a promising intervention for cognitive impairment in people with Mild Cognitive Impairment and age-related neurodegenerative diseases including Alzheimer's disease (AD) and Parkinson's disease (PD).[3–6] Therefore, this systematic review was required to establish the efficacy of this intervention and understand the optimal protocol to achieve cognitive effects.

RTMS delivers pulses of magnetic stimulation to induce currents in localised regions of neurons in the cerebral cortex. High stimulation frequencies, between 5 and 20 Hz, increase cortical excitability thereby inducing long-term potentiation (LTP-like) effects by enhancing synaptic transmission in the underlying grey matter.[7] Huang et al.[8] identified intermittent theta burst stimulation (iTBS) as an rTMS protocol that uses triplets of pulses at theta frequency (5 Hz) delivered in gamma frequency trains (50 Hz) that can adjust cortical excitability in a fraction of the time of traditional rTMS, with potentially more enhanced and enduring after-effects.[8]

Previous systematic reviews investigating the effects of rTMS in AD and MCI have found promising positive effects on cognition.[3,5,6] However, such reviews included studies with highly varied methodological approaches, including stimulating different brain regions and including both excitatory and inhibitory TMS protocols in the meta-analyses. This has led to limited conclusions regarding the optimal stimulation parameters and brain location to induce cognitive effects. The objective of the current systematic review was to streamline the evidence by investigating the cognitive effects of rTMS on a single stimulation site (the dorsolateral prefrontal cortex (DLPFC)) with a specific protocol (high-frequency excitatory rTMS). This focus was chosen based on evidence from the literature that high-frequency rTMS targeted on the DLPFC yields significant improvements in cognitive performance in MCI and AD, compared to other stimulation sites and protocols.[3,5,6]

The aim of this systematic review and meta-analysis was to examine the following questions: (1) Is there a reliable effect of DLPFC-targeted, high-frequency rTMS protocols on global cognitive function in older adults with neurodegenerative disease? (2) Do people with MCI show greater improvements in global cognitive function following the intervention than people with AD? (3) Do iTBS and traditional rTMS protocols differ in efficacy? (4) Does the number of stimulation sessions impact the effect? (5) Which cognitive domains show an improvement in performance following rTMS?

2 | METHODS

This review was registered with PROSPERO (CRD42021298315) and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) stated guidelines.[9]

2.1 | Search strategy

Citations were retrieved by searching the following databases; Pubmed, Embase, CENTRAL, Medline, PsychINFO, Google Scholar and ProQuest Dissertations in January 2022 and updated in October 2022. Retrieval time was from the date of database construction to the search date. The full search strategy is presented in Figure 1.

2.2 | Study selection

Two independent reviewers assessed all titles/abstracts and full-text articles for inclusion according to the following criteria; (1) Study type: trials, single blind, double blind or non-blind. (2) Participants: people with MCI or dementia related to AD or PD, (3) Intervention: an experimental group treated with a high-frequency (≥5 Hz) rTMS protocol (including iTBS) targeting the DLPFC only, with no additional treatment. (4) Comparison: a control group treated with sham (inactive or weak stimulation) or control stimulation (over a control site). (5) Outcome measures: a measure of at least one cognitive function using an objective and established neuropsychological or cognitive test. Any disagreements were resolved by consensus.

Reasons for exclusion: (1) no sham condition, (2) additional interventions such as cognitive training or drug treatment, (3) participants with no cognitive impairment and (4) not reported in English.

2.3 | Coding procedure

Definitions of the individual cognitive domains investigated are detailed in the Supplementary Information. A summary of the included cognitive tests is provided in Table A1.

2.4 | Global cognitive function

Global cognitive function refers to evaluations made by neuropsychological assessment tools which assess a variety of cognitive domains in short subsections to generate an overall score. The Mini-Mental State Exam (MMSE;[10]) is a widely used measure of global

1. repetitive transcranial magnetic stimulation.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]
2. rTMS.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]
3. intermittent theta burst stimulation.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]
4. iTBS.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]
5. 1 or 2 or 3 or 4
6. exp Alzheimer's Disease/
7. AD.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]
8. exp Mild Cognitive Impairment/
9. MCI.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]
10. exp Parkinson's Disease/
11. PD.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]
12. exp Dementia/
13. neurodegen*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]
14. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. (dorsolateral prefrontal cortex or dlPFC).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]
16. 5 and 14 and 15

FIGURE 1 Search strategy.

cognitive function in older adults with high test-retest reliability (0.80–0.95) and acceptable sensitivity (0.87) and specificity (0.82) to detect mild to moderate stages of dementia at a cut off score of 25.[11–13] Where the MMSE was not administered, the Montreal Cognitive Assessment (MoCA;[14]) was considered the most favourable alternative test of global cognitive function. Studies have shown the MoCA has high test-retest reliability (0.75–0.92) and acceptable sensitivity and specificity in detecting MCI (0.86;[15]).

