An Extensive Evaluation and Meta-Analysis of Transcranial Magnetic Stimulation's Effectiveness as a Treatment for Alzheimer's disease

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Abstract

Background: *For the treatment of Alzheimer's disease, repetitive transcranial magnetic stimulation (rTMS) is frequently employed. The impact of rTMS is still debatable, though. The current study's objective is to assess rTMS's impact on AD patients' cognitive function.*

Methods: *Before April 28, 2022, I conducted a thorough search of the pertinent literature in four main databases: PubMed, EMBASE, Web of Science, and the Cochrane Central Register of Controlled Trials [Central]. There were both cross-section studies and randomised controlled trials that compared the healing power of rTMS with no stimulation or sham stimulation.*

Results: *A total of 14 studies involving 513 AD patients were finally included for meta-analysis. It was found that rTMS significantly improved global cognitive function (SMD = 0.24, 95%CI, 0.12 to 0.36, P = 0.0001) and daily living ability (IADL: SMD = 0.64, 95%CI, 0.21to 1.08, P = 0.004) in patients with AD, but did not show improvement in language, memory, executive ability, and mood. In further analyses, rTMS at 10 Hz, on a single target with 20 sessions of treatment was shown to produce a positive effect. In addition, improvement in cognitive functions lasted for at least 6 weeks (SMD = 0.67, 95%CI, 0.05 to 1.30,P = 0.04).*

Conclusion: *rTMS can help AD patients with their everyday functioning and general cognition. Additionally, rTMS safety in AD patients with seizures needs to be taken into consideration. Our results should not be taken too seriously due to the limited sample size.*

Key-words: *Repetitive transcranial magnetic stimulation, Alzheimer's disease, cognitive function, activities of daily living, therapeutic efficacy*

I.   Introduction

One of the main causes of reliance, disability, and death, dementia is an acquired, gradual cognitive impairment that interferes with daily tasks. There are currently over 44 million dementia patients worldwide, and as the ageing population grows, it is predicted that number will triple by 2050. (Lane et al., 2018). Alzheimer's disease (AD), which affects 50–75% of dementia sufferers, is the most common cause of dementia. After the age of 65, its prevalence substantially doubles every five years (Albanese et al., 2014). Clinically, it primarily shows itself as cognitive impairment, aberrant psychomotor activities, and social disengagement, all of which considerably raise the risk of emotional discomfort and detrimental effects on both physical and mental health (Alzheimer's Association, 2021).

There are now five drugs approved by the FDA to treat AD, including glutamate receptor antagonists (memantine) and acetylcholinesterase inhibitors (Raina et al., 2008). Clinicians and researchers are searching for solutions in the area of non-pharmacological interventions due to the limited effectiveness of current pharmacological therapies for recovering brain functions. Transcranial magnetic stimulation (TMS) is a non-invasive treatment that may enhance cognitive ability and neuroplasticity. It is being given more thought as a possible therapeutic approach to treat AD.

A non-invasive neuro-modulation approach is transcranial magnetic stimulation (TMS). Its magnetic pulses pass through the layer separating the skin's surface from the brain's surface. Variations in the magnetic field's strength produce electric fields that can stimulate particular parts of the brain (Liao et al., 2015). According to Gangitano et al. (2002), it has the power to control not only the excitability of nerves and the operations of the cortices but also the activity of specific neurons (Mueller et al., 2014). In order to treat depression, pain, fibromyalgia, post-traumatic stress disorder, non-fluent aphasia following stroke, and cognitive impairment, it has been frequently employed (Lefaucheur et al., 2020). (Trung et al., 2019). Although numerous

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clinical trials (Cotelli et al., 2011; Ahmed et al., 2012; Koch et al., 2018) and meta-analyses (Dong et al., 2018; Lin et al., 2019; Wang et al., 2020; Teselink et al., 2021) have examined the effectiveness and safety of repetitive TMS (rTMS) for patients with AD, no consensus has been reached. The effects of single point stimulation, multi-point stimulation, the number of treatment sessions, and the combination of treatment with cognitive training on AD were not reported in a recent meta-analysis that summarised the findings from randomised controlled trials that were published in PubMed and Web of Science. In order to get a clear conclusion regarding the effectiveness of rTMS in managing AD from many angles, I therefore conducted this systematic review and meta-analysis on all RCT and cross-section studies published by April 28, 2022. Analysis was also done on how rTMS affected several cognitive domains as well as general cognitive functioning.

II. Materials and Methods

The present study was conducted by complying with the PRISMA guideline for systematic evaluation and meta-analysis (McInnes et al., 2018). This study was registered at PROSPERO1.

Search Approach for the Literature

Using the following keywords: "Alzheimer's Disease" or "Dementia of Alzheimer type" or "AD" and "transcranial magnetic stimulation" or "repetitive transcranial magnetic stimulation" or "TMS" or "rTMS" and ("randomized controlled trial" OR "controlled clinical trial" OR "cross-section" OR randomized OR placebo OR ", researcher (Tshetiz) independently searched literatures on PubMed, EMBASE, Web of Science, and the Randomized controlled trials and cross-section studies that were published before or on April 28, 2022, were chosen from among these articles. A senior investigator (Dr.Aditya) was invited to review the papers against the inclusion and exclusion criteria and endorse the final list of publications if there was any contradiction with the researcher.

Eligibility Criteria

According to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA), all full-text randomised controlled studies and cross-section studies published in English, the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM V) or 4th Edition (DSM IV), and rTMS was administered to an age- and sex-neutral population with an AD diagnosis were eligible. rTMS was the only different intervention for particular cortical regions, and sham rTMS in the same cortical regions was designated as the control conditions. Cognitive-related neurobehavioral outcomes included changes in any cognitive domain between pre- and post-intervention, as well as global cognition as assessed by objective (as opposed to subjective) cognitive measures. When an article appeared in more than one database, the one with the greatest number of patients or the most comprehensive information was used. When relevant data were given at various times, the most recent time point's results were used.

Data Extraction

Authors, year of publication, research type, population characteristics (such as age, sex ratio, years of education, the course of the disease, diagnosis criteria), type and characteristics of stimuli (including intensity, frequency, site, sessions of treatment), neurobehavioral outcomes [mean and standard deviation (SD), and adverse events—were all independently extracted by the researcher from each included study. Studies were mined for quality evaluations of the listed studies. We extracted changes in outcomes before and after treatment in a single group for cross-design clinical research. Results from clinical studies with several treatment groups were combined and analyzed. The respective authors were contacted to request the Mean and SD when they weren't provided in the text.

Quality Evaluation

The researcher evaluated the calibre of the methodologies used by the included studies in accordance with the evaluation criteria of the Cochrane risk of bias tool (Sterne et al., 2019). Any differences of opinion were settled through conversation or by bringing in a senior researcher. Each study's quality was evaluated in the following seven areas.
(1) creation of random sequences.
(2) concealing the allocation.
(3) Implementers and participants are rendered blind.
(4) Blinding the evaluation of the results.
(5) Reliability of the outcomes.
(6). Strict reporting
(7) Additional biases

Each aspect's bias risk was divided into three risk categories: low, high, and uncertain.

Data Analysis

The CochraneRev-Man 5.4 software was used for statistical analysis of the data, calculating and reporting the standardized mean difference (SMD) and 95% confidence interval for each major outcome. SMD describes how much an intervention affects outcome, and an effect of ≥ 0.8 is considered significant and potentially clinically relevant. Reports on global cognitive functions (MMSE, MoCA, ADAS-Cog, ACE-III), language (sentence comprehension test), memory (RAVLT), the ability to execute (TMT-A), daily life ability (IADL) and emotion (GDS) were included in the meta-analysis. I2 was used to evaluate the heterogeneity of the included studies: when I2 < 50%, it was considered to have low heterogeneity, and the fixed-effect model was used. When I2 value $\geq 50\%$, it was considered to have high heterogeneity, and the random-effects model was used to summarize the effect size.

If data from at least ten studies were available, a meta-regression analysis was performed to assess the relationship between age, scale choice, frequency of stimulation, site of stimulation, and number of sessions of treatment and TMS treatment outcomes. STATA17.0 software was used to construct funnel plots for qualitative evaluation of publication bias, Begg and Egger tests were used for quantitative evaluation. The data we used were changes in scores assessed using cognition assessment scales relative to baseline scores after completion of treatment. When score changes were not directly provided in the study, use the following formula to convert the data provided in the article:

$$\text{Mean change} = \text{mean final} - \text{mean baseline}$$

$$SD\ change = \sqrt{\text{SD baseline}^2 + \text{SD final}^2 - (2 \times \text{coeffcient} \times \text{SD baseline} \times \text{SD final})}$$

In all analysis, $p < 0.05$ was considered statistically significant.

