REVIEW ARTICLE

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Effects of repetitive transcranial magnetic stimulation on improvement of cognition in elderly patients with cognitive impairment: a systematic review and meta-analysis

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Objective: This systematic review and meta-analysis aimed to examine the effects of repetitive transcranial magnetic stimulation (rTMS) on cognitive function in older patients with cognitive impairment.

Methods: A literature search was performed for articles published in English using the 10 databases (MEDLINE, EMBASE, PsycINFO, INSPEC, the Cumulative Index to Nursing and Allied Health Literature Plus, AMED, Biological Sciences, ClinicalTrials.gov, the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews) from their inception to May 2016. The primary outcome was cognitive function as measured by the Mini-Mental State Examination or the Alzheimer's Disease Assessment Scale-cognitive subscale.

Results: Seven RCTs were included in the meta-analysis, with a sample of 107 active and 87 sham rTMS. Active rTMS was found to be more effective in improving cognition (Hedges' g = 0.48; 95% confidence interval 0.12 to 0.84).

Conclusions: High-frequency rTMS showed a benefit on cognition amongst older patients with mild to moderate Alzheimer's disease. rTMS was shown to have great potential as a safe and well-tolerated alternative intervention for cognition.

Key words: cognitive impairment; dementia; meta-analysis; systematic review; transcranial magnetic stimulation
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Introduction

The significant growth in the population with dementia has been highlighted as a public health priority (World Health Organization, 2012; Prince *et al.*, 2016). Cognitive impairment is the core symptom of dementia, and it determines the loss of independent functioning. Medications such as acetylcholinesterase inhibitors and *N*-methyl-D-aspartate receptor antagonists may improve cognition. Unfortunately, these drugs have only limited and transient effects and do not modify the natural course of the illness (O'Brien *et al.*, 2011). Some patients cannot tolerate or are not suited for these medications because of the side effects of medication or physical comorbidities. Despite recent advancements in the understanding of the pathological mechanisms, treatment options are still limited.

Transcranial magnetic stimulation (TMS) is a non-invasive intervention used to stimulate the brain by inducing electrical current via electromagnetic induction (Wassermann and Lisanby, 2001). Repetitive transcranial magnetic stimulation (rTMS) delivers a train of pulses at the same intensity over a period of time at a particular region of the brain. It either stimulates or suppresses neuronal activity,

depending on the frequency and the inter-train interval between pulses. The effect of rTMS is mediated by three possible mechanisms: direct targeting, distance effect and distributed modulation (Rotenberg *et al.*, 2014). Most rTMS studies have used direct targeting, which modulates the neuronal activities of the targeted dysfunctional area. Distance effect targets a neural area functionally linked to the area of dysfunction, whilst distributed modulation modulates brain activities via a specific brain network that is believed to provide effects beyond the stimulation duration by means of long-term potentiation and depression of synaptic processes (Muller *et al.*, 2014). rTMS has been widely studied in patients with various neuropsychiatric illnesses such as depression, epilepsy and chronic pain (Najib *et al.*, 2011) and is generally considered safe in healthy individuals (Rossi *et al.*, 2009).

In recent years, rTMS has been considered an alternative for the improvement of cognition in older patients with cognitive impairment (Liao *et al.*, 2015). With the changes in cortical plasticity, TMS enhances a specific type of cognition or skill by targeting the cortical area of interest. Recent studies have reported the beneficial effects of TMS on improving cognition with the application of high-frequency rTMS over the dorsolateral prefrontal cortex (DLPFC) in patients with dementia (Cotelli *et al.*, 2006; Cotelli *et al.*, 2008; Ahmed *et al.*, 2012; Haffen *et al.*, 2012; Rabey *et al.*, 2013). However, the relationships between the effect of rTMS and factors such as subject characteristics, target site, parameter setting, concurrent medication and cognitive training are largely unknown.

To our knowledge, only four recent review articles have been published that focused on the effects of rTMS on cognition in older patients with cognitive impairment (Elder and Taylor, 2014; Nardone *et al.*, 2014; Liao *et al.*, 2015; Pallanti and Marras, 2015) and only one was a meta-analysis (Liao *et al.*, 2015). Three reviews focused on patients with Alzheimer's disease (AD) (Haffen *et al.*, 2012; Rabey *et al.*, 2013; Elder and Taylor, 2014), and only one included all types of cognitive impairment (Cotelli *et al.*, 2008). The results of these reviews were contradictory. Nardone *et al.* (2014) and Liao *et al.* (2015) suggested that rTMS enhanced several cognitive functions in patients with AD. Elder and Taylor (2014) suggested a trend of improvement across a wide range of cognitive outcome measures after rTMS. Pallanti and Marras (2015) stated that the therapeutic effects of rTMS on cognitive deficits in AD had yet to be established.

The aforementioned findings highlight the significance of TMS as a treatment for dementia. However, the quality of these reviews is limited for several reasons. First, the searches have relied upon limited databases and search terms, which were not comprehensive and might have omitted relevant studies. Second, because most studies included only patients with AD, the efficacy of TMS in improving cognition amongst older patients with a milder form of cognitive impairment could not be stated. Third, none of these reviews included a clear and detailed overview of TMS parameters, and this, in turn, might limit the applicability of the findings. Furthermore, new randomised controlled trials (RCTs) have been published since the last review of Liao *et al.* (2015). Therefore, a comprehensive systematic review with meta-analysis, which includes trials that involve all types of cognitive impairment, a criterion-based assessment of the risk of bias and the new trials, is prudent to provide up-to-date evidence on the effects of rTMS on cognitive function in older patients with cognitive impairment.

Methods

Search strategy

A literature search was performed for articles published in English using the following databases: MEDLINE, EMBASE, PsycINFO, INSPEC, the Cumulative Index to Nursing and Allied Health Literature Plus, AMED, Biological Sciences, ClinicalTrials.gov, the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews, from their inception to May 2016. The search keywords are listed in Appendix 1.