2.5 | Study quality assessment

Two independent reviewers assessed the methodological quality of the included studies using the Cochrane Risk-of-Bias tool for randomized trials (RoB2), as recommended by the Cochrane Collaboration. RoB2 involves a structured assessment using signalling questions in five domains; allocation concealment, blinding of participants and personnel, blinding of outcome raters, missing data, appropriateness of outcome measures and other bias.

2.6 | Data extraction

One reviewer developed an extraction form and independently extracted the data. This was checked for quality and accuracy by a 2nd reviewer by examining the extracted data against the data reported in the original papers. Data extracted included sample size, participant characteristics, stimulation protocol and methods, adverse effects and outcome data (pre- and post-intervention means and standard deviations). A Plot Digitizer programme[16] was used to estimate means and standard deviations (SD) when data was presented in graph form only. When SD was not reported, it was estimated from standard error (SE) using the equation $SD = SE \times \sqrt{n}$ or from 95% confidence intervals using the equation $SD = \sqrt{n} \times$ (upper limit–lower limit)/3.92. Study data was not included in the analysis if values were reported as; (1) change-from-baseline scores, (2) *z*-scores, (3) composite scores combining results from multiple assessments.

2.7 | Meta analytic procedure

All analyses and plots were coded in R Studio (v4.1.2) using the packages {meta}[17] and {tidyverse}[18] and the guide by Harrer et al..[19] Means were transformed such that positive effect sizes indicated an improvement in cognitive performance. Random-effects, inverse variance models were performed to pool effect sizes (Hedge's g) for each cognitive domain and the restricted maximum likelihood estimator[20] was used to calculate the heterogeneity variance τ^2. Knapp-Hartung adjustments[21,22] were used to calculate the confidence interval around the pooled effect. Outliers were identified using the ''find.outliers'' function in the {dmetar} package.[23,24] Three subgroup distinctions were defined a-priori, including stimulation protocol (iTBS and traditional rTMS), and diagnosis (MCI and AD) and number of stimulation sessions.

3 | RESULTS

3.1 | Study selection and characteristics

The search identified 719 studies of which 26 were considered as potentially relevant. Following the full-text review, 16 studies published in peer-reviewed journals were included. Inter-rater agreement was high. The study selection flow chart is presented in Figure 2 and the individual study characteristics are presented in Tables B1–D1. The total included studies represented data from 474 participants with an average age of 67.7 years (61–72 years, SD = 3.5 years). On average participants had 12.5 years of education