III.   Results

Literature Screening

A total of 1,059 articles were found in 4 major databases using a variety of searching strategies. A total of 263 publications were excluded due to duplicates or incomplete basic information. Another 754 publications were excluded because they were irrelevant to the condition we were interested in, basic scientific research, or non-randomized controlled studies. When the full text was inspected, 2 were excluded because of the single arm nature, 5 because of inconsistent control measures were taken, 2 because of inconsistent outcome indices, 4 because of meeting summaries or reviews, 8 because of incomplete data, another 7 because they were study protocols. Finally, 14 articles were selected for meta-analysis (Figure 1).
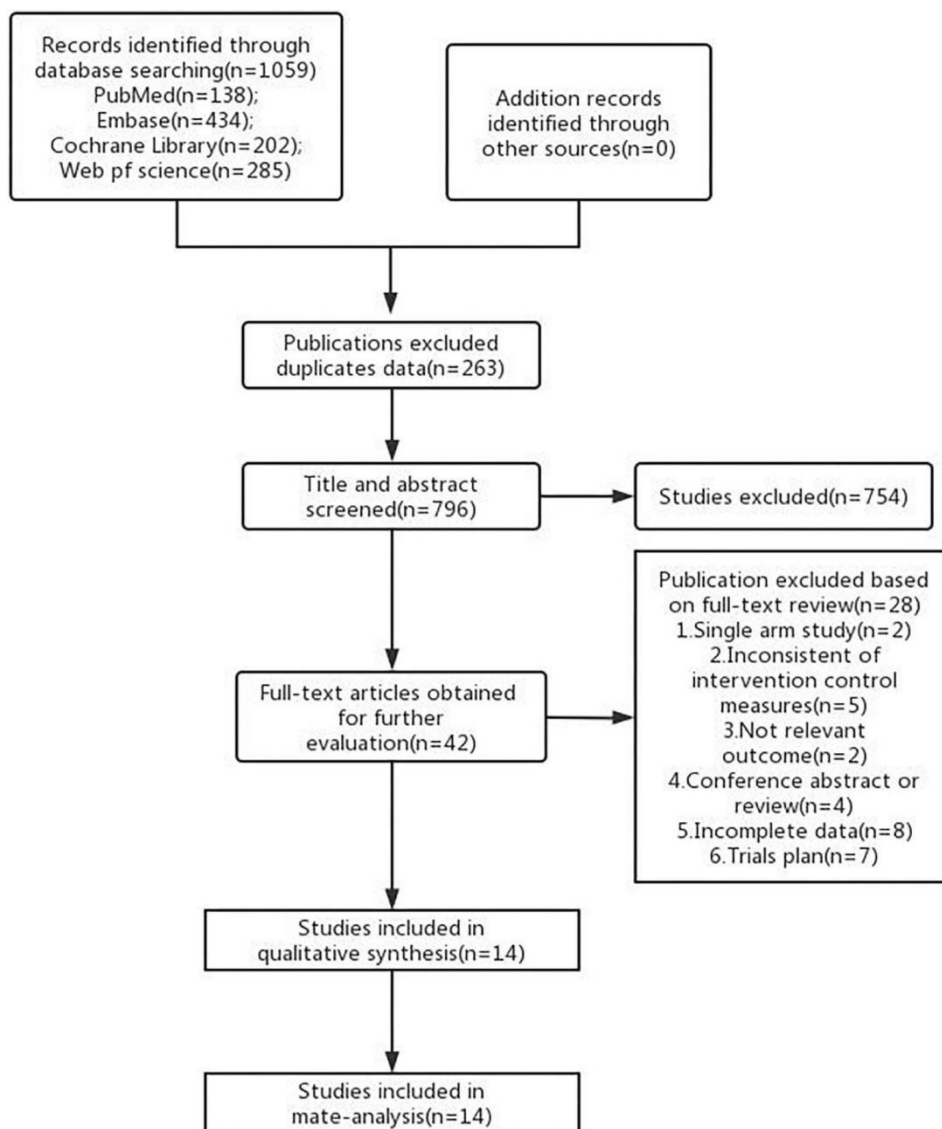
Figure 1. Diagram of literature searching and selection for meta-analysis.

Information of Included Studies

A total of 513 AD patients with varying degrees of severity were included in this meta-analysis. Their age ranged from 60 to 80 years and 53.5% of them were female. Demographic information of the participants was summarized in Table 1, types and characteristics of the stimuli in Table 2. Sham-rTMS was similar to the real rTMS in sound and feeling upon contacting with the head, but did not produce actual therapeutic effects. Generally, the coil was tilted away from the head to achieve the purpose of false stimulation. For example, in the study of Jia et al. (2021), the same coil was tilted 45° from the scalp so that one side of the coil was in contact with the scalp and the distance between the center of the coil and the target site was greater than 5 cm. Patients would also feel the noise and sensation caused by the same stimulation. In the study of Wu et al. (2015), the coil was flipped 180°, where the coil was perpendicular to the scalp in the study of Zhang et al. (2019). In other studies, special fake coil was used, or the coil was attached to the scalp, but no therapeutic stimuli were applied.

No.	Study (time)	Design	Participants (N)	Sex (M/F)	Mean age (years)	Mean education (years)	Mean disease duration (year)	Diagnostic criteria
1	Ahmed et al. (2012)	Parallel	rTMS-20HZ(15)	5/10	65.9	NA	3.9	NINCDS-ADRDA
			rTMS-1HZ(15)	6/9	68.6	NA	4.1	
			Sham(15)	5/10	68.3	NA	4.4	
2	Li et al. (2021)	Parallel	rTMS (37)	20/17	66	5.7	3.7	DSM-V
			Sham(38)	24/14	64.6	6.6	3.97	
3	Cotelli et al. (2011)	Parallel	rTMS(5)	NA	71.2	6.4	NA	NINCDS-ADRDA
			Sham(5)	NA	74.4	4.8	NA	
4	Jia et al. (2021)	Parallel	rTMS(35)	10/25	71.4	7.7	NA	DSM-V
			Sham(34)	11/23	73.4	7.5	NA	
5	Leocani et al. (2020)	Parallel	rTMS(16)	9/7	69.6	9.2	4.2	NINCDS-ADRDA
			Sham(12)	6/6	72.6	7.8	4.2	
6	Padala et al. (2020)	Parallel	rTMS(9)	8/1	74.3	NA	NA	NA
			Sham(11)	10/1	79.6	NA	NA	
7	Rabey et al. (2013)	Parallel	rTMS-COG(7)	5/2	72.6	NA	NA	DSM-V
			Sham(8)	5/3	75.4	NA	NA	
8	Wu et al. (2015)	Parallel	rTMS(26)	10/16	71.4	11.4	5.1	NINCDS-ADRDA
			Sham(26)	11/15	71.9	11.5	5.1	
9	Zhang et al. (2019)	Parallel	rTMS-COG(15)	3/12	69	12.4	3.53	NINCDS-ADRDA
			Sham(13)	3/10	68.5	11.9	3.62	
10	Zhao et al. (2017)	Parallel	rTMS(17)	7/10	69.3	4.8	NA	DSM-IV
			Sham(13)	6/7	71.4	4.9	NA	
11	Bagattini et al. (2020)	Parallel	rTMS-COG(27)	17/10	73.56	8.85	1.94	NA
			Sham(23)	12/11	73.35	7.91	1.67	
12	Koch et al. (2018)	Cross-section	rTMS/sham(14)	7/7	70	7.2	NA NA	NA
13	Turriziani et al. (2019)	Parallel	rTMS(7)	5/9	71.28	14.28	NA	NA
			Sham(7)		71.71	13	NA	
14	Vecchio et al. (2022)	Parallel	Real rTMS-COG(30)	14/16	71.07	13.87	NA	NA
			Sham rTMS-COG(17)	10/7	72.24	11.47	NA	
			Sham(16)	5/11	75.2	11.81	NA	

No, number; M, male; F, female; COG, cognitive training; NA, not reported.

Table 1. Demographic Characteristics of Included Trials.

High frequency rTMS (HFrTMS) was dominantly used by included studies with 7 studies adopting high frequency up to 20 Hz (Cotelli et al., 2011; Ahmed et al., 2012; Wu et al., 2015; Zhao et al., 2017; Koch et al., 2018; Bagattini et al., 2020; Li et al., 2021). Studies by Ahmed et al compared the effects of high (20Hz) and low frequencies (1Hz) (Ahmed et al., 2012). A study by Turriziani et al. (2019) used 1 Hz, and the other 6 studies used 10 Hz (Rabey et al., 2013; Leocani et al., 2020; Padala et al., 2020; Jia et al., 2021; Vecchio et al., 2022). The dorsolateral prefrontal cortex (DLPFC) was selected as the stimulation site in the majority of studies (10/14) (Cotelli et al., 2011; Ahmed et al., 2012; Rabey et al., 2013; Wu et al., 2015; Turriziani et al., 2019; Zhang et al., 2019; Bagattini et al., 2020; Padala et al., 2020; Li et al., 2021; Vecchio et al., 2022). Rabey et al. (2013) and Vecchio et al. (2022) stimulated Broca, Wernicke, L/R-DLPFC, and L/R pSAC. Zhao et al. (2017) stimulated four parietal P3/P4 and posterior temporal T5/T6. Regarding the type of coil used for stimulation, the H-type coil was used in the study of Leocani et al. (2020), whereas the rest of the studies used the "8" shaped coil. Among the 14 studies, the majority of them adopted 10 to 30 sessions, with a maximum of 54 and a minimum of 5 sessions.

