Journal of the Neurological Sciences 398 (2019) 184–191

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Research Paper

The role of repetitive transcranial magnetic stimulation (rTMS) in the treatment of cognitive impairment in patients with Alzheimer's disease: A systematic review and meta-analysis

Yan Lin[a], Wen-Jing Jiang[b], Pei-Yan Shan[b], Mei Lu[b], Tan Wang[b], Rui-Hua Li[a], Nan Zhang[a], Lin Ma[b,*]

[a] Department of Neurology, Qilu Hospital of Shandong University, Jinan 250012, China
[b] Department of Gerontology, Qilu Hospital of Shandong University, Jinan 250012, China

ARTICLE INFO

Keywords:
Alzheimer's disease
Transcranial magnetic stimulation
Cognitive impairment
MMSE
Systematic review
Meta-analysis

ABSTRACT

Background: Although repetitive transcranial magnetic stimulation (rTMS) has been considered a potentially effective treatment for cognitive impairment in patients with Alzheimer's disease (AD), previous studies have produced inconsistent results. The objective of this meta-analysis was to evaluate the effects of rTMS on cognitive function in patients with AD.

Methods: PubMed, EMBASE, Web of Science, MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for relevant terms. Abstracts of all papers were carefully reviewed, followed by data extraction, quality assessment, data synthesis and subgroup analyses.

Result: A total of 12 studies with 231 patients were included, with 8 randomized controlled studies and 4 self-controlled studies. Eleven studies used high frequency rTMS ($\geq$ 5 Hz), but only one study directly compared the difference between low-frequency (1 Hz) and high-frequency (20 Hz). Random-effects analysis revealed that rTMS could significantly improve cognition compared with sham-rTMS (SMD: 0.60, 95% CI: 0.35–0.85, $P < .0001$). In subgroup analyses, the effect for stimulation at a single target was 0.13 (95% CI: −0.35–0.62) and multiple targets 0.86 (95% CI: 0.18–1.54). Treatment for $\leq$3 sessions produced an effect of 0.29 (95% CI: −1.04–1.62), whereas treatment for $\geq$5 sessions produced an effect of 2.77 (95% CI: 2.22–3.32). No differences were found for rTMS combined with medication or cognitive training.

Conclusions: rTMS can significantly improve cognitive ability in patients with mild to moderate AD. Stimulation of multiple sites and long-term treatment are better at improving AD-associated cognitive performance. Furthermore, some novel interventional targets, like precuneus (PC), may be a more effective therapeutic site to improve memory in AD.

1. Introduction

Alzheimer's disease (AD) is the most common type of dementia among the elderly, and is characterized by memory loss, which is the core symptom. Other symptoms include loss of orientation, behavior abnormalities, lack of motivation, depression, and motor deficits [1–3]. Due to the suffering of patients and the burden on society, the need for early stage interventions has become increasingly pressing. Unfortunately, medications such as acetylcholinesterase inhibitors (AChE-I) and *N*-methyl-D-aspartic glutamate receptors have limited effects and do not improve the long-term prognosis [4,5].

Transcranial magnetic stimulation (TMS) is a noninvasive and painless technique that can stimulate and regulate the cortical function of the brain [6,7]. Repetitive transcranial magnetic stimulation (rTMS) involves trains of TMS pulses with various frequencies and intensities. It is a neuro-stimulation and neuro-modulation method that generates long-lasting effects, including decreases cortical excitability for low frequencies ($\leq$1 Hz) and increases in cortical excitability for high frequencies ($\geq$5 Hz) [7,8]. During the past 2 decades, many basic and clinical studies have demonstrated that rTMS can ameliorate the symptoms of AD and has potential as a therapeutic method [9–12].

Despite the growing body of evidence for positive effects of rTMS on AD patients, its therapeutic schedule and parameter design still requires further investigation. To the best of our knowledge, there have only

* Corresponding author.
E-mail address: malinqlyy@163.com (L. Ma).

https://doi.org/10.1016/j.jns.2019.01.038
Received 6 August 2018; Received in revised form 1 January 2019; Accepted 22 January 2019
Available online 24 January 2019
0022-510X/

been two meta-analyses focused on rTMS treatment effects on patients with AD [10,13], in which the sample sizes were small, and the results may not exactly detectable for inadequate statistical power. Therefore, the aim of this systematic review and meta-analysis is to provide up-to-date evidence on the role of rTMS therapeuty in AD patients and to provide a conclusion with better power.

2. Materials and methods

2.1. Literature search

Five databases were systematically searched (PubMed, EMBASE, Web of Science, MEDLINE and Cochrane Central Register of Controlled Trials [CENTRAL]), for trials published before July 2018 for any English language publication. The following key words were used: ('Alzheimer's Disease' OR 'dementia of Alzheimer type' OR 'mild cognitive impairment' OR 'cognitive disorder' OR 'AD' OR 'MCI') AND ('transcranial magnetic stimulation' OR 'repetitive transcranial magnetic stimulation' OR 'brain stimulation' OR 'TMS' OR 'rTMS'). Reference lists from the resulting articles were used to identify further relevant publications.

2.2. Inclusion and exclusion criteria

In order to include primary relevant published studies, the inclusion criteria were: (1) human research; (2) cognitive impairment was caused by AD; (3) cognitive impairment was measured by a scale, including the Mini Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA) or Assessment Scale-cognitive subscale (ADAS-cog); (4) rTMS was used as the sole treatment measure or in combination with other treatments, and compared with sham-rTMS, pharmacological treatments or cognitive training; (5) sufficient original data was provided; (6) clinical trials including intervention group and a control group. The exclusion criteria were: (1) cognitive impairment caused by other diseases; (2) degree of cognitive impairment too serious; (3) not having carried out any tests to assess the effects of rTMS on cognition in AD patients; (4) articles published in non-English languages; (5) articles published in the form of case report, comment, letter or review; (6) duplicate publications.