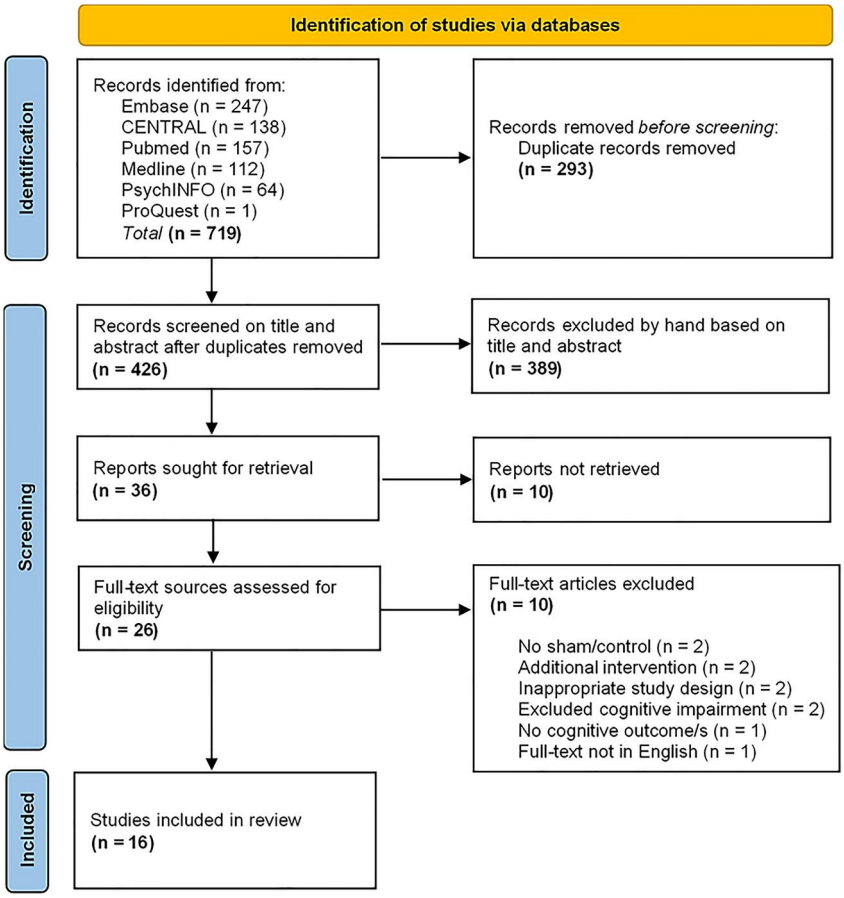

FIGURE 2 Study Selection Flow Diagram (PRISMA 2020) showing records identified and screened for searches in January 2022 and October 2022.

(SD = 2.8) and an average MMSE score of 18 (SD = 6.63), MoCA score of 23.22 (SD = 3.31); scores ≤26 indicate MCI or dementia. Participants' average disease duration was 5.2 years (SD = 3.3 years). Across the 16 studies, the average intervention length was 15 days (SD = 10.7) with 12 sessions (SD = 10.8) of TMS or sham/control stimulation. Two studies[25,26] included people with PD where cognitive impairment was interpreted from average MoCA scores ≤26, rather than from clinical diagnosis. The majority of studies (k = 12) stimulated the left hemisphere. One study included virtual reality training[27] as an additional intervention however, only data from the TMS-only and sham arms were included.

3.2 | Adverse events

Side effects are displayed in Table E1. In total, 66 adverse events were reported by five studies, of which 37 events were related to rTMS. Overall, stimulation was well tolerated with no reports of seizures or epilepsy. Side effects were generally transient and subsided after stimulation.

3.3 | Quality assessment

Of the 16 studies, 11 were rated as low risk, 3 showed some concerns and 2 were high risk. A summary of the quality assessment results is provided in Figure 3.[28–31] The main area of methodological concern identified in the quality assessment was the blinding of participants and assessors to the stimulation condition; 3 studies did not report participant blinding and in 1 study participants appeared to be aware of the intervention condition.[32] Only one study[32] reported blinding statistics. Two studies[26,33] reported that outcome assessors were aware of the intervention. One study[34] measured a variety of cognitive functions using the subsections from a single tool; the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS;[35]). This was deemed to be inappropriate as cognitive performance across various domains should not be interpreted from individual subsections of a test, rather the sum of the subsections should be interpreted as the overall measure of cognitive function.

3.4 | Global cognitive function

Of the 16 studies included in the review, post-intervention measures of global cognitive function, MMSE and MoCA raw means and SDs, were available for 8 studies. Within the 8 studies, there were 122 participants in the experimental group and 122 participants in the control group. The results of the meta-analysis showed a large effect size (g = 1.39), in which the experimental group showed significantly greater global cognitive function scores following the rTMS intervention, compared to the control group (95%CI, 0.34; 2.43; p = 0.017) as shown in Figure 4. This effect varied considerably

FIGURE 3 Quality assessment ratings expressed as percentage (%) risk of bias across domains (A) and individual studies (B). Weight = sample size.

across studies ($Q = 49.25$, $p < 0.0001$, $I^2 = 85.8\%$). No outliers were detected.

Full details of the following analyses are presented in the Supplementary Information. An influence analysis revealed two studies were contributing heavily to the effect[37,38] and following the removal of these studies, the effect remained large and significant ($p < 0.05$). Analysis of the baseline measures of global cognitive function showed no significant differences between the experimental and control groups. All subgroup analyses examining the effects of diagnosis, stimulation protocol and number of sessions and effect sizes for individual cognitive domains were not significant, indicating that rTMS improved all cognitive domains in MCI, AD and PD regardless of the stimulation type (rTMS or iTBS) or duration of the intervention.

3.5 | Publication bias

Publication bias was assessed for the eight studies included in the measure of global cognitive function. Visual inspection of the funnel plot in Figure 5 showed some asymmetry in the distribution of included