A number of studies reported cognitive performance at follow-up ranging from 1 to 10 months. Four studies reported adverse reactions during the treatment (Zhang et al., 2019; Leocani et al., 2020; Padala et al., 2020; Jia et al., 2021).

No.	Study (time)	Groups	Frequency	Stimulation protocol	Stimulation sites	Number of sessions	Length of follow-up
1	Ahmed et al. (2012)	rTMS-20HZ	20 Hz	90% of MT, 2000 pulses	L/R-DLPFC	5	4 and 12 weeks.
		rTMS-1HZ	1 Hz	100% of MT,2000 pulses			
		sham	\	the coil angled away from the head			
2	Li et al. (2021)	rTMS	20 Hz	100% of MT, 2000 pulses	L-DLPFC	30	12 weeks
		sham	\	used a pseudo-stimulus coil			
3	Cotelli et al. (2011)	rTMS	20 Hz,	100% of MT, 2000 pulses	L-DLPFC	10	8 weeks
		sham	\	used a sham coil			
4	Jia et al. (2021)	rTMS	10 Hz	100–110% of MT, 800 pulses	left lateral parietal cortex site	10	NA
		sham	\	the coil was rotated 45?away from the brain			
5	Leocani et al. (2020)	rTMS	10 Hz	120% of MT, 840 pulses	bilateral frontalparietal-temporal regions	16	NA
		sham	\	used a sham coil			
6	Padala et al. (2020)	rTMS	10 Hz	120% of MT, 3000 pulses	L-DLPFC	20	8 and 12 weeks
		sham	\	NA			
7	Rabey et al. (2013)	rTMS-COG	10 Hz	90–110 % of MT, 1300 pulses	Broca, Wernicke, L/R-DLPFC, L/R pSAC	54	NA
		sham	\	using a sham coil			
8	Wu et al. (2015)	rTMS	20 Hz	80% of MT, 1200 pulses	L-DLPFC	20	NA
		sham	\	the coils were turned 180°			
9	Zhang et al. (2019)	rTMS-COG	10 Hz	100% of RMT, 1000 pulses	L-DLPFC	20	4 weeks
		sham	\	the coils were turned 90°			
10	Zhao et al. (2017)	rTMS	20 Hz	NA	parietal P3/P4 and posterior temporal T5/T6	30	6 weeks
		sham	\	used a sham coil			
11	Bagattini et al. (2020)	rTMS-COG	20Hz	100% of MT, 2000 pulses	L-DLPFC	20	12 weeks
		sham	\	a 3-cm thick block of wood was placed between the coil and the scalp			
12	Koch et al. (2018)	rTMS	20Hz	100% of RMT, 1600 pulses	Precuneus	10	NA
		sham	\	used a sham coil			
13	Turriziani et al. (2019)	rTMS	1Hz	90% of MT, 600 pulses	R-DLPFC	10	4 weeks
		sham	\	\			
14	Vecchio et al. (2022)	Real rTMS -COG	10Hz	90–110% of MT, 1200–1400 pulses	Broca, Wernicke, L/R-DLPFC, L/R pSAC	30	40 weeks
		Sham rTMS -COG	\	using a sham coil			
		Sham	\	using a sham coil			

L, left; R, right; DLPFC, dorsolateral prefrontal cortex; pSAC, parietal somatosensory association cortex; MT, motor threshold.

Table 2. Description of repetitive transcranial magnetic stimulation (rTMS) intervention in the included studies.

Quality of Included Studies

The quality of included studies was independently assessed using the Revman software by two researchers. As shown in Table 2, only the study by Koch et al. (2018) used the cross design, and the rest were randomized controlled studies. These indicate that the overall quality of the included studies was good (Figure 2).
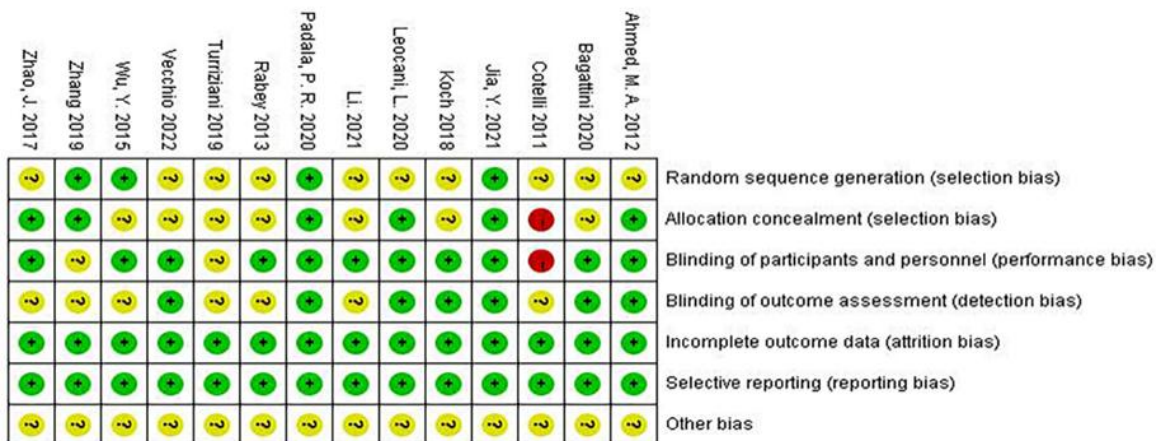

Figure 2. Analysis of risk of bias.

General Cognitive Functions and Repeated Transcranial Magnetic Stimulation

Thirteen studies assessed the impact of rTMS on global cognitive functions, namely, the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Addenbrooke's Cognitive Examination III (ACE-III) and the Alzheimer's Disease Assessment Scale-Cognitive Sub-scale (ADAS-Cog). Among these studies, 3 used the MMSE and ADAS-cog scales to assess patients' global cognitive status (Zhao et al., 2017; Zhang et al., 2019; Li et al., 2021), 6 studies counted MMSE results (Cotelli et al., 2011; Ahmed et al., 2012; Koch et al., 2018; Bagattini et al., 2020; Padala et al., 2020; Jia et al., 2021), and 4 studies counted ADAS-cog results (Rabey et al., 2013; Wu et al., 2015; Leocani et al., 2020; Vecchio et al., 2022). The above findings showed that rTMS significantly improved global cognitive functions (measured by MMSE or ADAS-Cog) in AD patients (SMD = 0.34,95% CI, 0.16 to 0.52, p = 0.0002, I2 = 0%, Figure 3).