2.3. Data extraction

Data from each article were examined and extracted independently by two authors. For each study, the relevant information included: (1) general characteristics: the first author, year of publication, number of participants, mean age, sex ratio, and baseline cognitive scores (MMSE or ADAS-cog); (2) study design, selection criteria, study durations and outcome measures; (3) treatment interventions: stimulating position, type of coil, intensity, frequency, number of sessions, total pulses of each session, and sham stimulation method. If publications appeared in more than one database, the one that contained the highest number of patients or most detailed information was included. If outcomes were reported at different time points, those from the latest time point were used. If studies presented insufficient data or uncertain information, we contacted the corresponding authors. If there is any disagreement between the current authors, discussion with another specialized reviewer was performed to reach consensus.

2.4. Statistical analysis and publication bias

All data were assembled using Cochrane Rev-Man 5.3 software (Review Manger of Cochrane Collaboration). Effect size was calculated by standardized mean difference (SMD) to estimate the treatment effect, and 95% confidence intervals (CI) were computed. Heterogeneity among the trials was quantified by the I^2 statistic, and a value > 50% was taken to indicate substantial heterogeneity. Because heterogeneity did in fact exist, random-effects models were used to obtain more reliable outcomes. Differences between groups were evaluated by planned subgroup analyses. For all analyses, $p < .05$ was considered statistically significant. Publication bias for these studies was evaluated as recommended by the Cochrane Handbook for Systematic Reviews of Interventions, and funnel plot were constructed [14]. The risks of bias for all the included studies were assessed by two statisticians.

3. Results

3.1. Literature search findings

A title search of the literature yielded a total of 1458 identified references, out of which 927 were excluded for duplication of data. By reading the titles and abstracts, 479 of those studies were excluded due to irrelevance to the current question, describing a basic science experiment, not being an RCT, or not having been published in a peer-reviewed journal. On examination of the full text of the remaining 59 articles, 24 were excluded for lacking a control group, 19 were excluded for not using scales to assess the effects of rTMS on cognition in AD patients, and 4 of were excluded for presenting incomplete data. Finally, we selected 12 studies for our meta-analysis (Fig. 1).

3.2. Basic characteristics of studies

The total of 12 studies included 231 patients with AD. Basic characteristics of the included articles are described in Table 1. To summarize, the number of participants randomized to active-rTMS was 156 (mean age: 70.48 ± 6.9 years), and the number randomized to sham-rTMS was 134 (mean age: 70.02 ± 6.3 years). Sham-rTMS was applied with the same stimulation parameters, except that the coil was elevated away, or held perpendicularly, or replaced by a special sham coil. Across all the participants, the mean disease duration was 4.77 ± 3.8 years, and the mean education time was 7.12 ± 3.4 years. The mean MMSE scores of the stimulation group ranged from 12.9 to 24.0, and the scores of the sham group ranged from 13.9 to 22.8. In eight studies, the participants were given drugs, while, in six studies, the participants were given cognitive training. The targets of rTMS stimulation in these studies comprised single sites or multiple sites. The single sites that were used included the left and right dorsolateral prefrontal cortex(DLPFC), PC, motor cortex, inferior frontal gyrus (IFG) and superior temporal gyrus (STG), and the multiple sites included two or more of these. Only one study used low frequency stimulation (1 Hz), comparing it to high frequency stimulation (20 Hz), while the other studies used high frequencies alone (5 Hz, 10 Hz, 20 Hz). Descriptions of the rTMS interventions in the included studies are provided in Table 2. In most of the studies , AD was diagnosed according to National Institute of Aging and Alzheimer's Association (NIA-AA) criteria. For outcome measures, nine studies used the MMSE to evaluate severe cognitive impairment, two studies used the Assessment Scale-Cognitive (ADAS-cog), while one study used Rey Auditory Verbal Learning test (RAVLT).

3.3. Study quality

The Cochrane Handbook was used to evaluate risk of bias for the included studies, and the results are summarized in Table 3. Randomization was used in all included studies. Ten trials described adequate sequence randomization, based on random sequence generation using random number tables or computer programs. Two studies reported allocation procedures with adequate concealment. Most studies were double-blind for both participants and evaluators. Thus, all of the included studies were judged to have a mild risk of bias.

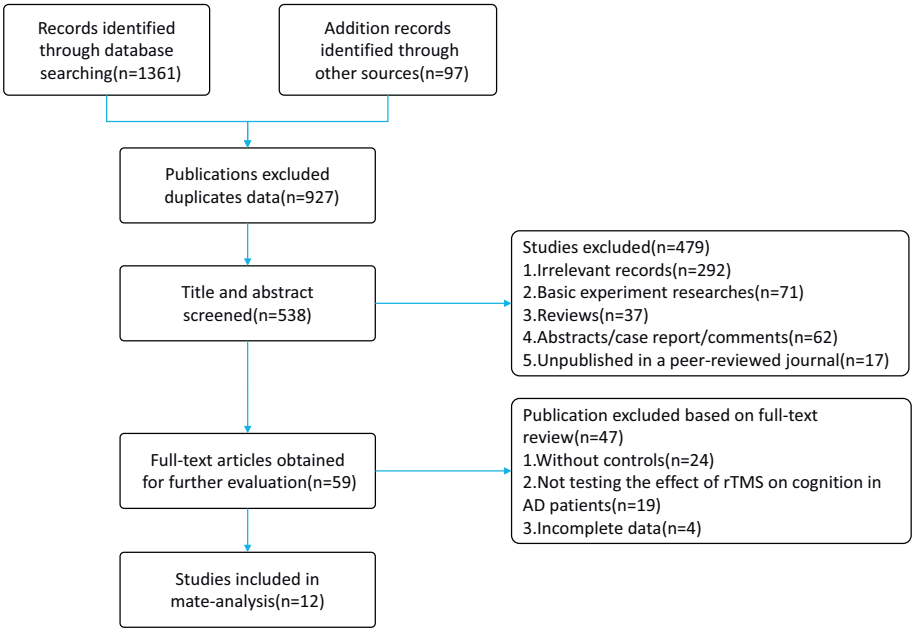


Fig. 1. Flowchart of systematic review.

3.4. Meta-analyses

We pooled the results and found a moderate effect of rTMS therapy on cognition in patients with AD (SMD = 0.60, 95% CI = 0.35–0.85), with an insignificant heterogeneity across studies (I^2 = 73%)(Fig. 2). To detect variable factors that might have influenced the cognitive outcomes, subgroup analyses were implemented.