Two authors (C. C. P. W. and W. C. S. M.) evaluated the titles and abstracts independently to determine whether the studies fulfilled the inclusion criteria. The reference lists of all included articles were reviewed for any unidentified studies. All RCTs, with both parallel and crossover designs, were included regardless of blinding or publication status (i.e. full papers or abstracts). Case studies, case series, open trials, ongoing studies, review articles and animal studies were excluded. If more than one paper had been published on the same study population, the most recent and informative one was included. Any disagreements were resolved by discussion or by an independent party (C. W. C.). The study was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Moher *et al.*, 2009).

Eligibility criteria

Studies were included if they fulfilled the criteria: (i) older adults were aged 60 years or older with a diagnosis of dementia or mild cognitive impairment (MCI); (ii) rTMS was used alone or in conjunction with other treatments (e.g. medication or cognitive training); (iii) sham TMS was applied; and (iv) the results of cognitive outcome measures of either the Mini-Mental State Examination (MMSE) or the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) were reported or provided upon request.

Data extraction

Two authors (C. C. P. W. and W. C. S. M.) independently extracted the data using a standardised data form and cross-checked the results for accuracy. Disagreements regarding data extraction were resolved by consensus between the authors or by an independent party (C. W. C.). For each trial, we extracted the relevant information to summarise the participant characteristics and psychiatric histories. The treatment procedures (TMS target, targeting method, intensity, frequency, number of sessions, total pulses per session, type of coil and sham stimulation), outcome measures, follow-up examinations and adverse effects were also recorded. For outcome data, the cognitive scores based on the MMSE or ADAS-cog were retrieved from the articles. If data were reported from multiple time points, those from immediately after the intervention were used. The corresponding authors of the studies were contacted for clarification or missing information.

Quality assessment

The methodological qualities of the trials included in the meta-analysis were examined by the two reviewers according to the six domains in the Cochrane Collaboration's tool for assessing the risk of bias (Higgins and Green, 2011): (i) sequence generation; (ii) allocation concealment; (iii) blinding of the participants; (iv) blinding of the assessors; (v) method of addressing incomplete outcome data; and (vi) selective reporting. The methodological quality was classified as a low, high or uncertain risk of bias in each domain.

Data synthesis and analysis

To examine the treatment effect, we carried out a meta-analysis by pooling the available data from the RCTs. The design of an RCT usually involves a parallel or crossover control group. Whilst the crossover design has the added advantage of statistical efficiency, the carryover effect is a concern (Mills *et al.*, 2009). Carryover occurs when the treatment in the first period has an effect that carries over to the second period. The residual effect could be theoretically reduced by a washout period, but it is difficult to determine an adequate washout period for rTMS, for which the treatment effect may range from hours to weeks. In view of this, we only synthesised the data from RCTs with parallel designs to ensure that the results of the meta-analysis truly demonstrated the effects of active TMS over sham.

For the outcome variables as measured by the MMSE and ADAS-cog, a pooled effect size was calculated using a random effects model and presented as the standardised mean difference (SMD) with 95% confidence intervals (CIs). We used random effects model because the estimates of the treatment effect were assumed to vary amongst trials because of real differences and sampling variability (Riley *et al.*, 2011). In addition, Hedges' g was given instead of Cohen's d to adjust for the problem of a small sample size and nonparametric distributions of outcomes. Forest plots were generated with Review Manager (RevMan v5.3; Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark). Heterogeneity between trials was assessed with the I^2, and a value of $>50\%$ was considered substantial heterogeneity (Higgins *et al.*, 2003). Database for the meta-analysis has been made publicly available via the Open Science Framework (https://osf.io/2qczw/).

Subgroup analysis

Subgroup analyses were performed to explore the potential sources of heterogeneity and effect modifiers. Heterogeneity amongst participants could be related to cognition-enhancing drugs, such as acetylcholinesterase inhibitor and memantine. Heterogeneity in treatments could be related to the TMS target site and concurrent cognitive training. Therefore, we used stratified meta-analyses to assess the effects of concurrent cognition-enhancing drugs (with cognition-enhancing drugs versus without cognition-enhancing drugs), target sites (single site

vs. multiple sites) and concurrent cognitive training (with training versus without training).

Results

Identification and selection of studies

The initial search yielded 12,310 results. After irrelevancies and duplicates were removed, the full text of 151 articles was examined. Amongst these, 124 reviews, commentaries, non-clinical trials or duplicated studies were excluded. We also excluded 14 case reports, case series or open-label trials. Finally, 13 articles (10 full text and three abstracts) were identified (Figure 1). Of these studies, nine were RCTs with a parallel control design and four had a crossover design. The data from seven parallel-group RCTs with complete outcome data (Cotelli *et al.*, 2011; Ahmed *et al.*, 2012; Brem *et al.*, 2013; Rabey *et al.*, 2013; Drumond Marra *et al.*, 2015; Wu *et al.*, 2015; Lee *et al.*, 2016) were synthesised in the meta-analysis.

Description of studies

Participants. Overall, 326 participants (mean age 65.2 to 76.3 years) who met the eligibility criteria