When subgroup analysis was conducted to discuss MMSE and ADAS-cog, respectively, rTMS still had a significant effect on the global cognitive functions of AD patients (MMSE: SMD = 0.59, 95%CI, 0.36 to 0.81, I2 = 87%; ADAS-cog: SMD = –0.34, 95%CI, –0.59 to –0.10, I2 = 42%) (Figure 3). It should be noted that the MMSE score is a positive indicator, and the higher the score, the better the cognitive status of patients.
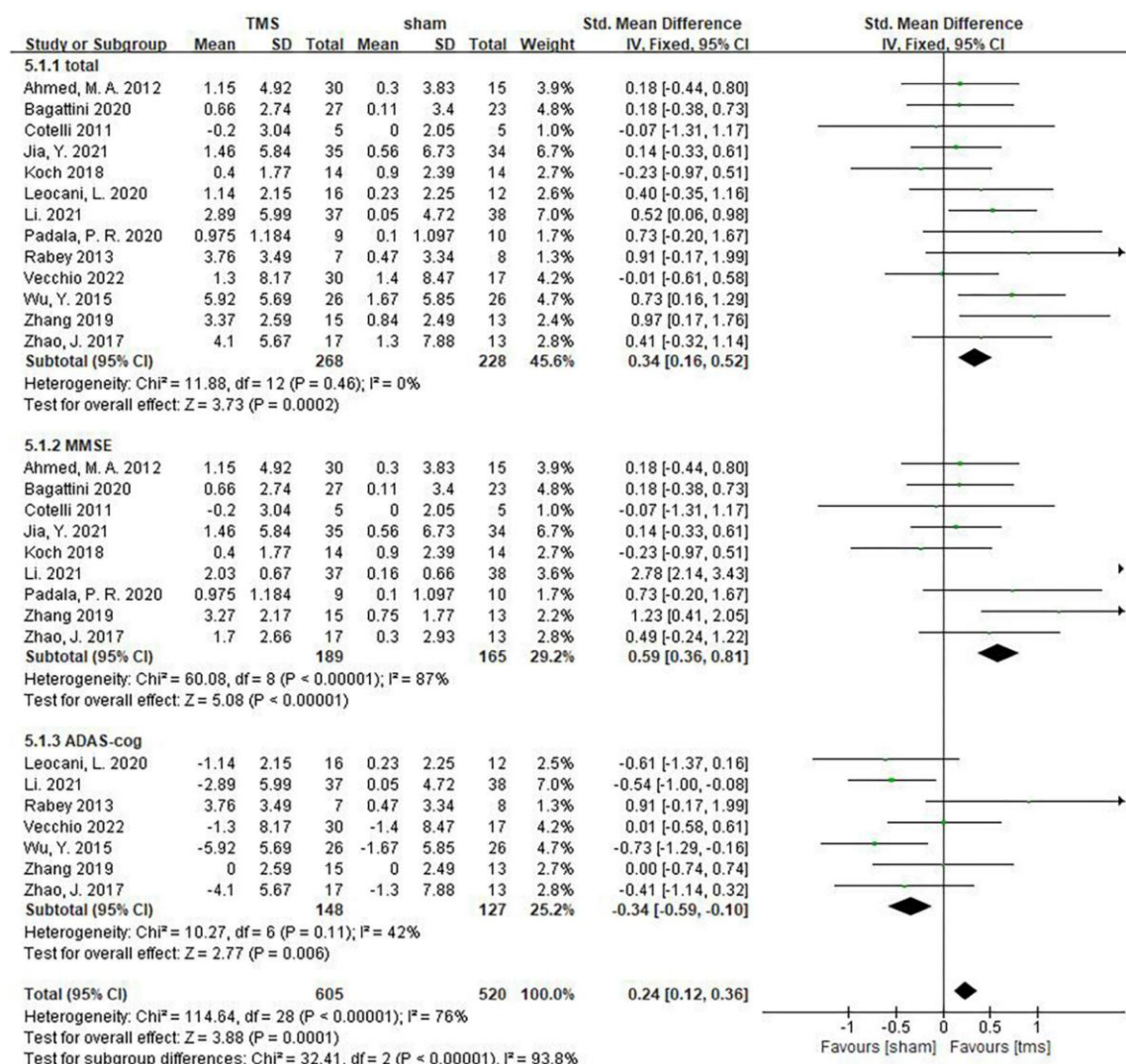

Figure 3. The effect of repetitive transcranial magnetic stimulation (rTMS) on global cognitive functions.

While ADAS-cog is a negative indicator, the lower the score, the better the cognitive status of patients. In our forest map, the abscissa is defined according to the MMSE score, that is, the left is the sham stimulation group, and the right is the rTMS treatment group. However, for the subgroup analysis of ADAS-cog, we accurately calculated the results of each study, so the SMD values of subgroups that fell on the left indicated that the rTMS treatment was effective. In particular, Zhao et al. (2017) additionally used the MoCA scale to show that rTMS had a significant treatment effect [rTMS change (Mean ± SD): 2.3 ± 6.36; sham change (Mean

± SD): 1.2 ± 7.02]. Zhang et al. (2019) also observed more significant results using the ACE-III scale [rTMS change (Mean ± SE): 11.77 ± 1.32; Sham change (Mean ± SE): 2.18 ± 1.43].

Inconsistencies exist in the rTMS intervention parameters among the included studies, and we conducted subgroup analyses on stimulation frequency, stimulation sites, and the number of sessions of treatment. As shown in Figure 4, compared with rTMS at 20 Hz, stimulation frequency at 10 Hz had a more significant effect (SMD = 0.29, 95%CI, 0.01 to 0.57, P = 0.04). When analyzing the influence of stimulating loci, it was found that single stimulation of L-DLPFC (SMD = 0.84, 95%CI, 0.08 to 1.59, P = 0.03) was more effective than multi-point stimulation (SMD = 0.30, 95%CI, 0.00 to 0.61, P = 0.05) (Figure 5).

In addition, the therapeutic effect was most significant when the number of treatment sessions was 20 (SMD = 0.61, 95%CI, 0.28 to 0.95, P = 0.0003), followed by treatment sessions over 20 (SMD = 0.39, 95%CI, 0.07 to 0.70, P = 0.02). No statistical difference was observed when the number of treatment sessions was less than 20 (SMD = 0.16, 95%CI, –0.12 to 0.45, P = 0.26) (Figure 6). Some of the studies in the meta-analysis also provided participants with supplemental cognitive training when assessing the impact of rTMS on global cognition, but the content of cognitive training varied between studies (Rabey et al., 2013; Zhang et al., 2019; Bagattini et al., 2020; Vecchio et al., 2022).
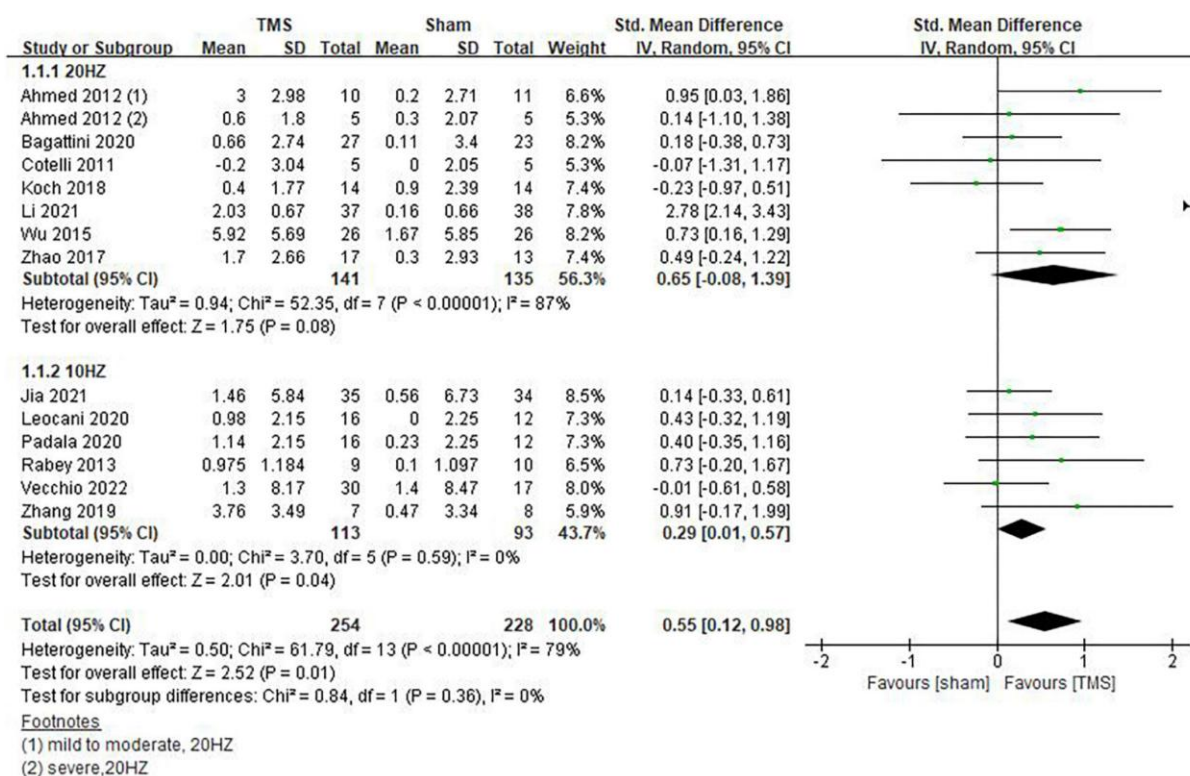