Four studies (including 56 participants) [15–18] used single site stimulation, while eight studies (including 175 participants) [6,19–25] used multiple site stimulation. The subgroup analysis of stimulation sites revealed a mean effect size of 0.13(95% CI = −0.35–0.62) for trials with "single target" designs. The mean effect size for trial with "multiple target" designs was 0.86 (95% CI = 0.18–1.54) (Fig. 3).

The session numbers of the studies included in the meta-analysis ranged from only one session [19] to 54 sessions [20]. Most studies used either < 3 sessions or > 5 sessions, so we analyzed the difference between short-term treatment(≤3sessions) and long-term treatment (≥5sessions). The subgroup analysis revealed that the mean effect size for studies with short-term treatment (including 56 participants) was 0.29 (95% CI = −1.04–1.62), and studies with long-term treatment (including 175 participants) showed a mean effect size of 2.77 (95% CI = 2.22–3.32). These results indicate that long-term rTMS treatment produced better cognitive improvement than short-term rTMS treatment (Fig. 4).

Additional subgroup analyses involved rTMS combined with medication and rTMS combined with cognitive training. The efficacy of the rTMS-combined-with-medication group (including 151 participants) was 0.60 (95% CI = 0.30–0.90), not statistically different from the rTMS-stimulation-only group (including 80 participants) efficacy of 0.62 (95% CI = 0.17–1.06)(Fig. 5). The subgroup analysis for cognitive training yielded similar results, with no significant discrepancy found between the groups. rTMS without cognitive training (including 112 participants) produced an efficacy of 0.40 (95% CI = 0.04–0.76), whereas rTMS combined with cognitive training (including 119 participants) had an efficacy of 0.79 (95% CI = 0.44–1.13)(Fig. 6).

There was only one study [21] that directly compared the difference

Table 1
Demographic characteristics of the included trails.

Study (time)	Participants (N)		Gender (M/F)	Mean age (years)	Disease duration (years)	Education (years)	Medication
1. Cotelli (2008)	Total	24	NR	76.3	NR	6.8 ± 3.1	No
2. Bentwich (2011)	Total	8	7/1	75.4 ± 4.4	2.6 ± 0.6	10.8 ± 2.2	No
3. Cotelli (2011)	Active Control	5 5	2/8	71.2 ± 6.1 74.4 ± 3.8	NR	6.4 ± 1.3 4.8 ± 0.4	Cholinesterase inhibitor
4. Ahmed (2012)	Active(HF) Active(LF) Control	10 11 11	16/29	65.9 ± 5.9 68.6 ± 6.7 68.3 ± 4.9	4.1 ± 2.4	> 6	No
5. Trebbastoni (2012)	Active Control	11 11	3/8	78.9 ± 1.4 75.2 ± 1.3	NR	NR	Cholinesterase inhibitor
6. Rabey (2013)	Active Control	7 8	10/5	72.6 ± 8.9 75.4 ± 9.1	NR	NR	Cholinesterase inhibitor
7. Eliasova (2014)	Total	10	6/4	75.0 ± 7.5	3.9	9–12	No
8. Rabey (2016)	Total	30	17/13	NR	NR	NR	No
9. Lee (2016)	Active Control	18 8	11/15	71.6 ± 6.8	9.9 ± 3.9	NR	Donepezil
10. Junwu (2016)	Active Control	17 13	13/17	70.8 ± 5.6 69.3 ± 5.8	NR	4.9 ± 2.3	Donepezil
11. Nguyen (2017)	Total	10	5/5	73.0 ± 7.2	5 ± 2.3	NR	No
12. Koch (2018)	Total	14	7/7	70.0 ± 5.1	13.8 ± 5.1 (month)	7.2 ± 3.0	No

N, number; M, male; F, female; NR, not report.

Table 2
Description of rTMS intervention in the included studies.

Study (time)	Stimulation position	Intensity (% MT)	Frequency (Hz)	Total pulses of per session	Number of session	Cognitive training	MMSE/ADAS-Cog/RAVLT (mean ± SD)	
1. Cotelli (2008)	R-DLPFC L-DLPFC	90	20	10 pulses, 20 trains	1	no	After Before	17.0 ± 2.5 17.0 ± 3.0
2. Bentwich (2011)	Broca Wernicke R.L-DLPFC R.L-pSAC	90–110	10	1200(20pulsess, 20 trains × 3)	54	yes	After Before	63.0 ± 17.8 61.4 ± 14.4
3. Cotelli (2011)	L-DLPFC	100	20	2000(40pulses, 50trains × 1)	20	no	Active Control	16.4 ± 2.8 14.5 ± 3.7
4. Ahmed (2012)	R.L-DLPFC	90/100	20 1	2000(1000/100 pulses × 2/20trains)	5	no	Active (HF) Active (LF) Control	22.6 ± 1.5 16.8 ± 4.1 14.4 ± 3.2
5.Trebbastoni (2012)	L-motor cortex(M1)	120	5	10pulses,10trains	3	no	Active Control	20.1 ± 3.2 20.5 ± 3.2
6. Rabey (2013)	Broca Wernicke R.L-DLPFC R.L-pSAC	90–110	10	1300(20pulses,20 trains × 2 + 25trains)	30	yes	Active Control	24.1 ± 1.3 20.8 ± 1.2
7. Eliasova (2014)	IFG STG	90	10	2250(50pulses, 45trains)	2	no	After Before	80.7 ± 8.9 79.0 ± 10.9
8. Rabey (2016)	NR	90–110	10	1300(20pulses,20 trains × 3 + 5trains)	30	yes	After Before	20.5 ± 1.4 18.1 ± 1.4
9. Lee (2016)	Broca Wernicke R/L DLPFC R/L pSAC	90–110	10	1200(20pulses,20 trains × 3)	30	yes	Active Control	24.4 ± 4.6 25.7 ± 4.6
10. Junwu (2016)	P3/P4 T5/T6	90–110	20	200pulses/train	30	yes	Active Control	25.5 ± 4.6 24.2 ± 4.1
11. Nguyen (2017)	Broca Wernicke R/L prefrontal cortex R/L parietal cortex	100	10	1300(20pulses,20 trains × 3 + 5trains)	3	yes	After Before	18.8 ± 1.9 17.8 ± 1.5
12. Koch (2018)	PC	100	20	1600(42-s trains spaced-out by 28 s)	10	no	Active Control	3.0 ± 2.6 2.4 ± 2.9

L, left; R, right; DLPFC, dorsolateral prefrontal cortex; pSAC, parietal somatosensory association cortex; IFG, inferior frontal gyrus; STG, superior temporal gyrus; VTX, vertex; M1, motor cortex; PC, precuneus; MT, motor threshold; MMSE, Mini-Mental State Examination; NR, not report; ADAS-cog, Alzheimer's Disease Assessment Scale—cognitive subscale; RAVLT: Rey Auditory Verbal Learning test.