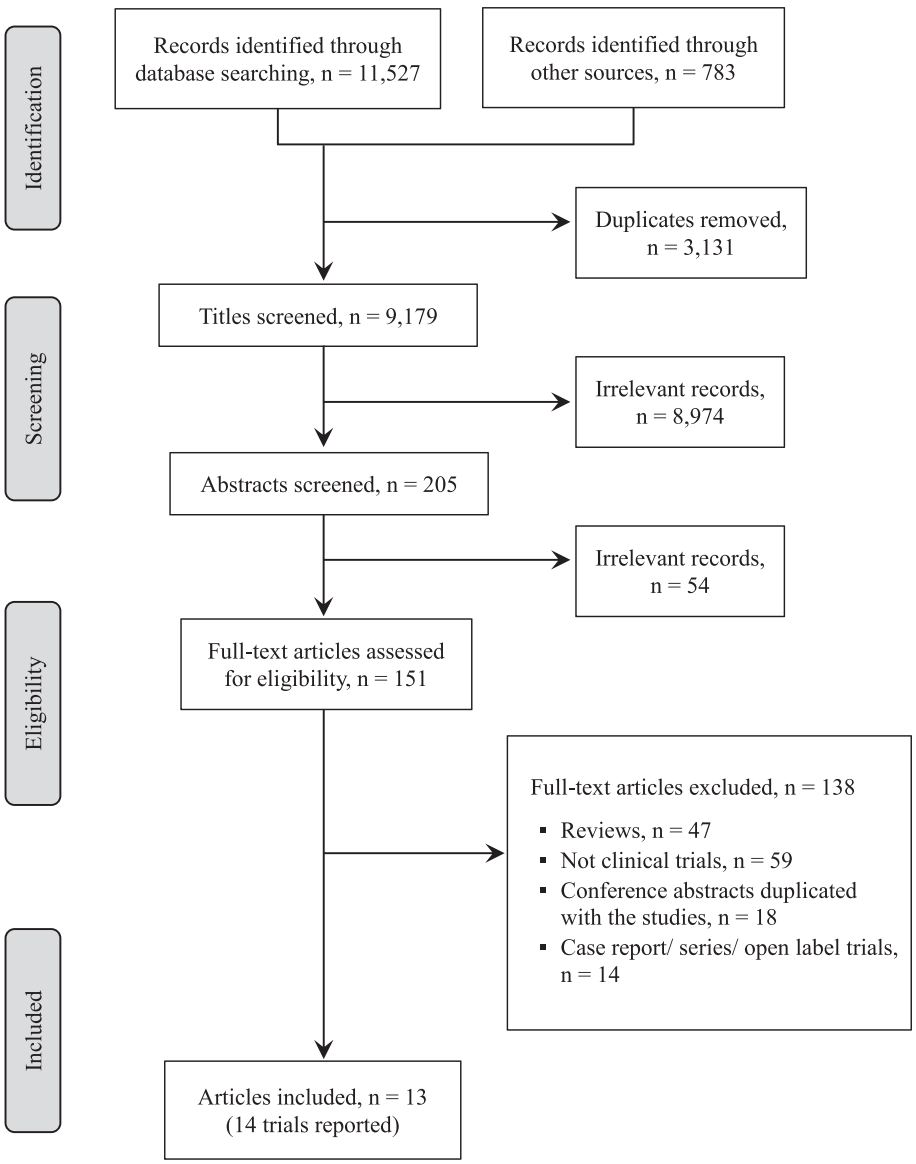

Figure 1 Flowchart of systematic review.

were included. Nine studies reported gender information with a female-to-male ratio of 1.39:1. Most participants had mild to moderate AD, with mean MMSE scores ranging from 13.8 to 26.9. Only two studies targeted subjects with MCI (Turriziani *et al.*, 2012; Drumond Marra *et al.*, 2015). In three studies, no concomitant psychotropic medication was used (Ahmed *et al.*, 2012; Turriziani *et al.*, 2012; Drumond Marra *et al.*, 2015); in seven studies, the participants took cognition-enhancing drugs for dementia (Cotelli *et al.*, 2008; Cotelli *et al.*, 2011; Brem *et al.*, 2013; Rabey *et al.*, 2013; Ash *et al.*, 2014; Rutherford *et al.*, 2015; Lee *et al.*, 2016); and in one study, risperidone was used to control behavioural and psychological symptoms of dementia (Wu *et al.*, 2015) (Table 1).

Transcranial magnetic stimulation parameters. Most studies used a figure-of-eight coil, one study used an H-coil (Coppi *et al.*, 2015) and three studies did not report which type of coil was used (Ash *et al.*, 2014; Rutherford *et al.*, 2015; Lee *et al.*, 2016). All studies involved the frontal/prefrontal region as the TMS target sites: seven studies used the DLPFC as the sole target (either unilaterally or bilaterally) (Cotelli *et al.*, 2008; Cotelli *et al.*, 2011; Ahmed *et al.*, 2012; Turriziani *et al.*, 2012; Drumond Marra *et al.*, 2015; Rutherford *et al.*, 2015; Wu *et al.*, 2015); three studies targeted the same combination of sites involving Broca's area, Wernicke's area, the DLPFC and the parietal cortex (Brem *et al.*, 2013; Rabey *et al.*, 2013; Lee *et al.*, 2016). Coppi *et al.* (2015) and Ash *et al.* (2014) reported using the fronto-parietal–temporal lobes and prefrontal areas, respectively, without specifying the exact target site. Regarding the targeting method, six studies used magnetic resonance imaging-guided navigation (Cotelli *et al.*, 2008; Cotelli *et al.*, 2011; Turriziani *et al.*, 2012; Rabey *et al.*, 2013; Anderkova *et al.*, 2015; Lee *et al.*, 2016) and three studies used a non-imaging-based technique (Ahmed *et al.*, 2012; Drumond Marra *et al.*, 2015; Rutherford *et al.*, 2015), either a 5-cm rule to locate the DLPFC (Pascual-Leone *et al.*, 1996) or an electroencephalography 10–20 system to locate the brain area.

Turriziani *et al.* (2012) used low-frequency rTMS (1 Hz), and two other studies involved low-frequency rTMS (Ahmed *et al.*, 2012; Ash *et al.*, 2014). All the other studies applied high-frequency pulses (10 or 20 Hz). All intensities listed were the resting motor threshold ranging from 80% to 120%. Two studies applied different intensities in different areas (Rabey *et al.*, 2013; Lee *et al.*, 2016). Continuous pulses were used in all studies, with different interval lengths between trains. Most studies used 1,200 to 2,250 pulses per session, except for Coppi *et al.* (2015), who used 840 pulses with an H-coil, and Rutherford *et al.* (2015), who used 4000 pulses per session (Table 2).