Figure 4. Impact of repetitive transcranial magnetic stimulation (rTMS) stimulation frequency on global cognitive functions.
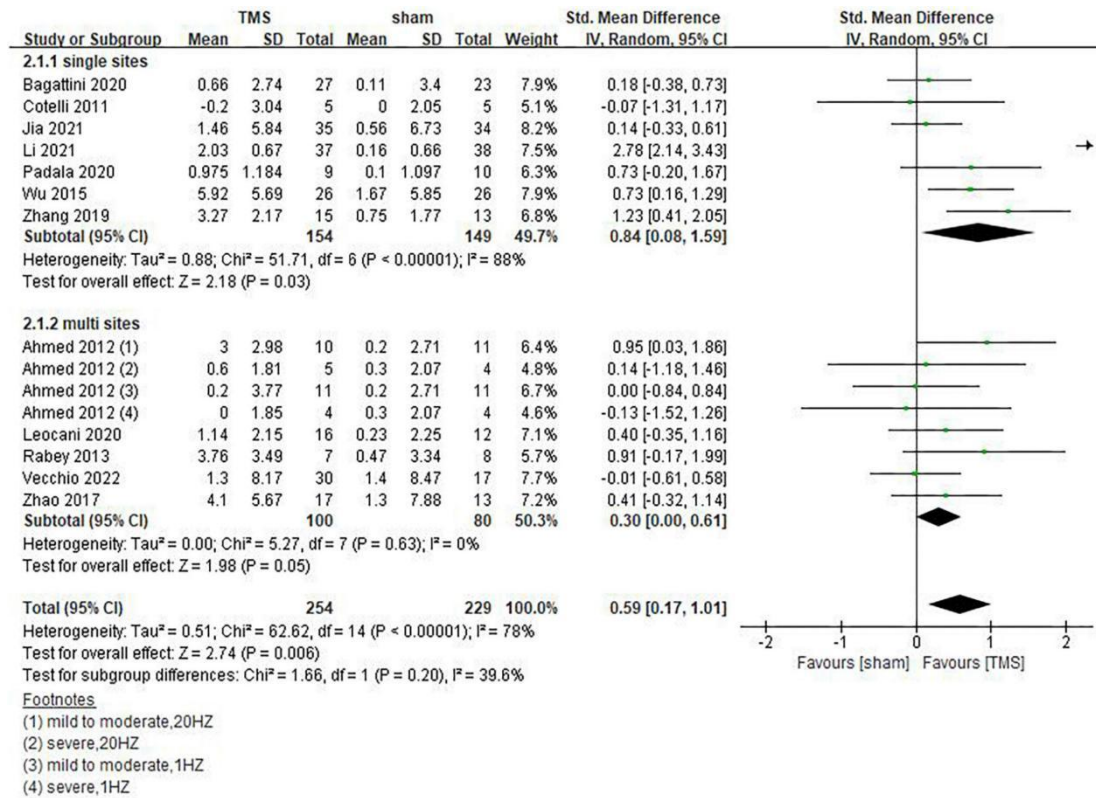
Study or Subgroup	TMS Mean	SD	Total	sham Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.1.1 single sites								
Bagattini 2020	0.66	2.74	27	0.11	3.4	23	7.9%	0.18 [-0.38, 0.73]
Cotelli 2011	-0.2	3.04	5	0	2.05	5	5.1%	-0.07 [-1.31, 1.17]
Jia 2021	1.46	5.84	35	0.56	6.73	34	8.2%	0.14 [-0.33, 0.61]
Li 2021	2.03	0.67	37	0.16	0.66	38	7.5%	2.78 [2.14, 3.43]
Padala 2020	0.975	1.184	9	0.1	1.097	10	6.3%	0.73 [-0.20, 1.67]
Wu 2015	5.92	5.69	26	1.67	5.85	26	7.9%	0.73 [0.16, 1.29]
Zhang 2019	3.27	2.17	15	0.75	1.77	13	6.8%	1.23 [0.41, 2.05]
Subtotal (95% CI)			154			149	49.7%	0.84 [0.08, 1.59]
Heterogeneity: Tau² = 0.88; Chi² = 51.71, df = 6 (P < 0.00001); I² = 88%								
Test for overall effect: Z = 2.18 (P = 0.03)								
2.1.2 multi sites								
Ahmed 2012 (1)	3	2.98	10	0.2	2.71	11	6.4%	0.95 [0.03, 1.86]
Ahmed 2012 (2)	0.6	1.81	5	0.3	2.07	4	4.8%	0.14 [-1.18, 1.46]
Ahmed 2012 (3)	0.2	3.77	11	0.2	2.71	11	6.7%	0.00 [-0.84, 0.84]
Ahmed 2012 (4)	0	1.85	4	0.3	2.07	4	4.6%	-0.13 [-1.52, 1.26]
Leocani 2020	1.14	2.15	16	0.23	2	12	7.1%	0.40 [-0.35, 1.16]
Rabey 2013	3.76	3.49	7	0.47	3.34	8	5.7%	0.91 [-0.17, 1.99]
Vecchio 2022	1.3	8.17	30	1.4	8.47	17	7.7%	-0.01 [-0.61, 0.58]
Zhao 2017	4.1	5.67	17	1.3	7.88	13	7.2%	0.41 [-0.32, 1.14]
Subtotal (95% CI)			100			80	50.3%	0.30 [0.00, 0.61]
Heterogeneity: Tau² = 0.00; Chi² = 5.27, df = 7 (P = 0.63); I² = 0%								
Test for overall effect: Z = 1.98 (P = 0.05)								
Total (95% CI)			254			229	100.0%	0.59 [0.17, 1.01]
Heterogeneity: Tau² = 0.51; Chi² = 62.62, df = 14 (P < 0.00001); I² = 78%								
Test for overall effect: Z = 2.74 (P = 0.006)								
Test for subgroup differences: Chi² = 1.66, df = 1 (P = 0.20), I² = 39.6%								

Footnotes
(1) mild to moderate,20HZ
(2) severe,20HZ
(3) mild to moderate,1HZ
(4) severe,1HZ

Figure 5. Impact of repetitive transcranial magnetic stimulation (rTMS) stimulation site of rTMS on global cognitive functions.

Study or Subgroup	TMS Mean	SD	Total	Sham Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
3.1.1 <20 session								
Ahmed 2012 (1)	3	2.98	10	0.2	2.71	11	3.8%	0.95 [0.03, 1.86]
Ahmed 2012 (2)	0.6	1.81	5	0.3	2.07	4	1.8%	0.14 [-1.18, 1.46]
Ahmed 2012 (3)	0.2	3.77	11	0.2	2.71	11	4.5%	0.00 [-0.84, 0.84]
Ahmed 2012 (4)	0	1.85	4	0.3	2.07	4	1.6%	-0.13 [-1.52, 1.26]
Cotelli 2011	-0.2	3.04	5	0	2.05	5	2.1%	-0.07 [-1.31, 1.17]
Jia 2021	1.46	5.84	35	0.56	6.73	34	14.1%	0.14 [-0.33, 0.61]
Koch 2018	0.4	1.77	14	0.9	2.39	14	5.7%	-0.23 [-0.97, 0.51]
Leocani 2020	1.14	2.15	16	0.23	2.25	12	5.5%	0.40 [-0.35, 1.16]
Subtotal (95% CI)			100			95	39.2%	0.16 [-0.12, 0.45]
Heterogeneity: Chi² = 4.75, df = 7 (P = 0.69); I² = 0%								
Test for overall effect: Z = 1.12 (P = 0.26)								
3.1.2 =20 session								
Bagattini 2020	0.66	2.74	27	0.11	3.4	23	10.2%	0.18 [-0.38, 0.73]
Padala 2020	0.975	1.184	9	0.1	1.097	10	3.6%	0.73 [-0.20, 1.67]
Wu 2015	5.92	5.69	26	1.67	5.85	26	10.0%	0.73 [0.16, 1.29]
Zhang 2019	3.27	2.17	15	0.75	1.77	13	4.7%	1.23 [0.41, 2.05]
Subtotal (95% CI)			77			72	28.4%	0.61 [0.28, 0.95]
Heterogeneity: Chi² = 4.72, df = 3 (P = 0.19); I² = 36%								
Test for overall effect: Z = 3.61 (P = 0.0003)								
3.1.3 >20 session								
Li 2021	2.89	5.99	37	0.05	4.72	38	14.9%	0.52 [0.06, 0.98]
Rabey 2013	3.76	3.49	7	0.47	3.34	8	2.7%	0.91 [-0.17, 1.99]
Vecchio 2022	1.3	8.17	30	1.4	8.47	17	8.9%	-0.01 [-0.61, 0.58]
Zhao 2017	4.1	5.67	17	1.3	7.88	13	5.9%	0.41 [-0.32, 1.14]
Subtotal (95% CI)			91			76	32.4%	0.39 [0.07, 0.70]
Heterogeneity: Chi² = 2.95, df = 3 (P = 0.40); I² = 0%								
Test for overall effect: Z = 2.42 (P = 0.02)								
Total (95% CI)			268			243	100.0%	0.36 [0.19, 0.54]
Heterogeneity: Chi² = 16.52, df = 15 (P = 0.35); I² = 9%								
Test for overall effect: Z = 4.01 (P < 0.0001)								
Test for subgroup differences: Chi² = 4.10, df = 2 (P = 0.13), I² = 51.2%								