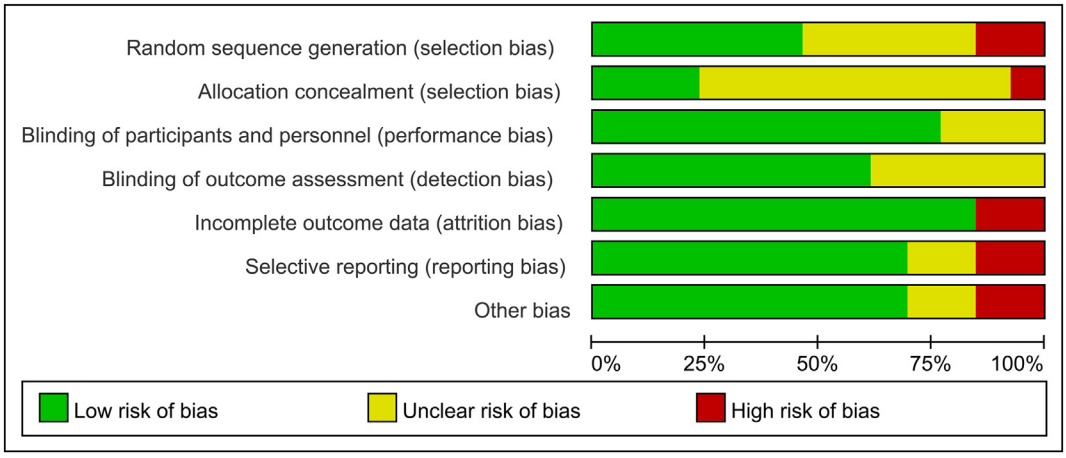
between low-frequency (1 Hz) and high-frequency (20 Hz) stimulation. It demonstrated that high-frequency produced greater improvement in cognition than low-frequency stimulation ($p < .05$).

4. Discussion

The purpose of this systematic review and meta-analysis was to evaluate the beneficial effects of rTMS on AD patients with mild to moderate cognitive impairment. Due to limited sample sizes and heterogeneity, previous studies have reached divergent conclusions. Because several high-quality RCTs on rTMS in AD have been published recently, an updated meta-analysis appears to be called for. In this meta-analysis, 12 RCTs including 231 patients compared the efficacy of rTMS group with control groups receiving only sham rTMS. Our results are consistent with most previous reports in that rTMS had significant positive effects on cognition with medium effect size (SMD = 0.60).

To determine which factor has the greatest effects on cognitive outcome and which are sources of heterogeneity, subgroup analyses were performed for stimulation sites, session numbers, medication and cognitive training. The subgroup analysis revealed that stimulation of multiple sites improve cognition more than stimulation of single sites. The most common choices for single site stimulation were the left dorsolateral prefrontal cortex (L-DLPFC) and PC [18,26]. L-DLPFC is a functionally and structurally heterogeneous region of the brain

Table 3
The risks of bias of included studies based on the Cochrane's handbook.



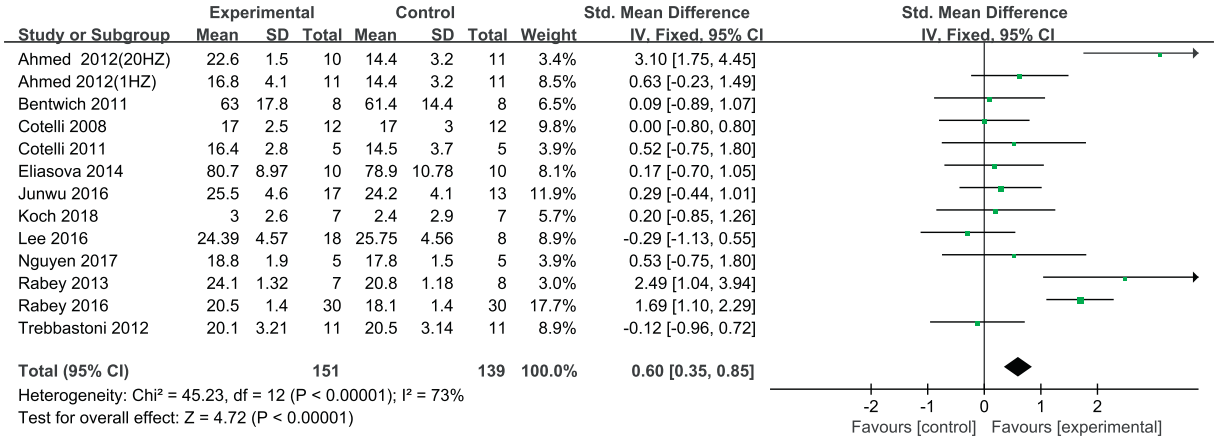


Fig. 2. Forest plot: mean differences in effect of rTMS on patients with Alzheimer's disease with 95% CI.

implicated in cognition, and PC is a promising region for improving memory ability in AD patients. High frequency rTMS on these regions can induce a temporary facilitation or suppression in cortical excitability, and hyperexcitability is the key of rTMS to the treatment AD patients' memory loss. The most common choices for multi-site stimulation were the left and right DLPFC. As to whether bilateral DLPFC stimulation is better than unilateral DLPFC stimulation, different researchers have reached different conclusions. Liao et al. [13] published a meta-analysis included a total of 94 mild to moderate AD patients and found that right or bilateral DLPFC stimulation is better than stimulation of the left DLPFC alone. Haffen et al. [27] reported a case in which two weeks of rTMS treatment of the left DLPFC did not improve cognition as evaluated by MMSE. Cotelli et al. [15].reported that stimulation over the left DLPFC significantly improved the percentage of correct responses in auditory sentence comprehension, but no significant differences were confirmed in other language abilities or memory. Another recently published meta-analysis focused on studies by Drumond Marra et al. [28] and Wu et al. [29] which found that high-frequency rTMS of the left DLPFC had more beneficial effects on cognition, with stimulation of multiple functional areas making no difference. However the patients in these two studies were not simply confined to AD, other diseases such as frontotemporal dementia , Lewy body dementia , vascular dementia and dementia of unknown etiology were also included. Our meta-analysis found that it was more effective to stimulate multiple sites, but that this variable may be confounded with the number of sessions. In this meta-analysis the studies that used multi-site stimulation (8 studies,177 participants) were a large degree the same studies that used long-term treatment (9 studies,175 participants), which was also found to have a positive effect in the statistical analysis. Thus, it is currently difficult to say whether the crucial factor is the breadth of stimulation or the time course of stimulation. Further study is needed to resolve this issue.