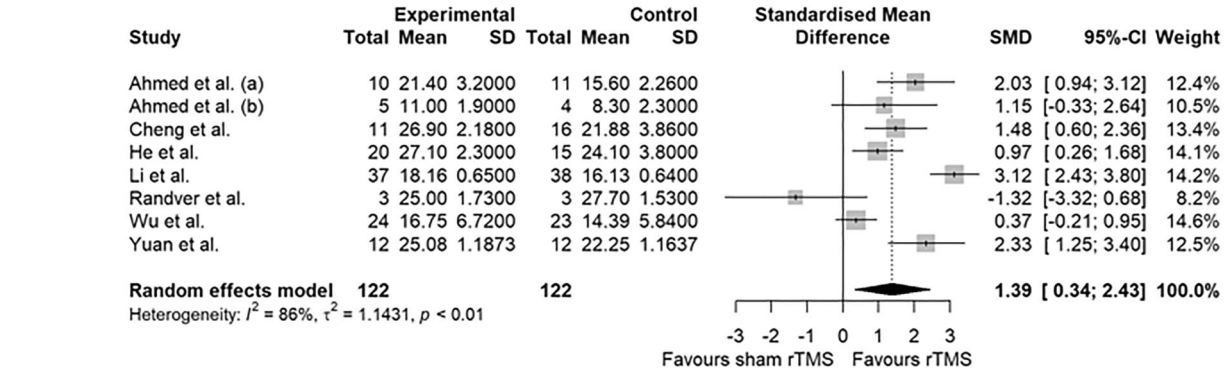

FIGURE 4 Forest plot showing individual and pooled repetitive transcranial magnetic stimulation (rTMS) effect sizes (Hedge's g) for global cognitive function. Ahmed et al.[36] described statistics from 2 groups (Ahmed et al., (A) mild-moderate AD; Ahmed et al., (B) severe AD) therefore, those data were included as multiple independent units in the meta-analysis. Abbreviations: SMD, standardized mean difference; SD, standard deviation.

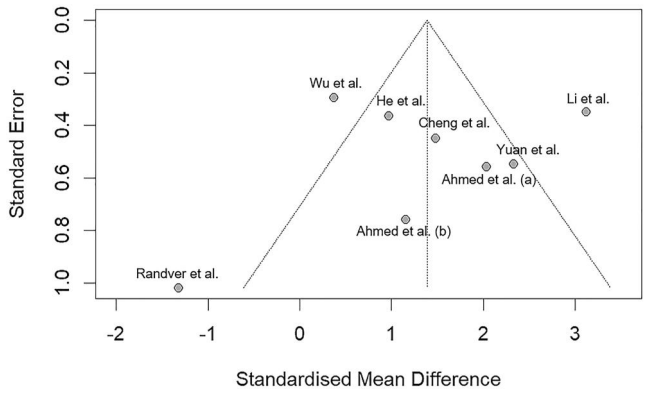

FIGURE 5 Funnel plot to examine evidence for publication bias. Asymmetry of points around the line by the standard error suggest the presence of publication bias. The vertical dotted line denotes the meta-analytic effect size for the effect of global cognitive function (g = 1.39).

studies. However, this appeared not to be due to small study effects as studies with smaller samples fell within the funnel and the study with the largest sample[37] showed the greatest effect. Therefore, the included studies appeared not to show evidence of publication bias.

4 | DISCUSSION

This systematic review and meta-analysis investigated the efficacy of high-frequency rTMS over the DLPFC on cognitive function in people with age-related neurodegenerative diseases. Overall, the results supported improved global cognitive function in the rTMS group compared to the control group following the intervention. Our results are consistent with previous systematic reviews indicating enhancement of cognitive function in MCI, AD and PD, following rTMS intervention.[3–6] The positive effect size we observed for global cognitive function (standardized mean difference, SMD = 1.39) was greater than for previous reviews (e.g.,[3]; SMD = 0.77;[6]; SMD = 0.83) that included studies with highly varied methods, stimulation locations and parameters (i.e. both excitatory and inhibitory). This suggests that high-frequency stimulation over the DLPFC may be a preferable protocol and site brain location to induce cognitive enhancement in people with neurodegenerative diseases.

Several of the included studies[32,34,37,39–41] combined rTMS with neuroimaging to further understand the potential mechanisms underlying the rTMS effects on cognition. Enhanced connectivity of multiple brain networks following rTMS has been correlated with improved cognitive function in participants with MCI.[32,34,41] Other neuromechanisms may include greater efficiency of neurotransmitter uptake in the hippocampus,[40] greater default mode network activation[39,42] and enhanced cortical plasticity[37] following rTMS. These findings suggest that high-frequency rTMS over the DLPFC promotes neuroplasticity by enhancing functional connectivity with distributed regions and networks involved in cognitive processing, therefore restoring or compensating for reduced function.