Transcranial magnetic stimulation sessions. The number of TMS sessions ranged from 1 to 30, and most studies included five sessions per week. In addition to the assessments before and immediately after the intervention, eight studies also assessed the effects of TMS at follow-up periods from 1 to 4.5 months. Four studies examined the effects of TMS combined with cognitive training; three used similar systems (NeuroAD System, Neuronix Ltd., Yokneam, Israel) to combine TMS and cognitive training in an interlaced fashion (Brem *et al.*, 2013; Rabey *et al.*, 2013; Lee *et al.*, 2016); and one instructed its participants to perform cognitive training between the pulse trains (Rutherford *et al.*, 2015) (Table 2).

Adverse effects. Four studies reported adverse effects of rTMS, including headache, cervical and scalp pain, burning scalp and non-specific minor discomfort (Anderkova *et al.*, 2015; Drumond Marra *et al.*, 2015; Rutherford *et al.*, 2015; Wu *et al.*, 2015). Wu *et al.* (2015) reported one participant with mild extrapyramidal reactions. Five studies found no adverse effects (Cotelli *et al.*, 2008; Cotelli *et al.*, 2011; Ahmed *et al.*, 2012; Rabey *et al.*, 2013; Lee *et al.*, 2016), and the remaining provided no information on adverse effects (Table 2).

Quality assessment

Table 3 lists the methodological qualities of the seven trials included in the meta-analysis. There was limited information to assess the risk of bias of Brem *et al.* (2013) because it was published as an abstract. Although all included trials were reported to be randomised, only two studies reported adequate sequence randomisation with the use of a random number generator or a random number table (Drumond Marra *et al.*, 2015; Wu *et al.*, 2015). Only one study had adequate reporting of allocation concealment (Drumond Marra *et al.*, 2015). All studies except for Brem *et al.* (2013) were reported to have blinded both participants and assessors. All studies except two (Brem *et al.*, 2013; Drumond Marra

Table 1 Demographic characteristics of the included studies

Study	Study design	Participants (*n*)		Gender (M/F)	Mean age (years)	Diagnosis	Medications	MMSE[g]/MoCA[h]/ADAS-cog[i] (mean ± SD)			
								Active rTMS		Sham rTMS	
		Active	Sham					Before	After	Before	After
Cotelli *et al.* (2008)	Crossover	24 in total		N/A	76.3	AD	Cholinesterase inhibitor	17.0 ± 2.2[g]		Self-control study	
Cotelli *et al.* (2011)	Parallel	5	5	2/8	72.8	Probable moderate AD	Cholinesterase inhibitor	16.2 ± 2.7[g]	16.0 ± 3.3	16.0 ± 2.0	16.0 ± 2.1
Ahmed *et al.* (2012)[a]	Parallel	30	15	16/29	68.4	Probable AD	No	13.7 ± 3.8[g]	16.1 ± 3.3	13.9 ± 3.9	13.7 ± 2.5
Turriziani *et al.* (2012)[b]	Crossover	8 in total		6/2	66.4	MCI	No	26.9 ± 2.0[g]		Self-control study	
Brem *et al.* (2013)	Parallel	6	6	6/6	70.1	Mild to moderate AD	Yes	21.0 ± 3.0[g]	N/A	21.7 ± 3.0	N/A
Rabey *et al.* (2013)	Parallel	7	8	10/5	74.1	Mild to moderate AD	Cholinesterase inhibitor	22.0 ± 1.6[g]	N/A	22.0 ± 1.4	N/A
Ash *et al.* (2014)[c]	Parallel	40 in total		N/A	N/A	Mild to moderate AD	AD medication	N/A	N/A	N/A	N/A
Anderkova *et al.* (2015)[d]	Crossover	20 in total		9/11	73	MCI or AD	N/A	24.0 ± 3.4[g]		Self-control study	
Coppi *et al.* (2015)[e]	Parallel	30 in total		N/A	70.2	AD	N/A	17.3 ± 5.8[g]	N/A	17.3 ± 5.8	N/A
Drumond Marra *et al.* (2015)	Parallel	15	19	12/22	65.2	MCI	No	27.7 ± 1.6[g]	27.9 ± 1.2	28.0 ± 1.1	27.7 ± 1.9
Rutherford *et al.* (2015)[f]	Crossover	10 in total		N/A	N/A	Probable AD	AD medication	5–26[h,j]	N/A	5–26	N/A
Wu *et al.* (2015)	Parallel	26	26	21/31	71.7	Probable AD	Risperidone	30.1 ± 6.1[i]	24.2 ± 5.2	29.3 ± 6.3	27.7 ± 5.2
Lee *et al.* (2016)	Parallel	18	8	11/15	71.6	Mild to moderate AD	Donepezil	22.4 ± 2.9[g]	23.9 ± 4.4	22.8 ± 2.5	24.5 ± 4.9

M, male; F, female; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; ADAS-cog, Alzheimer's Disease Assessment Scale—cognitive subscale; rTMS, repetitive transcranial magnetic stimulation; TMS, transcranial magnetic stimulation; SD, standard deviation; N/A, not available; AD, Alzheimer's Disease; MCI, mild cognitive impairment; MT, motor threshold.

[a]Of the 30 patients in the active group, 15 patients received TMS with 20 Hz, 20 trains × 100 pulses at 90%MT and 15 patients received TMS with 1 Hz, 2 trains × 1000 pulses at 100%MT.

[b]Each patient received sham and active rTMS over left dorsolateral prefrontal cortex and right dorsolateral prefrontal cortex.

[c]Patients were randomly assigned to receive either active (10 or 1 Hz) or sham rTMS treatment.

[d]Each patient received three stimulation sessions (over right inferior frontal gyrus, right superior temporal gyrus and vertex) in a random order.

[e]Patients were randomly assigned to receive either active or sham rTMS treatment.

[f]Patients were randomly assigned to two groups: (S-R) receiving sham treatment and then real treatment and (R-S) receiving real treatment and then sham treatment.

[g]Used to assess cognitive function of the participants.

[h]Used to assess cognitive function of the participants.

[i]Used to assess cognitive function of the participants.

[j]Range of MoCA score.