The subgroup analysis of number of sessions showed that the pooled effect of rTMS with long-term treatment was moderate (mean effect size, 2.77), while the effect of short-term treatment was very small (mean effect size, 0.29). As we known, rTMS is a non-invasive and painless technology that can detect and regulate the cortical excitability and functions [30,31]. Previous studies have demonstrated that repetitive and long-term stimulation produced stronger and longer-lasting effects on patients with neurodegenerative disease, especially AD and Parkinson's disease [12,32–34]. This meta-analysis is consistent with the previous studies in suggesting that long-term stimulation lead to

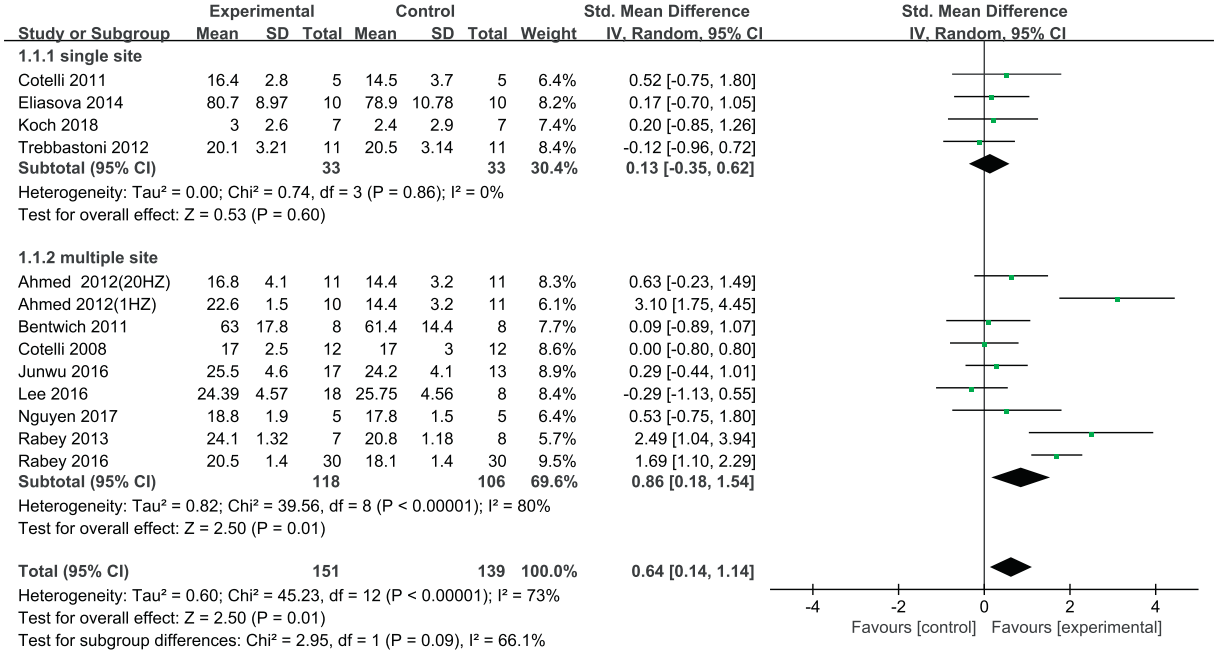


Fig. 3. Forest plot: mean differences in stimulation sites subgroup with 95% CI.

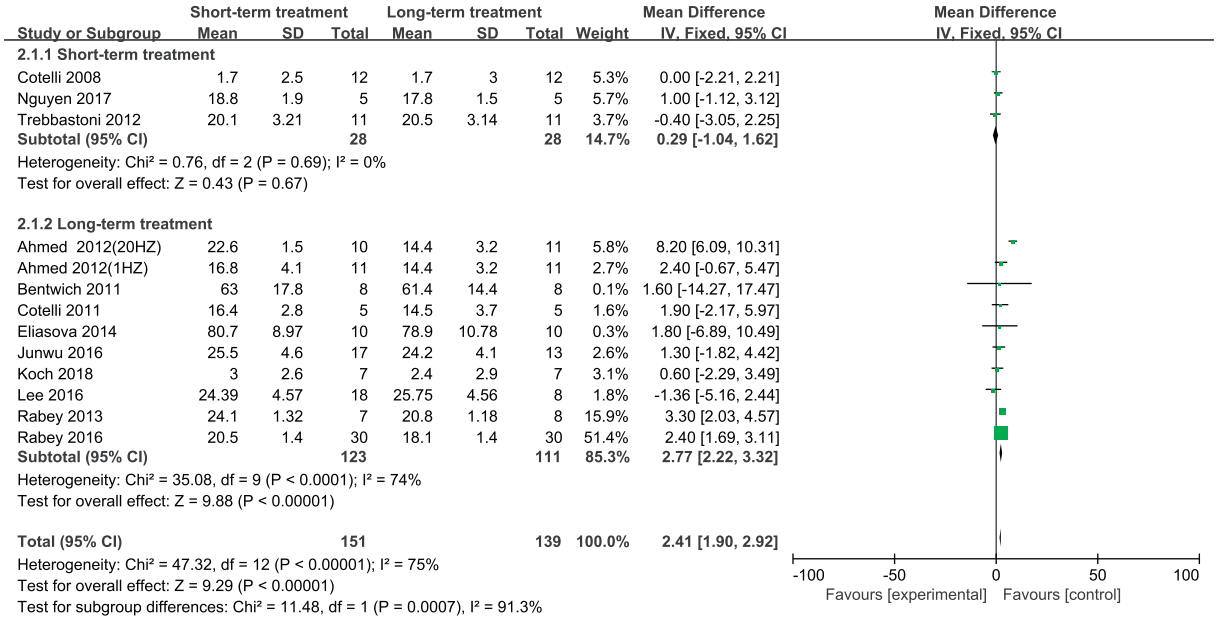


Fig. 4. Forest plot: mean differences in session numbers subgroup with 95% CI.

better rTMS effects.