In comparison to other available treatments for people with age-related neurodegenerative diseases, rTMS appears to be a safe, targeted and effective treatment with very few reported side effects. Systematic review evidence of drug treatment efficacy has shown cholinesterase inhibitors have a small positive effect (MD = 0.23) on cognition in AD, and no effect on cognition in MCI.[43,44] Such drug treatments are also accompanied by a wide range of side effects.[45] A review of non-pharmacological interventions by Wang et al.[46] found large positive effects of cognitive stimulation (MD = 1.94), physical exercise (MD = 1.76), multi-domain interventions (MD = 1.66), music therapy (MD = 1.50) and cognitive training (MD = 1.07) on MMSE scores in people with MCI. In contrast to non-pharmacological interventions, rTMS directly targets neuronal activity in the DLPFC, influencing neurotransmitter uptake and connectivity across networks to support cognitive function, without the need for individuals to adapt, adhere and maintain significant lifestyle changes.

The effects of DLPFC stimulation lateralisation remain unclear. The majority of studies reviewed, stimulated the left hemisphere (12/16), but an insufficient number of studies stimulating the right or bilateral hemispheres were available to compare effect sizes. Few studies adequately justified why stimulation was targeted over the

left hemisphere rather than the right. One reason for stimulating the left hemisphere may be because cognitive control appears to be disproportionately dependent on the integrity of the left prefrontal cortex (PFC). Evidence from head injured patients has shown those with left PFC damage performed worse on measures of executive function compared to those with right PFC damage.[47,48] Furthermore, connectivity analysis has revealed the left DLPFC is an optimal region to stimulate in MCI.[49] Neuroimaging studies have demonstrated a leftward lateralisation in the prefrontal cortex is associated with performance on various cognitive functions including working memory and executive function[50] and a rightward lateralisation for spatial attention.[51] As the effects of rTMS can be observed in distal, connected regions to the DLPFC,[41] it is therefore plausible that left hemisphere stimulation could cause activity changes in the right hemisphere and vice versa. Future studies could identify how DLPFC-targeted rTMS over a single hemisphere affects neuroplasticity in the contralateral hemisphere providing insight into laterality effects.

In this systematic review we aimed to identify factors which may influence the efficacy of this treatment intervention. Firstly, it is worth noting that the MCI group included different diagnoses such as amnestic MCI and PD-related MCI. Whilst these diagnoses have different aetiologies, the intervention was designed to target the cognitive symptoms only therefore we grouped these participants into MCI to represent an earlier or milder stage of cognitive decline. The lack of apparent difference in global cognitive function between MCI and AD following rTMS suggest both groups benefited from the intervention. At baseline, global cognitive function scores showed greater cognitive decline in AD (M = 16.4, SD = 2.44) than MCI (M = 23.7, SD = 2.68). These results suggest that rTMS can improve cognition at more progressed stages of neurodegeneration such as AD. Traditional rTMS and iTBS protocols also showed no difference in efficacy, suggesting that they are both effective methods of inducing cognitive and neuroplasticity changes in individuals with neurodegenerative diseases. However future studies should consider administering iTBS due to the shorter stimulation time and fewer adverse effects reported compared to traditional rTMS.[8]

4.1 | Methodological considerations

Various methodological issues were identified within the included studies from which recommendations for future research can be ascertained. Firstly, all studies dosed DLPFC stimulation by obtaining a measure of individual resting or active motor threshold (RMT/AMT) to determine the intensity of magnetic field strength to administer. Whilst MT dosimetry is common practise in TMS research, some studies have reported no correlation between motor threshold and cortical sensitivity in non-motor brain areas[52] and high inter-individual variability in the electrical fields between the motor cortex and prefrontal cortex.[53,54] A promising new approach to dosing TMS intensity is personalized electric field modelling,[53] which may produce a more accurate measure of individualised stimulation intensity to administer to the DLPFC, and may be implemented by future TMS studies.

A further methodological issue was the lack of an appropriate measure of global cognitive function. Studies either used an inappropriate tool such as the Dementia Rating Scale 2 (DRS-2;[55]) which includes measures of home and personal life or studies produced a composite score as a measure of global cognitive function by averaging the results from test of individual cognitive domains. Additionally, the MoCA and MMSE were frequently used as screening tools for inclusion or as baseline measures of demographic information, but some studies did not complete a post-intervention measure using these tools. Furthermore, some studies were fairly limited as global cognitive function was the only reported measure of cognitive function. Future studies should report the MMSE or MoCA before and after the stimulation period to assess the change in cognitive function and use multiple tests of individual cognitive domains to more broadly assess the impact of rTMS on cognition.

4.2 | Strengths and limitations

Strengths of the current review include the use of stringent inclusion/exclusion criteria, the high quality of included studies and the examination of several possible moderators of the effect. However, whilst the overall effect size was significant and large, the results could be constrained by various limitations. Firstly, the number of included studies and number of participants was small so the results should be interpreted with caution. Sixteen studies were included in the systematic review but only half of these were included in the estimate of the effect size for global cognitive function due to issues with the outcome measure used or lack of access to raw scores. A further limitation was the high between-study heterogeneity evident in the analysis. This may have been due to differences between the MMSE and MoCA measurements and heterogeneity in the study design including the intervention duration, number of sessions, stimulation protocol, localisation method, and outcome measures. Further studies with large sample sizes are required to ascertain whether this effect is reliable.