Table 2 Description of TMS intervention in the included trials

Study	TMS target	Targeting method	Type of coil	Frequency (Hz)	Intensity (%MT)	Total pulses per session	Number of session	Sham stimulation	Cognitive training	Outcome measures on cognitive symptoms	Follow-up	Adverse effects
Cotelli *et al.* (2008)	L/R DLPFC, Cz	Neuroimaging	Figure of eight	20	90	500 ms from the onset of the 70 visual stimulus	1	Coil perpendicular to the scalp	No	Action–object picture naming task	No	No adverse effects
Cotelli *et al.* (2011)	L DLPFC	Neuroimaging	Figure of eight	20	100	2000 (40 pulses, 50 trains)	20 (5 per week)	Sham coil	No	MMSE, picture naming	8 weeks	No adverse effects
Ahmed *et al.* (2012)[a]	L/R DLPFC	Non-imaging-based technique	Figure of eight	1 and 20	90/100	2000 (100/1000 pulses, 20/2 trains)	5 (5 per week)	Coil angled away from the scalp	No	MMSE	1 and 3 months	No adverse effects
Turriziani *et al.* (2012)[b]	L/R DLPFC	Neuroimaging	Figure of eight	1	90	600	2 (3 weeks b/w sessions)	Coil angled away from the scalp	No	Non-verbal recognition memory task	No	N/A
Brem *et al.* (2013)	Broca, Wernicke, L/R DLPFC, L/R parietal cortex	N/A	Figure of eight	10	120	1200 (20 pulses, 20 trains × 3)	30 (5 per week)	N/A	Yes	ADAS-cog, MMSE	1 month	N/A
Rabey *et al.* (2013)	Wernicke, L/R DLPFC, L/R pSAC	Neuroimaging	Figure of eight	10	90–110	1300 (20 pulses, 20–25 trains × 3)	30 (5 per week) +24 (2 per week)	Sham coil	Yes	ADAS-cog	6 weeks and 4.5 months	No adverse effects
Ash *et al.* (2014)[c]	Prefrontal areas	N/A	N/A	1 and 10	N/A	N/A	N/A	N/A	N/A	N/A	8 weeks	N/A
Anderkova *et al.* (2015)[d]	R IFG, R STG, VTX	Neuroimaging	Figure of eight	10	90	2250 (50 pulses, 45 trains)	3 (at least 1-day interval b/w sessions)	Control stimulation site	No	TMT-A/B, Stroop, CVSET	No	Painful scalp sensations
Coppi *et al.* (2015)[e]	Fronto-parietal–temporal lobes	N/A	H-coil	10	120	840 (20 pulses, 42 trains)	12 (3 per week) +4 (1 per week)	N/A	N/A	ADAS-cog, Word recognition improvement	8 weeks	N/A
Drumond Marra *et al.* (2015)	L DLPFC	Non-imaging-based technique	Figure of eight	10	110	2000 (50 pulses, 40 trains)	10 (5 per week)	Sham coil	No	MMSE, RBMT, WMS, WAIS, RAVLT, Stroop, TMT-A/B	1 month	Headache, cervical pain, scalp pain, burning scalp
Rutherford *et al.* (2015)[f]	L/R DLPFC	Non-imaging-based technique	N/A	20	90–100	4000 (40 pulses, 50 trains for each side)	10 (5 per week) +3 extra	2-cm-thick wooden block inserted b/w coil and patient	Yes	ADAS-cog, word image association, associative memory	No	Minor discomfort, minor headache
Wu *et al.* (2015)	L DLPFC	N/A	Figure of eight	20	80	1200	20 (5 per week)	Coils turned 180°	No	ADAS-cog	No	Mild extrapyramidal reactions,

(*Continues*)

Table 2. (Continued)

Study	TMS target	Targeting method	Type of coil	Frequency (Hz)	Intensity (%MT)	Total pulses per session	Number of session	Sham stimulation	Cognitive training	Outcome measures on cognitive symptoms	Follow-up	Adverse effects
Lee *et al.* (2016)	Broca, Wernicke, L/R DLPFC, L/R pSAC	Neuroimaging	N/A	10	90–110	1200	30 (5 per week)	Sham coil	Yes	ADAS-cog, MMSE	6 weeks	transient headache No adverse effects

L, left; R, right; DLPFC, dorsolateral prefrontal cortex; Cz, vertex; MT, motor threshold; MMSE, Mini-Mental State Examination; N/A, not available; ADAS-cog, Alzheimer's Disease Assessment Scale—cognitive subscale; pSAC, parietal somatosensory association cortex; IFG, inferior frontal gyrus; STG, superior temporal gyrus; VTX, vertex; b/w, between; TMT-A/B, Trail Making Test A and B; Stroop, Stroop Color–Word Interference Test; CVSET, Complex Visual Scene Encoding Task; RBMT, Rivermead Behavioural Memory Test; WMS, Wechsler Memory Scale; WAIS, Wechsler Adult Intelligence Scale; RAVLT, Rey Auditory Verbal Learning Test; TMS, transcranial magnetic stimulation; rTMS, repetitive transcranial magnetic stimulation.

[a]Of the 30 patients in the active group, 15 patients received TMS with 20 Hz, 20 trains × 100 pulses at 90%MT and 15 patients received TMS with 1 Hz, 2 trains × 1000 pulses at 100%MT.

[b]Each patient received sham and active rTMS over left DLPFC and right DLPFC.

[c]Patients were randomly assigned to receive either active (10 or 1 Hz) or sham rTMS treatment.

[d]Each patient received three stimulation sessions (over right inferior frontal gyrus, right superior temporal gyrus and vertex) in a random order.

[e]Patients were randomly assigned to receive either active or sham rTMS treatment.

[f]Patients were randomly assigned to two groups: (S-R) receiving sham treatment and then real treatment and (R-S) receiving real treatment and then sham treatment.

et al., 2015) adequately addressed the handling of incomplete outcome data. All studies were free of reporting bias.

Effect of transcranial magnetic stimulation intervention

The meta-analysis of eight trials including 194 participants (107 with active treatment and 87 with sham treatment) showed a moderate effect of rTMS on cognition (SMD = 0.48, 95% CI 0.12 to 0.84), with an insignificant heterogeneity between trials (I^2 = 26%) (Figure 2).