Subgroup analysis found that combining rTMS with medication (8 studies,151 participants) or cognitive training (6 studies, 119 participants) did not improve outcomes. This is different from meta-analysis of Cheng et al. [10], which found that rTMS without cognition-enhancing drugs but with cognitive training could better improve the cognitive ability in AD patients. Although rTMS combined with cognitive training did not produce additional cognitive improvement in our meta-analysis, we consider it likely that rTMS combined with cognitive training (rTMS-COG) may yield greater enhancement. A possible explanation for the result is that the numbers of participants was small and the sample sizes of the groups were in disequilibrium, the largest group include 30 participants, while the smallest group include 8 participants. Rabey et al. [6,25] revealed significant cognitive improvement in AD patients using rTMS-COG, which suggested that rTMS-COG represents a useful adjuvant therapy for AD patients. In order to better confirm this point, further studies need to be included.

We found only one study [21] directly comparing low-frequency and high-frequency rTMS in AD-associated cognition, so subgroup analysis could not be performed. However, numerous studies demonstrated that high-frequency rTMS is more appropriate than low-frequency rTMS for treating AD [35,36]. Therefore, selecting an optimal rTMS frequency is critical.

Several limitations of our present meta-analysis should be taken into account. First, the number of studies and sample size in our meta-analysis were small. Second, although we evaluated the efficacy of rTMS, we did not assess the effect of duration due to inadequate data. Third, the presence of heterogeneity between studies was inevitable,

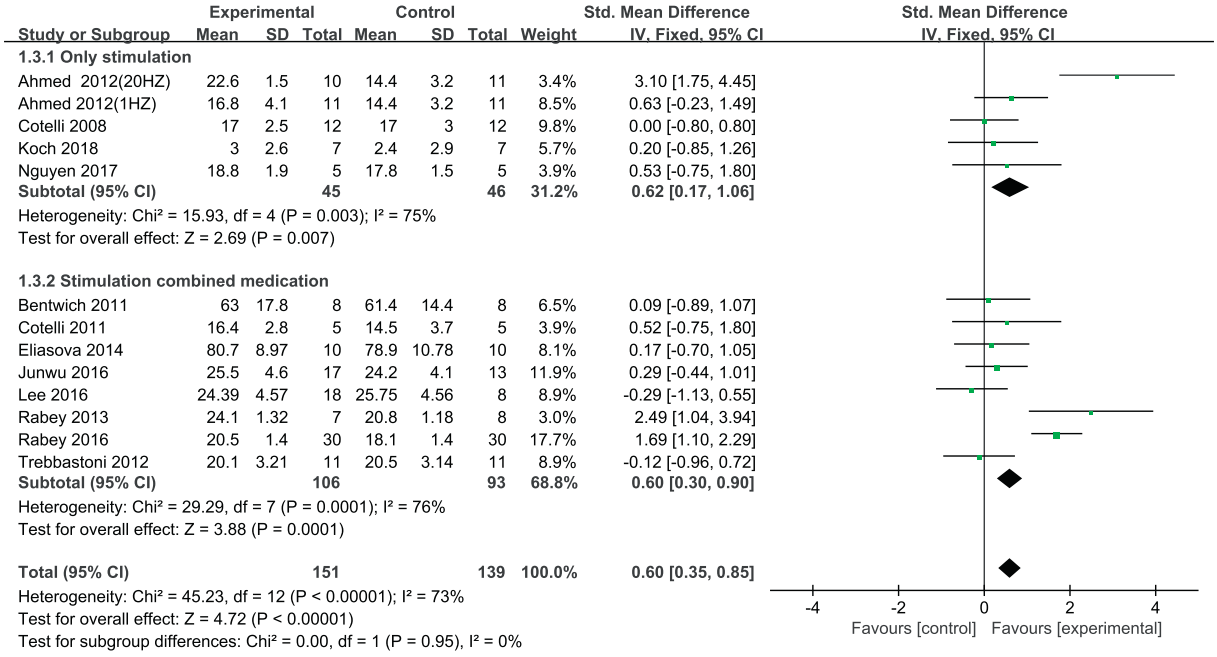


Fig. 5. Forest plot: mean differences in combining with medication subgroup with 95% CI.