Footnotes
(1) mild to moderate,20HZ
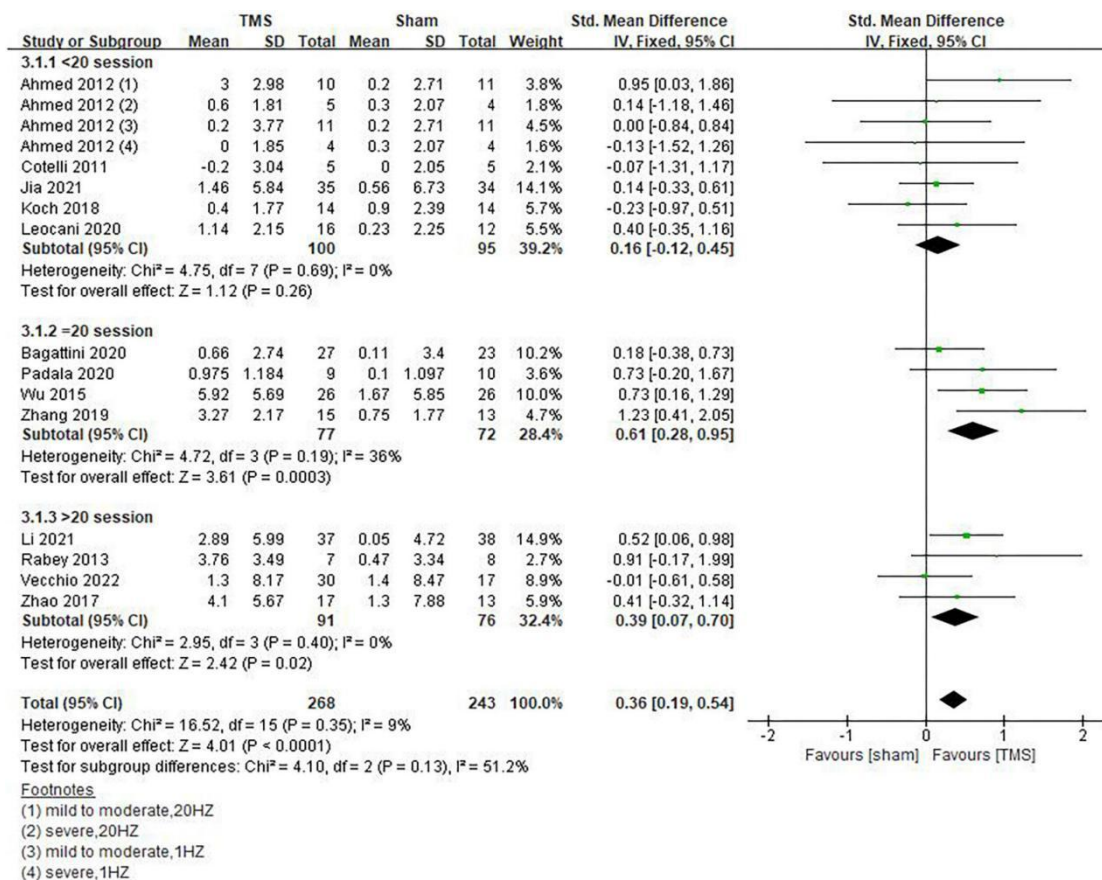(2) severe,20HZ
(3) mild to moderate,1HZ
(4) severe,1HZ

Figure 6. Influence of sessions of repetitive transcranial magnetic stimulation (rTMS) treatment on global cognitive functions.
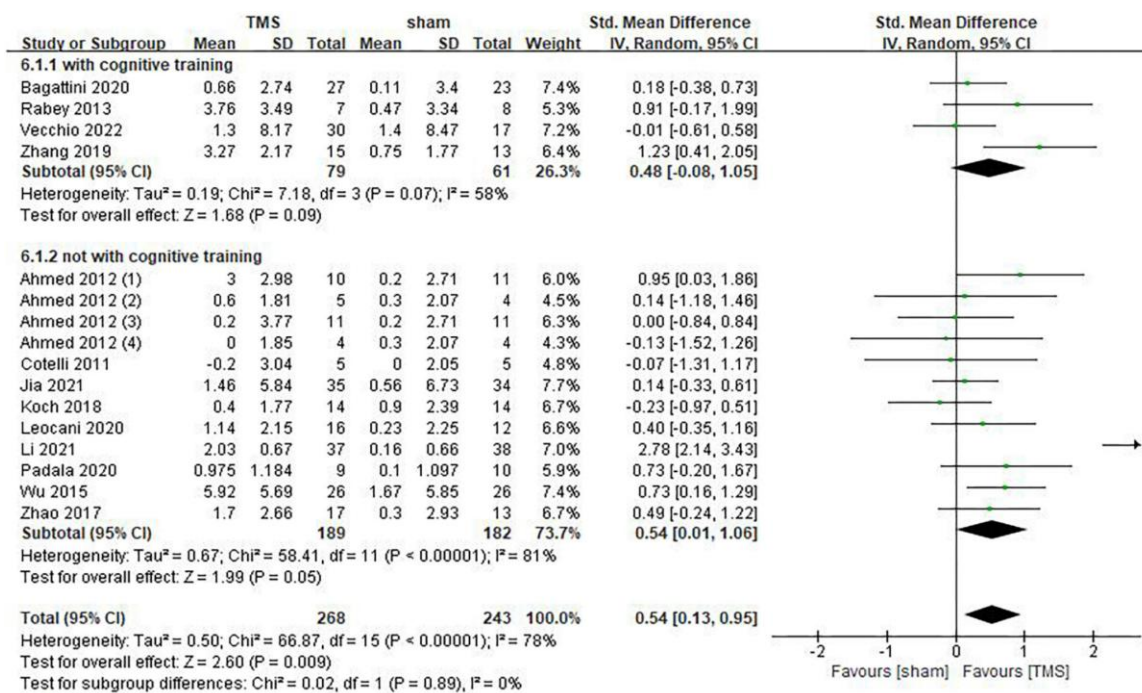
Figure 7. Influence of repetitive transcranial magnetic stimulation (rTMS) combined cognitive training on global cognitive functions.
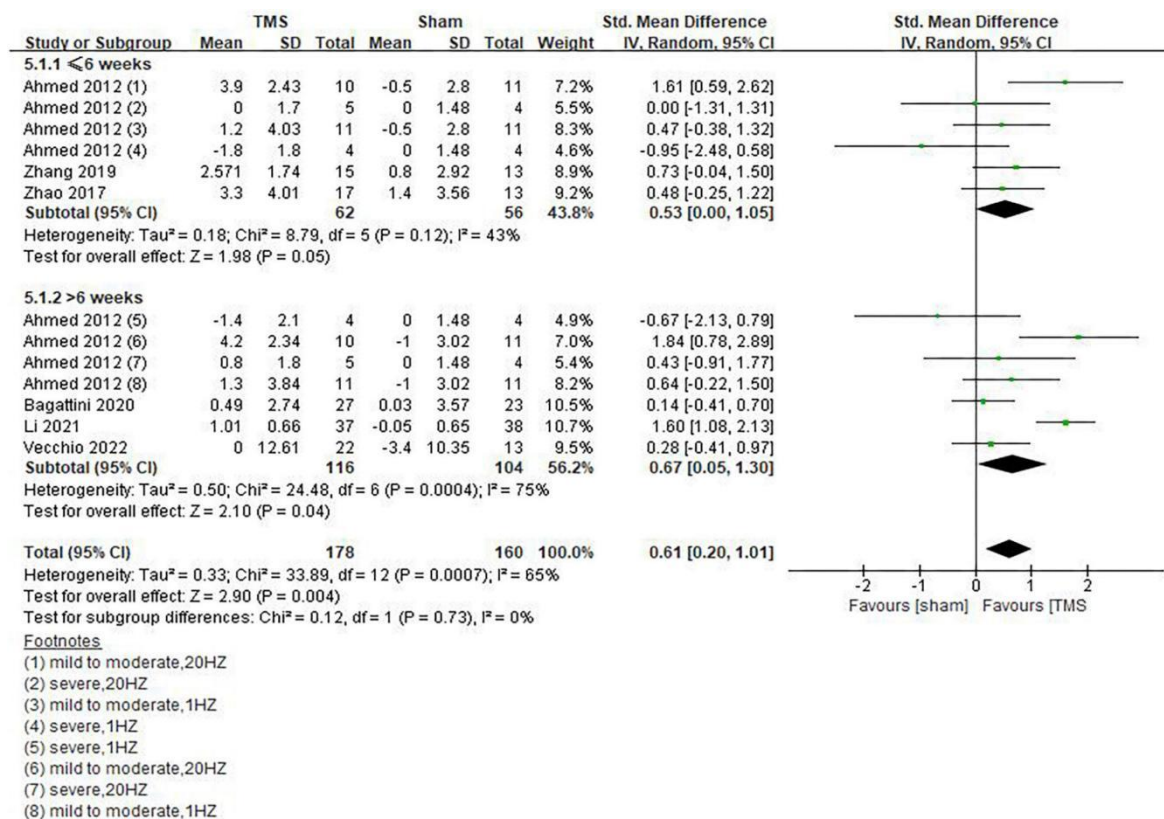

Figure 8. Post-treatment effects of repetitive transcranial magnetic stimulation (rTMS) on global cognitive functions.