5 | CONCLUSIONS

This review demonstrated that high frequency rTMS targeting the DLPFC has a positive effect on global cognitive function in people with neurodegenerative diseases. The between-study heterogeneity (mainly driven by two papers) and small number of studies included suggest these results should be interpreted with caution. This review specifically highlights the need for further high-quality, blinded rTMS intervention studies on larger samples of neurodegenerative populations that also provide evidence of longitudinal effects. Further recommendations include a focus of stimulation on the left DLPFC, utilizing more robust within subject intensity scaling for iTBS, and more specific cognitive measures for accurate assessments of cognitive improvements.

AUTHOR CONTRIBUTIONS

Author contributions are as follows: Amy Miller and Melanie Rose Burke conceived the idea, performed the literature screening and quality analysis. Amy Miller conducted the literature search, completed the statistical analyses and the manuscript draft. Alisha A. Juma assisted with the literature screening. Melanie Rose Burke, Richard J. Allen and Rumana Chowdhury revised the manuscript.

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CONFLICT OF INTEREST STATEMENT

No competing interests were identified within the team of authors.

DATA AVAILABILITY STATEMENT

Data will be made publicly available following acceptance for publication.

ORCID

Amy Miller https://orcid.org/0000-0002-8549-5158
Richard J. Allen https://orcid.org/0000-0002-1887-3016
Melanie Rose Burke https://orcid.org/0000-0002-2561-053X

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX A

TABLE A1 Cognitive tests included in the meta-analyses.

Cognitive domain	Test	Study/studies
Global cognitive function	MMSE	Ahmed et al. (2012) (a), Ahmed et al. (2012) (b), Li et al. (2021), Wu et al. (2022)
	MoCA	Cheng et al. (2022), He et al. (2021), Randver et al. (2019), Yuan et al. (2021)
Complex executive function	Symbol digits modalities test	Buard et al. (2018), Wu et al. (2022)
	Berg's card sorting	Hill et al. (2020)
	WAIS-III coding	Randver et al. (2019)
Attention	Trail making task A	Randver et al. (2019), Sedlácková et al. (2009)
	Brief Test of Attention	Buard et al. (2018)
	Digit span forwards	Wu et al. (2022)
Working memory	AVLT immediate	Cui et al. (2019), Wu et al. (2022)
	Digit span backwards	Randver et al. (2019)
	CVLT short delay	Buard et al. (2018)
	WAIS-III Sequencing	Drumond Marra et al. (2015)
	2-Back task	Hill et al. (2020)
Verbal fluency	Boston naming test	Buard et al. (2018), Wu et al. (2022)
	Verbal fluency test	Drumond Marra et al. (2015), Sedlácková et al. (2009)
Inhibition	DKEFS colour-word	Buard et al. (2018)
	Stroop colour-word	Wu et al. (2022)
Task shifting	Trail making task B	Buard et al. (2018), Drumond Marra et al. (2015), Randver et al. (2019), Sedlácková et al. (2009)

Note: Cognitive and neuropsychological assessment tools selected for each study and entered into the meta-analyses.

Abbreviations: AVLT, Auditory Verbal Learning Test; CVLT, California Verbal Learning Test; DKEFS, Delis–Kaplan Executive Function System; MMSE, Mini Mental State Exam; MoCA, Montreal Cognitive Assessment; WAIS-III, Wechsler Adult Intelligence Scale 3.

APPENDIX B

TABLE B1 Subject demographic characteristics.

First author, year	*N*	Age (years)	% female	Diagnosis	Diagnostic criteria	Disease duration (years)	Years of education	MoCA	MMSE	LED (mg/day)
Ahmed et al. (2012)	30	67.10 ± 5.40	66.66	AD	NINCDS-ADRDA	4.15 ± 2.4	NR	NR	16.9 ± 2.75	NR
Buard et al. (2018)	46	68.50 ± 7.60	77.00	PD-MCI	MDS Taskforce criteria	NR	15.4 ± 3.0	25.0 ± 3.2	9.2 ± 1.7	594.9 ± 414.7
Cheng et al. (2022)	27	72.80 ± 6.00	37.00	PD-MCI	UKPDSBB	NR	NR	23.1 ± 3.1	NR	627.30 ± 298.65
Cui et al. (2019)	21	73.95 ± 8.73	61.90	aMCI	NIA-AA criteria for MCI	NR	12.47 ± 3.91	NR	27.14 ± 2.39	NR