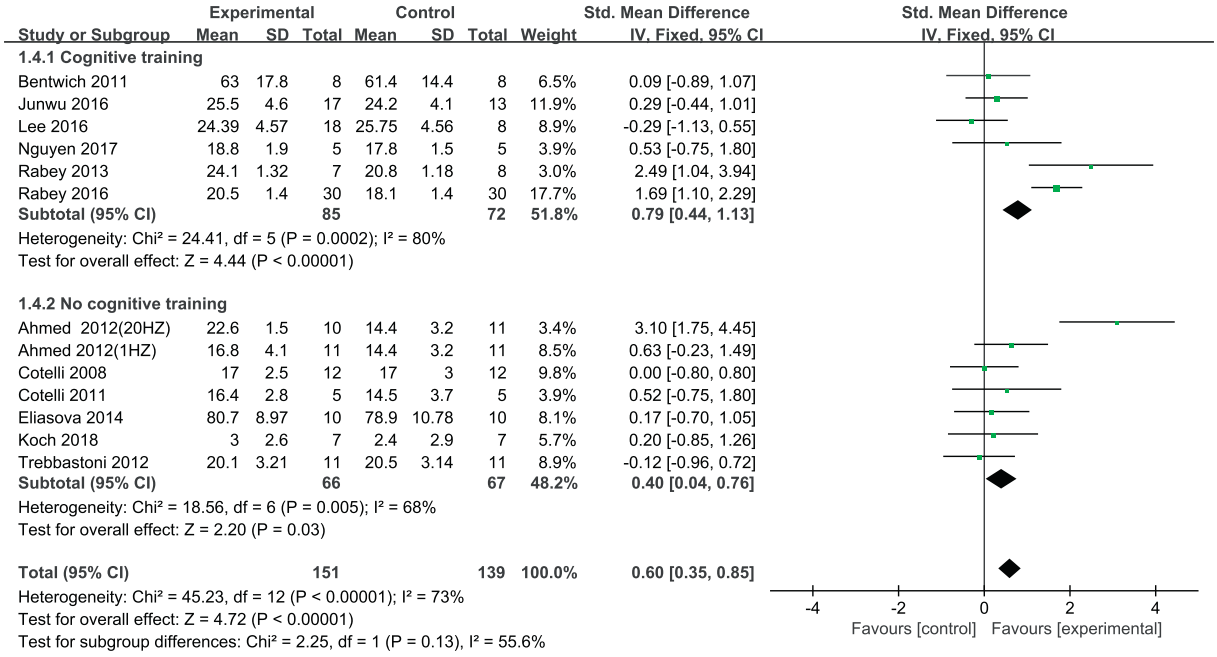


Fig. 6. Forest plot: mean differences in combining with cognitive training subgroup with 95% CI.

and this inconsistency may have influenced our results. To avoid this problem, we selected the most appropriate RCTs based on rigorous inclusion and exclusion criteria. Finally, we only used several evaluation scales to assess cognitive function, which do not give a comprehensive evaluation in AD patients.

5. Conclusion

In conclusion, our meta-analysis provided evidence that rTMS therapy in patients with AD can significantly improve cognitive ability. Stimulating multiple sites (mostly bilateral DLPFC) and long-term treatment are more effective in improving AD-associated cognitive performance. Some novel interventional targets, like PC, may be a more effective therapeutic site to improve memory in AD. Further researches with larger samples are needed to explore the optimal parameters and verify the effect of rTMS on cognition in AD patients.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Source of funding

Study supported by the National Science Foundation for Young Scientists of China (81100972, 81701058), Natural Science Foundation of Shandong Province for Doctoral Fund of China (ZR2016HB37, ZR2017PH027).

Acknowledgements

None.

References

[1] S. Brini, H.R. Sohrabi, J.J. Peiffer, M. Karrasch, H. Hamalainen, R.N. Martins, et al., Physical activity in preventing Alzheimer's disease and cognitive decline: a narrative review, Sports Med. 48 (1) (2018) 29–44.
[2] M. Prince, R. Bryce, E. Albanese, A. Wimo, W. Ribeiro, C.P. Ferri, The global prevalence of dementia: a systematic review and metaanalysis, Alzheimer's Dement. 9 (1) (2013) 63–75 e2.
[3] A.K. Folkerts, M. Roheger, J. Franklin, J. Middelstadt, E. Kalbe, Cognitive interventions in patients with dementia living in long-term care facilities: systematic review and meta-analysis, Arch. Gerontol. Geriatr. 73 (2017) 204–221.
[4] S.O. Bachurin, E.V. Bovina, A.A. Ustyugov, Drugs in clinical trials for Alzheimer's disease: the major trends, Med. Res. Rev. 37 (5) (2017) 1186–1225.
[5] J. Deguil, L. Ravasi, Y. Lamberty, A. Auffret, P. Payoux, C. Leroy, et al., Early development of symptomatic drugs in AD: a systematic review of the use of biomarkers, CNS Neurol. Disord. Drug Targets 15 (7) (2016) 823–836.
[6] J.M. Rabey, E. Dobronevsky, Repetitive transcranial magnetic stimulation (rTMS) combined with cognitive training is a safe and effective modality for the treatment of Alzheimer's disease: clinical experience, J. Neural Transm. 123 (12) (2016) 1449–1455.
[7] Z. Ni, R. Chen, Transcranial magnetic stimulation to understand pathophysiology and as potential treatment for neurodegenerative diseases, Transl. Neurodegener. 4 (2015) 22.
[8] A. Andreou, P. Holland, S. Akerman, O. Summ, J. Fredrick, P. Goadsby, Transcranial magnetic stimulation and potential cortical and trigeminothalamic mechanisms in migraine, Brain 139 (Pt 7) (2016) 2002–2014.
[9] J.P. Lefaucheur, N. Andre-Obadia, A. Antal, S.S. Ayache, C. Baeken, D.H. Benninger, et al., Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS), Clin. Neurophysiol. 125 (11) (2014) 2150–2206.
[10] C. Cheng, C. Wong, K. Lee, A. Chan, J. Yeung, W. Chan, Effects of repetitive transcranial magnetic stimulation on improvement of cognition in elderly patients with cognitive impairment: a systematic review and meta-analysis, Int. J. Geriatr. Psychiatry 33 (1) (2018) e1–e13.
[11] A. Benussi, F. Di Lorenzo, V. Dell'Era, M. Cosseddu, A. Alberici, S. Caratozzolo, et al., Transcranial magnetic stimulation distinguishes Alzheimer's disease from frontotemporal dementia, Neurology 89 (7) (2017) 665–672.
[12] L. Anderkova, I. Rektorova, Cognitive effects of repetitive transcranial magnetic stimulation in patients with neurodegenerative diseases - clinician's perspective, J. Neurol. Sci. 339 (1–2) (2014) 15–25.
[13] X. Liao, G. Li, A. Wang, T. Liu, S. Feng, Z. Guo, et al., Repetitive transcranial magnetic stimulation as an alternative therapy for cognitive impairment in Alzheimer's disease: a meta-analysis, J. Alzheimer's Dis. 48 (2) (2015) 463–472.
[14] J. Higgins, D. Altman, P. Gøtzsche, P. Jüni, D. Moher, A. Oxman, et al., The Cochrane Collaboration's tool for assessing risk of bias in randomized trials, BMJ 343 (2011) d5928.
[15] M. Cotelli, M. Calabria, R. Manenti, S. Rosini, O. Zanetti, S.F. Cappa, et al., Improved language performance in Alzheimer's disease following brain stimulation, J. Neurol. Neurosurg. Psychiatry 82 (7) (2011) 794–797.
[16] A. Trebbastoni, F. Gilio, F. D'Antonio, C. Cambieri, M. Ceccanti, C. de Lena, et al., Chronic treatment with rivastigmine in patients with Alzheimer's disease: a study on primary motor cortex excitability tested by 5 Hz-repetitive transcranial magnetic stimulation, Clin. Neurophysiol. 123 (5) (2012) 902–909.
[17] I. Eliasova, L. Anderkova, R. Marecek, I. Rektorova, Non-invasive brain stimulation of the right inferior frontal gyrus may improve attention in early Alzheimer's disease: a pilot study, J. Neurol. Sci. 346 (1–2) (2014) 318–322.
[18] G. Koch, S. Bonnì, M.C. Pellicciari, E.P. Casula, M. Mancini, R. Esposito, Transcranial magnetic stimulation of the precuneus enhances memory and neural activity in prodromal Alzheimer's disease, NeuroImage 169 (2018) 302–311.
[19] M. Cotelli, R. Manenti, S.F. Cappa, O. Zanetti, C. Miniussi, Transcranial magnetic stimulation improves naming in Alzheimer's disease patients at different stages of