My Results showed that rTMS combined with cognitive training had no statistically significant effect on global cognitive functions (SMD = 0.48, 95%CI, –0.08 to 1.05, P = 0.09), but rTMS without combined cognitive training seemed to be superior to the former in improving global cognitive functions. The statistical significance of the results remains to be explored (SMD = 0.54, 95%CI, 0.01 to 1.06, P = 0.05) (Figure 7). Among the included studies, 6 reported post-treatment effects (Ahmed et al., 2012; Zhao et al., 2017; Zhang et al., 2019; Bagattini et al., 2020; Li et al., 2021; Vecchio et al., 2022). Results showed that rTMS had a better effect when the follow-up time was > 6 weeks (SMD = 0.67, 95%CI, 0.05 to 1.30, P = 0.04) than ≤6 weeks (SMD = 0.53, 95%CI, 0.00 to 1.05, P = 0.05) (Figure 8).

Influence of Repetitive Transcranial Magnetic Stimulation on Daily Living
Among the studies we included, 3 (Cotelli et al., 2011; Ahmed et al., 2012; Padala et al., 2020) analyzed daily living using the IADL scale. Their results showed that rTMS could significantly improve the daily living ability of AD patients (SMD = 0.64, 95%CI: 0.21–1.08, P = 0.007) (Figure 9).

Study or Subgroup	TMS Mean	SD	Total	Sham Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Ahmed, M. A. 2012	1.8	2.6	10	-0.1	3.3	11	24.9%	0.61 [-0.27, 1.49]
Ahmed, M. A. 2012	1.4	2.87	5	-0.4	1.04	4	10.1%	0.70 [-0.68, 2.09]
Ahmed, M. A. 2012	1.4	4.13	11	-0.1	3.3	11	27.0%	0.39 [-0.46, 1.23]
Ahmed, M. A. 2012	0.1	1.51	4	-0.4	1.04	4	9.8%	0.34 [-1.07, 1.74]
Cotelli 2011	0	1.8	5	0	1.7	5	12.6%	0.00 [-1.24, 1.24]
Padala, P. R. 2020	1.025	1.934	9	-2.425	1.703	10	15.7%	1.82 [0.71, 2.92]
Total (95% CI)			44			45	100.0%	0.64 [0.21, 1.08]

Heterogeneity: Chi² = 5.87, df = 5 (P = 0.32); I² = 15%
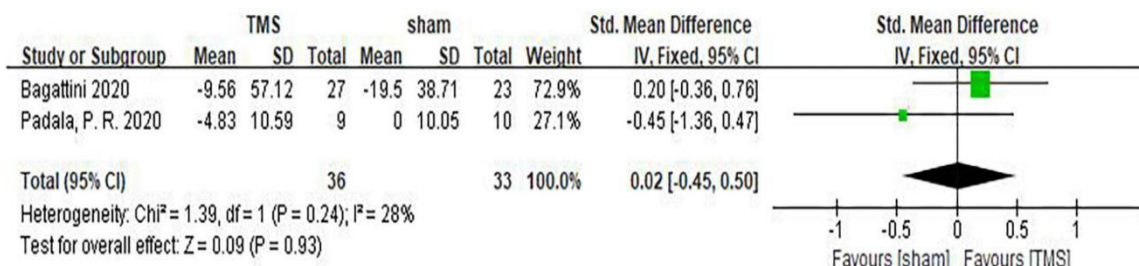Test for overall effect: Z = 2.88 (P = 0.004)

Figure 9. Forest plot showing the effect of repetitive transcranial magnetic stimulation (rTMS) on IADL of AD patients with 95% CI.

Impact of Repetitive Transcranial Magnetic Stimulation on Language
In the study of Cotelli et al. (2011), the sentence comprehension test was used to evaluate the listening comprehension of AD patients, and the results showed that rTMS had a significant therapeutic effect on language. In contrast, in the study of Jia et al. (2021), the language results of the MMSE scale did not show significant improvement. In the study by Zhang et al. (2019), although the therapeutic effect of rTMS on language was observed by the ACE-III scale, the result was not statistically significant (P = 0.08). In addition, Zhao et al. (2017) showed significant improvement in speech function in patients treated with rTMS, and the results were statistically significant (P = 0.003). However, it was not clearly explained in this study how the language function score was obtained. According to the research content of Zhao et al. (2017), we inferred that the conclusion was obtained by comprehensive calculation of the results of ADAS-cog, MMSE, MoCA and WHO-UCLA AVLT scale.

Impact of repetitive transcranial magnetic stimulation on memory
Koch et al. (2018) and Bagattini et al. (2020) used RAVLT-IR and RAVLT-DR tests to evaluate the memory function of patients. Since both tests belong to the RAVLT sub-scale and they are strongly correlated, so the results of these two tests were combined for analysis. However, the rTMS group did not show superiority to the sham stimulation group (SMD = 0.22, 95%CI, –0.09 to 0.54, P = 0.17) (Figure 10). In addition, Turriziani et al. (2019) found that AD patients did not show any difference in the Rey's 15 words immediate recall and Rey's 15 words 15-min delayed recall. However, a study by Zhang et al. (2019) showed that rTMS significantly improved the memory function in patients who received cognitive training [real TMS-CT change (Mean ± SE): 3.87 ± 0.82; Sham TMS-CT change (Mean ± SE): 0.29 ± 1.07]. A note is that this conclusion was drawn from ACE-III results.
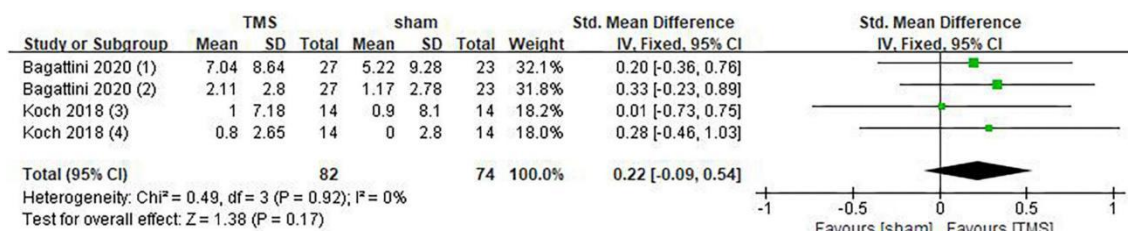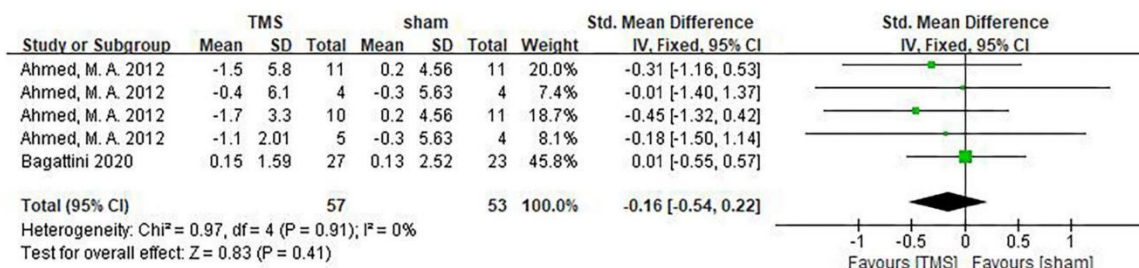
Figure 10. Forest plot showing the effect of repetitive transcranial magnetic stimulation (rTMS) on RAVLT of AD patients with 95% CI.

Impact of repetitive transcranial magnetic stimulation on executive ability

In studies by Bagattini et al. (2020) and Padala et al. (2020), rTMS showed no positive effect when the "Visuospatial Ability" and "Writing Movement Speed" were evaluated using the TMT A test (SMD = 0.02, 95%CI, –0.45 to 0.50, P = 0.93) (Figure 11). However, a positive trend was observed in a study by Zhang et al. (2019) on attention and visuospatial function assessed using the ACE-III scale.

Figure 11. Forest plot showing the effect of repetitive transcranial magnetic stimulation (rTMS) on TMT-A of AD patients with 95% CI.

Influence of Repetitive Transcranial Magnetic Stimulation on Emotion

Studies by Ahmed et al. (2012) and Bagattini et al. (2020) assessed psychological and emotional changes of AD patients using the GDS scale. It can be seen from the forest plot, there was no statistical difference in psychological and emotional improvement between the TMS treatment group and the sham stimulation group (SMD: –0.16, 95%CI: –0.54~0.22, P = 0.41) (Figure 12). In another study by Padala et al. (2020), Clinical Global Impression-improvement (CGI-I) and Clinical Global Impression-Severity (CGI-S) were used to assess the overall mental state of AD patients. It was found that rTMS treatment significantly improved mental state as shown by CGI-S [1.4 (0.5 to 2.3), P = 0.005]. In the rTMS group, CGI-S was significantly better compared to that of the baseline (P < 0.001), whereas no significant difference was found between the baseline and after sham stimulation (P = 0.238) in the sham group. In contrast, when CGI-I was used to assess psychological and emotional changes [–2.56 (–3.5 to –1.6), P < 0.001], both rTMS and sham stimulation significantly improved CGI-I compared to the baseline.