TABLE B1 (Continued)

First author, year	N	Age (years)	% female	Diagnosis	Diagnostic criteria	Disease duration (years)	Years of education	MoCA	MMSE	LED (mg/day)
Drumond Marra et al. (2015)	34	65.15 ± 3.80	64.20	MCI	PDC	NR	13.75 ± 4.55	24.35 ± 2.05	NR	NR
Esposito et al., 2022	27	67.85 ± 9.28	48.15	MCI	NIA-AA criteria for MCI	NR	NR	NR	NR	NR
He et al. (2021)	35	72.40 ± 6.60	34.30	PD-MCI	UKPDSBB	2.6 ± 1.3	NR	24.7 ± 3.2	NR	626.15 ± 309.35
Hill et al. (2020)	14	71.07 ± 5.11	28.60	PD	QSBB	4.86 ± 4.85	NR	25.93 ± 2.70	NR	NR
Lang et al. (2020)	41	68.60 ± 8.35	34.10	PD-MCI	UKPDSBB	5.83 ± 4.4	13.3 ± 2.45	22.93 ± 4.2	NR	921.03 ± 459.2
Li et al. (2021)	75	65.28 ± 8.18	41.33	AD	DSM-V	3.84 ± 1.69	6.2 ± 3.86	NR	16.05 ± 0.69	NR
Padala et al. (2018)	9	65.60 ± 9.30	11.00	MCI	PDC	NR	NR	NR	NR	NR
Randver et al. (2019)	6	61.33 ± 11.89	50.00	PD-MCI	QSBB	5.16 ± 1.72	13.16 ± 2.86	24.65 ± 2.9	NR	400.0 ± 109.55
Sedlácková et al. (2009)	10	63.70 ± 6.70	10.00	PD	UKPDSBB	7.8 ± 6.5	13.5 ± 2.4	NR	NR	802.5 ± 325.5
Trung et al. (2019)	28	69.30 ± 6.25	32.14	PD-MCI	UKPDSBB	8.32 ± 4.85	15.7 ± 3.15	24.85 ± 2.5	NR	922.5 ± 646
Wu et al. (2022)	47	66.40 ± 8.12	34.04	AD	NINCDS-ADRDA	NR	9.62 ± 4.37	14.3 ± 5.53	21.12 ± 4.67	NR
Yuan et al. (2021)	24	64.88 ± 4.83	54.17	aMCI	PDC	3.88 ± 2.25	11.58 ± 2.26	22.42 ± 1.20	NR	NR

Note: Data in columns 3, 7, 8, 9 and 10 are expressed as mean ± SD.

Abbreviations: AD, Alzheimer's Disease; aMCI, Amnestic Mild Cognitive Impairment; DSM-V, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; LED, Levodopa Equivalent Dose; MCI, Mild Cognitive Impairment; MDS, The Movement Disorder Society PD-MCI Task Force diagnostic criteria for PD-MCI; MoCA, Montreal Cognitive Assessment; *N*, sample size; NIA-AA, National Institute on Aging-Alzheimer's Association criteria for MCI due to AD; NINCDS-ADRADA, National Institute of Neurological Communicative Disorders and Stroke/Alzheimer disease and Related Disorders Association; NR, not reported; PD, Parkinson's Disease; PDC, Petersen's Diagnostic Criteria; PD-MCI, Parkinson's Disease Mild Cognitive Impairment; QSBB, Queen's Square Brain Bank Criteria, UKPDSBB, UK Parkinson's Disease Society Brain Bank Diagnostic Criteria.

APPENDIX C

TABLE C1 Stimulation protocol.

First author, year	Stimulation	AMT/ RMT	% threshold	Frequency (Hz)	No. pulses/ session	No. sessions	Duration (days)	Post-intervention follow-up
Ahmed et al. (2012)	rTMS	RMT	90	19	2000/ hemisphere	5	5	1 month & 3 months
Buard et al. (2018)	rTMS	RMT	90	20	750/hemisphere	10	14	/
Cheng et al. (2022)	iTBS	RMT	90	50	600	10	14	3 months
Cui et al. (2019)	rTMS	RMT	90	10	1500	10	14	2 months
Drumond Marra et al. (2015)	rTMS	MT	110	10	2000	10	14	40 days
Esposito et al. (2022)	rTMS	RMT	80	10	2000	20	28	6 months

(Continues)

TABLE C1 (Continued)