cognitive decline, Eur. J. Neurol. 15 (12) (2008) 1286–1292.
[20] J. Bentwich, E. Dobronevsky, S. Aichenbaum, R. Shorer, R. Peretz, M. Khaigrekht, et al., Beneficial effect of repetitive transcranial magnetic stimulation combined with cognitive training for the treatment of Alzheimer's disease: a proof of concept study, J. Neural Transm. 118 (3) (2011) 463–471.
[21] M.A. Ahmed, E.S. Darwish, E.M. Khedr, Y.M. El Serogy, A.M. Ali, Effects of low versus high frequencies of repetitive transcranial magnetic stimulation on cognitive function and cortical excitability in Alzheimer's dementia, J. Neurol. 259 (1) (2012) 83–92.
[22] J. Lee, B.H. Choi, E. Oh, E.H. Sohn, A.Y. Lee, Treatment of Alzheimer's disease with repetitive transcranial Magnetic stimulation combined with cognitive training: a prospective, randomized, double-blind, placebo-controlled study, J. Clin. Neurol. 12 (1) (2016) 57–64.
[23] J. Zhao, Z. Li, Y. Cong, J. Zhang, M. Tan, H. Zhang, et al., Repetitive transcranial magnetic stimulation improves cognitive function of Alzheimer's disease patients, Oncotarget 8 (20) (2017) 33864–33,871.
[24] J.P. Nguyen, A. Suarez, G. Kemoun, M. Meignier, E. Le Saout, P. Damier, et al., Repetitive transcranial magnetic stimulation combined with cognitive training for the treatment of Alzheimer's disease, Neurophysiol. Clin. 47 (1) (2017) 47–53.
[25] J.M. Rabey, E. Dobronevsky, S. Aichenbaum, O. Gonen, R.G. Marton, M. Khaigrekht, et al., Repetitive transcranial magnetic stimulation combined with cognitive training is a safe and effective modality for the treatment of Alzheimer's disease: a randomized, double-blind study, J. Neural Transm. (Vienna) 120 (5) (2013) 813–819.
[26] R. Nardone, F. Tezzon, Y. Höller, S. Golaszewski, E. Trinka, F. Brigo, et al., Transcranial magnetic stimulation (TMS)/repetitive TMS in mild cognitive impairment and Alzheimer's disease, Acta Neurol. Scand. 129 (6) (2014) 351–366.
[27] E. Haffen, G. Chopard, J. Pretalli, E. Magnin, M. Nicolier, J. Monnin, et al., A case report of daily left prefrontal repetitive transcranial magnetic stimulation (rTMS) as an adjunctive treatment for Alzheimer's disease, Brain Stimul. 5 (3) (2012) 264–266.
[28] H. Drumond Marra, M. Myczkowski, C. Maia Memória, D. Arnaut, P. Leite Ribeiro, C. Sardinha Mansur, et al., Transcranial magnetic stimulation to address mild cognitive impairment in the elderly: a randomized controlled study, Behav. Neurol. 2015 (2015) 287843.
[29] Y. Wu, W. Xu, X. Liu, Q. Xu, L. Tang, S. Wu, Adjunctive treatment with high frequency repetitive transcranial magnetic stimulation for the behavioral and psychological symptoms of patients with Alzheimer's disease: a randomized, double-blind, sham-controlled study, Shanghai Arch. Psychiatry 27 (5) (2015) 280–288.
[30] S. Vucic, M.C. Kiernan, Transcranial magnetic stimulation for the assessment of neurodegenerative disease, Neurotherapeutics 14 (1) (2017) 91–106.
[31] S. Murphy, L. Palmer, T. Nyffeler, R. Müri, M. Larkum, Transcranial magnetic stimulation (TMS) inhibits cortical dendrites, Elife 5 (2016) e13598.
[32] W.Y. Hsu, Y. Ku, T.P. Zanto, A. Gazzaley, Effects of noninvasive brain stimulation on cognitive function in healthy aging and Alzheimer's disease: a systematic review and meta-analysis, Neurobiol. Aging 36 (8) (2015) 2348–2359.
[33] B. Luber, S.H. Lisanby, Enhancement of human cognitive performance using transcranial magnetic stimulation (TMS), NeuroImage 85 (2014) 961–970.
[34] Y. Chou, P. Hickey, M. Sundman, A. Song, N. Chen, Effects of repetitive transcranial magnetic stimulation on motor symptoms in Parkinson's disease: a systematic review and meta-analysis, JAMA Neurol. 72 (4) (2015) 432–440.
[35] R. Nardone, F. Tezzon, Y. Holler, S. Golaszewski, E. Trinka, F. Brigo, Transcranial magnetic stimulation (TMS)/repetitive TMS in mild cognitive impairment and Alzheimer's disease, Acta Neurol. Scand. 129 (6) (2014) 351–366.
[36] R. Nardone, J. Bergmann, M. Christova, F. Caleri, F. Tezzon, G. Ladurner, et al., Effect of transcranial brain stimulation for the treatment of Alzheimer's disease: a review, Int. J. Alzheimer's Dis. 2012 (2012) 687909.