Concurrent cognition-enhancing drugs. Trials with concurrent cognition-enhancing drugs (Cotelli *et al.*, 2011; Brem *et al.*, 2013; Rabey *et al.*, 2013; Lee *et al.*, 2016) showed no significant improvement in cognition after active rTMS (SMD = 0.66, 95% CI −0.21 to 1.53). A significant rTMS effect was found amongst those without cognition-enhancing drugs (Ahmed *et al.*, 2012; Drumond Marra *et al.*, 2015; Wu *et al.*, 2015) (SMD = 0.44, 95% CI 0.08 to 0.80) (Figure 3).

Target sites and concurrent cognitive training. Subgroup analyses involving target sites and concurrent cognitive training had the same grouping of trials. Three trials with multiple target sites also reported using concurrent cognitive training (Brem *et al.*, 2013; Rabey *et al.*, 2013; Lee *et al.*, 2016). Five trials had single target site with no concurrent cognitive training (Cotelli *et al.*, 2011; Ahmed *et al.*, 2012; Drumond Marra *et al.*, 2015; Wu *et al.*, 2015). The results in these two subgroup analyses (target sites and concurrent cognitive training) were identical.

The pooled analysis of trials with a single target, mainly the DLPFC (Cotelli *et al.*, 2011; Ahmed *et al.*, 2012; Drumond Marra *et al.*, 2015; Wu *et al.*, 2015), showed improvement in cognition after active rTMS (SMD = 0.39, 95% CI 0.05 to 0.73). The effect was not significant amongst trials with multiple targets (Brem *et al.*, 2013; Rabey *et al.*, 2013; Lee *et al.*, 2016) (SMD = 0.94, 95% CI −0.09 to 1.97) (Figure 3).

No significant rTMS effect was reported amongst trials with concurrent cognitive training (Brem *et al.*, 2013; Rabey *et al.*, 2013; Lee *et al.*, 2016) (SMD = 0.94, 95% CI −0.09 to 1.97). Trials without cognitive training (Cotelli *et al.*, 2011; Ahmed *et al.*, 2012; Drumond Marra *et al.*, 2015; Wu *et al.*, 2015) showed improvement in cognition after active rTMS (SMD = 0.39, 95% CI 0.05 to 0.73) (Figure 3).

Table 3 The risks of bias of the included trials in meta-analysis using Cochrane's criteria

Authors (year)	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants (performance bias)	Blinding of assessors (detection bias)	Incomplete outcome data addressed (attrition bias)	Selective reporting (reporting bias)
Cotelli *et al.* (2011)	?	?	+	+	+	+
Ahmed *et al.* (2012)	?	?	+	+	+	+
Brem *et al.* (2013)	?	?	?	?	?	+
Rabey *et al.* (2013)	?	?	+	+	+	+
Drumond Marra *et al.* (2015)	+	+	+	+	?	+
Wu *et al.* (2015)	+	?	+	+	+	+
Lee *et al.* (2016)	?	?	+	+	+	+

'+', low risk of bias; '−', high risk of bias; '?', uncertain risk.

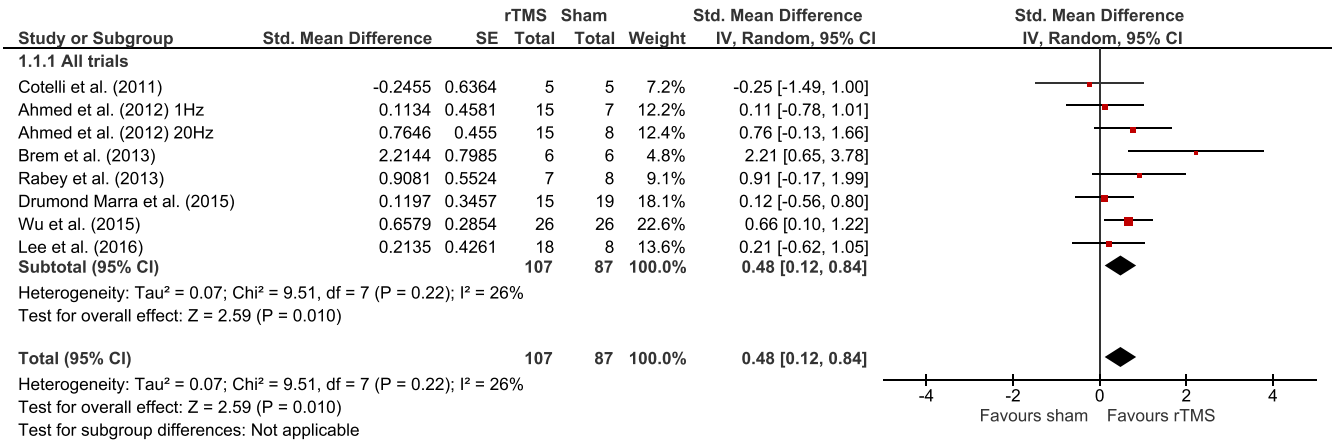

Figure 2 Meta-analysis of active versus sham repetitive transcranial magnetic stimulation (rTMS) on improving cognition in elderly with cognitive impairment. SE, standard error; CI, confidence interval. [Colour figure can be viewed at wileyonlinelibrary.com]

Results of individual studies not included in meta-analysis

The studies that were not included in the meta-analysis also reported an improvement in specific or general cognition after rTMS. Cotelli *et al.* (2008) demonstrated that one session of high-frequency rTMS applied over the left or right DLPFC improved naming performance in patients with mild to severe AD. Turriziani *et al.* (2012) reported a superior positive effect on non-verbal recognition memory performance with one session of low-frequency rTMS over the right DLPFC. Application of high-frequency rTMS over the bilateral DLPFC (Rutherford *et al.*, 2015), right inferior frontal gyrus or right superior temporal gyrus (Anderkova *et al.*, 2015) significantly improved cognition. In addition, deep rTMS over the prefrontal or fronto-parietal–temporal lobes in patients with AD enhanced cognition (Ash *et al.*, 2014; Coppi *et al.*, 2015), where high-frequency rTMS was suggested to have a better effect than low-frequency rTMS (Ash *et al.*, 2014).