First author, year	Stimulation	AMT/ RMT	% threshold	Frequency (Hz)	No. pulses/ session	No. sessions	Duration (days)	Post-intervention follow-up
He et al. (2021)	iTBS	RMT	100	50	NR	10	14	3 months
Hill et al. (2020)	iTBS	AMT	80	50	600	2	2	/
Lang et al. (2020)	iTBS	AMT	80	50	2000	6	7	1 month
Li et al. (2021)	rTMS	RMT	100	20	2000	30	42	3 months
Padala et al. (2018)	rTMS	RMT	120	10	3000	10	14	/
Randver et al., 2019	rTMS	RMT	80	10	500	6	21	/
Sedlácková et al. (2009)	rTMS	RMT	100	10	1350	1	1	/
Trung et al. (2019)	iTBS	AMT	80	50	600	6	7	1 month
Wu et al. (2022)	iTBS	RMT	70	50	600 (1800/day)	42	14	10 weeks
Yuan et al. (2021)	rTMS	RMT	80	10	400	20	28	/

Abbreviations: /, not applicable; AMT, active motor threshold; Duration (days), intervention length; iTBS, intermittent theta burst stimulation; NR, not reported; RMT, resting motor threshold; rTMS, repetitive transcranial magnetic stimulation.

APPENDIX D

TABLE D1 Stimulation protocol continued.

First author, year	Study design	Lateralisation	Location method	Neuronavigation	Atlas or 10-20 electrode	Group coordinates (x, y, z)	Sham/ Control	Sham Method
Ahmed et al. (2012)	BS	B	NR	N	/	/	S	Coil tilted away from head
Buard et al. (2018)	BS	B	Individual functional coordinates	Y	/	NR	S	Placebo coil (10–20 mA)
Cheng et al. (2022)	BS	L	10-20 electrode placement system	N	F3 electrode	/	S	Placebo coil (<5% power)
Cui et al. (2019)	BS	R	Head measurement	N	/	/	S	Coil tilted away from head
Drumond Marra et al. (2015)	BS	L	Head measurement	N	/	/	S	Placebo coil (<10% power)
Esposito et al. (2022)	BS	B	Head measurement	N	/	/	S	Placebo coil (<5% power)
He et al. (2021)	BS	L	10-20 electrode placement system	N	F3 electrode	/	S	Placebo coil (<5% power)
Hill et al. (2020)	C	L	10-20 electrode placement system	N	F3 electrode	/	S	NR
Lang et al. (2020)	BS	L	Group coordinates past research	Y	MNI	[−48, 26, 36]	S	Placebo coil (<5% power)
Li et al. (2021)	BS	L	Group coordinates past research	Y	MNI	[−44, 40, 29]	S	Placebo coil (0% power)
Padala et al. (2018)	BS	L	Head measurement	N	/	/	S	Placebo coil (0% power)
Randver et al. (2019)	BS	L	NR	Y	NR	/	S	Coil tilted away from head

TABLE D1 (Continued)

First author, year	Study design	Lateralisation	Location method	Neuronavigation	Atlas or 10-20 electrode	Group coordinates (x, y, z)	Sham/ Control	Sham Method
Sedlácková et al. (2009)	C	L	Frameless sterotaxy	N	/	[−40, 32, 30]	C	Left OCC stimuated
Trung et al. (2019)	BS	L	Group coordinates past research	Y	MNI	[−48, 36, 26]	S	Placebo coil (0% power)
Wu et al. (2022)	BS	L	Group coordinates past research	Y	MNI	[−38 44 26]	S	Placebo coil (<5% power)
Yuan et al. (2021)	BS	L	Head measurement	N	/	/	S	Coil tilted away from head

Abbreviations: /, not applicable; 10-20 system, International 10-20 system for electrode placement; B, bilateral; BS, between-subjects; C, control stimulation; C, crossover; L, left hemisphere; MNI, Montreal Neurological Institute and Hospital coordinate system; NR, not reported; OCC = occipital cortex; R, right hemisphere; S, sham stimulation; WS, within-subjects.

APPENDIX E

TABLE E1 Reported adverse effects.

Adverse effects	Active TMS	Sham/control
Scalp pain	15	4
Headache	11	5
Discomfort over stimulation site	12	0
Discomfort over eye	3	0
Eyelid/facial twitching	3	0
Mild blurry vision/dizziness	2	0
Concentration difficulties	1	0
Other	2	2
Unrelated (during testing)	2	1
Unrelated (outside testing)	3	0
Total	54	12

Note: Adverse effects are symptoms or side-effects reported during the stimulation session or intervention period. Other: Tinnitus, burning scalp, tooth discomfort, insomnia. Unrelated (occurred during testing): cervical pain, fainting due to dehydration, medication-induced hallucinations. Unrelated (occurred outside the lab): hospitalised due to TIA, hospitalised due to kidney stones, burst vein in eye, mild-flu.