Discussion

Our review is the most detailed and extensively searched systematic review and meta-analysis to date with the largest sample size (13 articles, 326 subjects). Our results support the benefit of rTMS on cognition amongst older patients with cognitive impairment with a moderate effect size of 0.48. Most included studies used high-frequency (10 or 20 Hz) continuous pulses with 840 to 4,000 total pulses per session and performed five times per week, with at least five sessions, and the participants mainly had mild to moderate AD. rTMS was noted to be safe and feasible, and no serious adverse effects were reported.

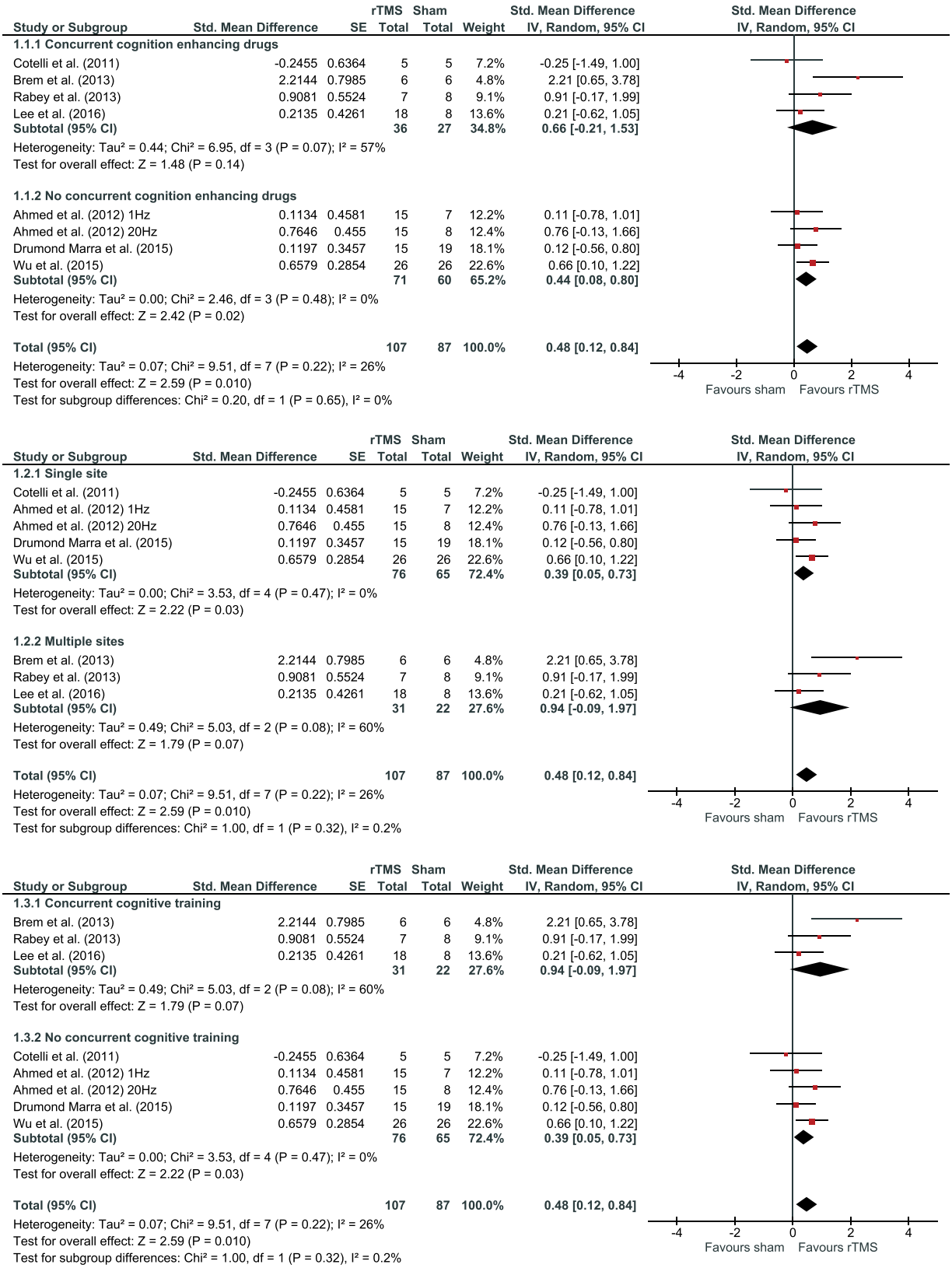

Figure 3 Subgroup analyses of active versus sham repetitive transcranial magnetic stimulation (rTMS) on improving cognition in elderly with cognitive impairment. SE, standard error; CI, confidence interval. [Colour figure can be viewed at wileyonlinelibrary.com]

Subgroup analysis

In theory, rTMS may have a potential synergistic or additive effect when combined with cognition-enhancing drugs. However, in our subgroup analyses, the trials without concurrent cognition-enhancing drugs showed significant improvement in cognition, whilst those with concurrent cognition-enhancing drugs did not show significant improvement. The finding was opposite to our expectation and could be explained by the sample size difference in subgroups. Trials without concurrent cognition-enhancing drugs had much larger sample size ($n = 131$) than those with concurrent cognition-enhancing drugs ($n = 63$). The negative finding in the later subgroup was likely due to inadequate power. The possibility of rTMS as an adjuvant therapy for cognitive impairment along with cognition-enhancing drugs for dementia remains uncertain. For the accurate effect of combining cognition-enhancing drugs with rTMS to be detected and for the mechanism of this effect to be further understood, future RCTs should include data on cortical excitability and structural and functional imaging in addition to the neuropsychological tests.

Subgroup analyses involving target sites and concurrent cognitive training had the same grouping of trials. The results in these two subgroup analyses (target sites and concurrent cognitive training) were identical. It could not be determined whether the results were due to multiple target sites, concurrent cognitive training or both.

Several studies reported that stimulation of multiple functional areas of the brain in the same session (Brem *et al.*, 2013) or the addition of cognitive training had an additional benefit on cognition (Luber and Lisanby, 2014). Our findings show the opposite. There are a few possible explanations for the results. First, the effects on cognition of stimulating multiple functional areas are not straightforward; they could be synergistic or cancellative (Fox *et al.*, 2005). It is difficult to predict which combination of activated areas would result in a synergistic or cancellation effect. Second, although rTMS was suggested to have a synergistic effect when combined with cognitive training via long-term potentiation or depression (Hoogendam *et al.*, 2010), the effect may not be significant in practice. Finally, the sample size of the group with multiple target sites and concurrent cognitive training was much smaller than that of the other group, which showed a significant effect on cognition. Inadequate power may explain the insignificant results amongst trials with multiple sites and concurrent cognitive training. Therefore, any conclusions regarding the effects of multiple target sites or concurrent cognitive training in the same session of rTMS would be premature.

Factors affecting the effect of rTMS

Demographic characteristics such as age and education level, the type and severity of dementia and the amount of brain atrophy possibly mediate the effects of rTMS. Most participants in this review had mild to moderate AD, and a few had MCI. There were limited studies of other types of dementia such as vascular dementia and frontotemporal dementia. Only one study (Anderkova *et al.*, 2015) suggested a negative correlation between the amount of brain atrophy and the effects of rTMS. Thus, the applicability of rTMS in patients with MCI or a more severe grade of AD awaits further investigation.

The DLPFC is the most common target of rTMS. Its therapeutic value has been well proven in this review and in previous studies. Whilst a previous meta-analysis suggested that the right or bilateral DLPFC instead of the left DLPFC was linked with a therapeutic effect on cognitive function (Liao *et al.*, 2015), caution should be paid because the subgroup analysis was based on very few studies with small sample sizes for which quality was not ensured. Also, meta-analysis of Liao *et al.* (2015) did not include two large-scale RCTs (Drumond Marra *et al.*, 2015; Wu *et al.*, 2015), both of which suggested a significant therapeutic effect of high-frequency rTMS over the left DLPFC region. It is still too early to conclude whether the left, right or bilateral DLPFC had superior effects. In addition to the DLPFC, other areas such as the right inferior frontal gyrus, right superior temporal gyrus, Broca's area, Wernicke's area and the parietal cortex were chosen as candidate sites for rTMS, and all showed initial promising results. More data would be required to substantiate the choice of target sites.

Consistent with previous studies, the effectiveness of high-frequency rTMS is supported over low-frequency rTMS. Only three studies with relatively small sample sizes included low-frequency rTMS. One showed a positive effect after one session of low-frequency rTMS (Turriziani *et al.*, 2012), one reported that high-frequency rTMS had a better effect on cognition than low-frequency rTMS (Ash *et al.*, 2014) and one found that low-frequency rTMS had no superior effect on cognition (Ahmed *et al.*, 2012).

Safety issues related to repetitive transcranial magnetic stimulation in elderly

No serious adverse effects such as seizure or death were reported in any of the 13 articles included. Only mild discomfort such as headache, scalp or neck pain was reported in a small number of subjects. There was no evidence to suggest that older adults were more susceptible to serious or mild adverse effects of rTMS than young adults.

Quality of evidence

Even though most of the included RCTs had a low risk of performance, detection, attrition and reporting bias, selection bias remained inadequately addressed. We recommend a detailed description of the random sequence generation and allocation concealment in future studies. RCTs with larger sample sizes with a parallel design are required for conclusive evidence.

Comparison with previous evidence

Our results are largely compatible with those of the previous reviews and meta-analyses, which also supported a benefit of rTMS on cognition (Nardone *et al.*, 2014; Liao *et al.*, 2015). Compared with the previous meta-analysis that identified seven studies with 94 patients (Liao *et al.*, 2015), our review included the two latest high-quality RCTs (Wu *et al.*, 2015; Lee *et al.*, 2016) using rigorous design with the largest samples to date. We also excluded three studies with crossover designs to minimise any possible carryover effect (Liao *et al.*, 2015).

Limitations

This study has several limitations. First, we used only the MMSE or ADAS-cog scores as the outcome measures; hence, other specific cognitive functions such as attention, language and executive functions could not be adequately addressed in this review. Second, we did not examine the duration of effect because there were inadequate data for analysis. Third, most subjects in this review had mild to moderate AD. There were limited trials on the effects in types of cognitive impairment other than AD and in different levels of severity, such as MCI and severe dementia. The effectiveness of rTMS in these subjects remains unknown.

Conclusion

High-frequency rTMS showed a benefit in cognition amongst older subjects with mild to moderate AD and had a good safety profile in the current systematic review and meta-analysis. rTMS was shown to have great potential as an alternative intervention for cognition. Further research on the mechanism, the optimal parameters and settings of rTMS and the effects of concurrent cognitive training or medications is important for the development of this new intervention in clinical practice.

Conflict of interest

None declared.

Key points

- Repetitive transcranial magnetic stimulation (rTMS) is effective in improving cognition amongst elderly with mild to moderate Alzheimer's disease.
- rTMS was shown to have great potential as a safe and well-tolerated alternative intervention for cognition.
- Further investigation is required to examine the optimal rTMS treatment parameters.

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Appendix A.

'transcranial magnetic stimulation', 'TMS or rTMS or sham', 'brain stimulation (therapy or treatment or intervention)', '(magnetic or transcranial) stimulation', '(magnetic or electromagnetic or electro-magnetic) and (stimulation or field or coil)', 'repetitive (transcranial magnetic stimulation or TMS)', 'rhythmic (transcranial magnetic stimulation or TMS)', '(electric or magnetic or electromagnetic or current or deep brain) stimulation' and dementia: 'dementia', 'Alzheimer', 'frontotemporal lobar degeneration', 'frontolobar degeneration', 'frontal lobar degeneration', 'vascular cognitive dementia' and 'lewy body'