Figure 12. Forest plot showing the effect of repetitive transcranial magnetic stimulation (rTMS) on GDS of AD patients with 95% CI.

Publication Bias and Sensitivity Analysis

I firstly used funnel plots to qualitatively assess publication bias, and our results showed that funnel plots were visually symmetric (Figure 13). Then we conducted quantitative evaluation through Begg and Egger tests, and results showed that publication bias was present [Begg (P = 0.0748) and Egger (P = 0.0040)]. Therefore, pruning and filling tests were used for verification. After pruning and filling, our results did not change, suggesting that they were still robust (Figure 13). In addition, it should be pointed out that the methods of random sequence generation and concealment in the study by Cotelli et al. (2011) were not reported, suggesting a highly potential bias risk (Figure 2). After excluding this study, the influence of rTMS on AD patients (SMD = 0.57; 95% CI = 0.39, 0.76; P < 0.00001, I2 = 83%) was still significantly higher than those in the sham stimulation group. We then conducted a sensitivity analysis using the leave one method, interactively deleting each study and recalculating the summary SMD.

The data showed that the heterogeneity of the results changed significantly when the study of Li et al. (2021) was excluded alone. But the results were still statistically significant (SMD = 0.36, 95%CI = 0.17–0.55; P = 0.0002, I2 = 54%). Meta-regression analysis was used to explore the source of heterogeneity, and the results showed that sample size, age and TMS treatment effect were not significant at the level of 5%, that is, sample size and age were not considered as the source of heterogeneity (sample size: P = 0.177; age: P = 0.952). Scale selection and TMS treatment effect were significant at the level of 1%, stimulation frequency was significant at the level of 5%. We have conducted subgroup analysis on rTMS stimulation frequency, number of stimulation sites, and number of sessions using different cognitive scales.
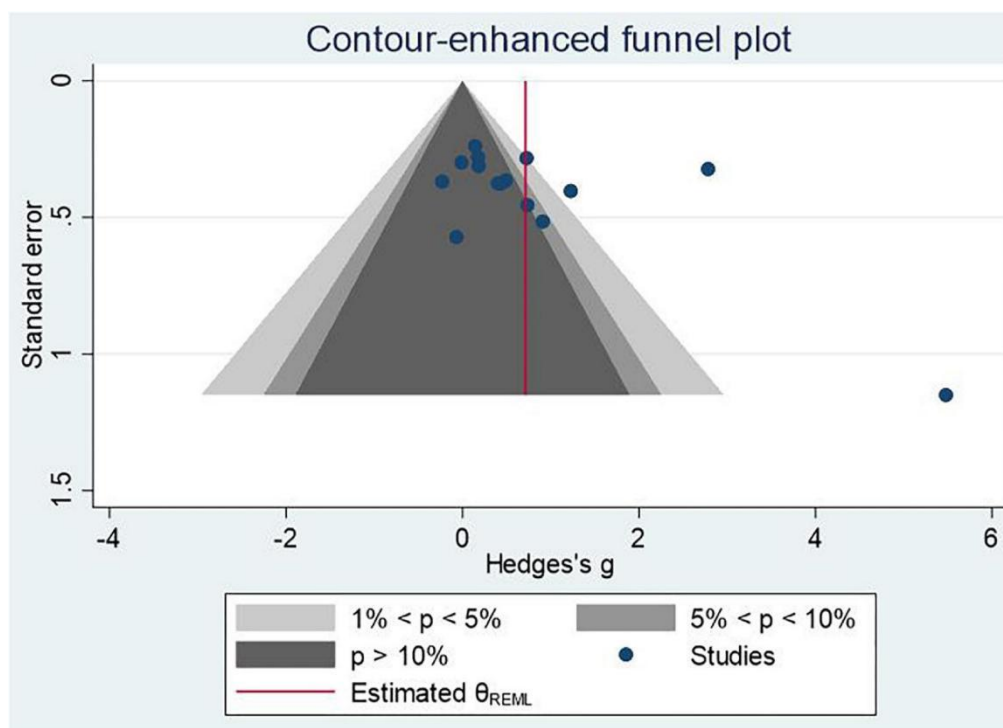
Figure 13. Funnel plot for publication bias and result of clipping test.

Adverse Reactions

Adverse reactions were reported in 4 of 14 studies (Zhang et al., 2019; Leocani et al., 2020; Padala et al., 2020; Jia et al., 2021). The main adverse reactions included local scalp discomfort or headache. In a study by Jia et al. (2021), two patients (one in the rTMS group and the other in the sham group) reported transient fatigue. It has to be mentioned that no case of seizure was recorded.

IV.   Discussion

The improvement of cognitive function following rTMS treatment or sham stimulation was compared in 14 studies, encompassing a total of 513 AD patients with varied degrees of disease severity. In comparison to sham stimulation, we discovered that rTMS dramatically enhanced global cognitive abilities. We discovered that rTMS was beneficial in enhancing daily living capacity when each cognitive domain was included for further investigation. Our findings are in line with the majority of other studies showing that rTMS improves cognition and everyday functioning in AD patients. rTMS can enhance the plasticity and excitability of the cerebral cortex

(Pennisi et al., 2011), which will subsequently improve the cognitive performance of AD patients. Previous research has shown that AD patients' cortical plasticity is impaired (Di Lorenzo et al., 2020), which causes a decline in cognitive functions and self-care ability (Di Lorenzo et al., 2019). Although neural plasticity could not be tested in our investigation, the enhanced performance in some domains and across the board suggests that rTMS may enhance brain plasticity. Cognitive impairment includes alterations in executive, visuospatial, speech, memory and other aspects. Our meta-analysis showed that rTMS can improve global cognitive functions in patients with AD, which is consistent with findings of a previous meta-analysis study (Lin et al., 2019). Thirteen of our included studies assessed global cognitive functions in patients with AD using scales, such as MMSE, MoCA, ACE-III and ADAS-cog with consistent and positive results (Cotelli et al., 2011; Ahmed et al., 2012; Rabey et al., 2013; Wu et al., 2015; Koch et al., 2018; Zhang et al., 2019; Bagattini et al., 2020; Leocani et al., 2020; Padala et al., 2020; Jia et al., 2021; Li et al., 2021; Vecchio et al., 2022).

Even though individual studies in the research we considered had good findings in language, memory, executive function, and affective cognition, the pooled findings were not statistically significant. Language is a tool for symbolically communicating. Grammar, semantics, and pronunciation are the three facets of language. In human social contact, verbal communication is crucial. One of the most prevalent functional deficits in cognitive decline is language impairment, which first manifests in the early stages of AD. Performance on language tasks is a crucial diagnostic indicator for AD and moderate cognitive impairment. Fluency in language, naming, semantic awareness, and discourse processing are the key areas where it shows up (Taler and Phillips, 2008). The language assessment scale, which includes the aphasia screening test, Boston Naming test, Word Fluency test, double-listening test, expression vocabulary test, Peabody Graph word test, adult reading test, marking test, and language test of the Wechsler Intelligence Test, is a frequently used technique for evaluating language disorders. Few studies have examined the effects of rTMS on the language cognitive domain in AD patients, and the study's assessment techniques varied, which made it challenging to perform additional statistical analysis. Therefore, we described the relevant articles one by one. Cotelli et al. (2011) evaluated the patients' listening comprehension ability through the Sentence Comprehension test and obtained positive results. However, in the study of Zhang et al. (2019) and Jia et al. (2021), the results of language function measured by MMSE and ACE-III, respectively, were not statistically significant. In the study of memory cognitive domain, Koch et al. (2018) and Bagattini et al. (2020) used RAVLT as an evaluation tool to conduct the study, and the results showed that there was no significant statistical difference between the TMS treatment group and the sham stimulation control group. In terms of executive ability, Bagattini et al. (2020) and Padala et al. (2020) did not show positive effects of rTMS when TMT A test was used to evaluate "visuospatial ability" and "writing motor speed." However, Zhang et al. (2019) observed positive results in "attention" and "visuospatial ability" using the ACE-III scale.

Age-related difficulties, such as diminished activities of daily living (ADL) and instrumental ADL (IADL), account for 35% of the population aged 65 and over and may make it challenging for senior persons to live independently (Kiyoshige et al., 2019). According to Koyano et al. (1991), IADL refers to a person's capacity for using public transportation, purchasing daily necessities, preparing meals, paying bills, managing bank accounts, and other activities. It also refers to a person's level of autonomy and independence with regard to carrying out activities at home and in the community. In terms of daily living ability, positive results were found in IADL indicators in studies of Cotelli et al. (2011); Ahmed et al. (2012), and Padala et al. (2020).

Previous studies have found that rTMS treatment has definite effects on depression and other psychiatric disorders (Health Quality Ontario, 2016; De Risio et al., 2020). In a study on the effect of rTMS on patients with treatment-refractory depression, positive response of patients was related to the increased volume of the left amygdala and the unchanged volume of the hippocampus, whereas the neutral response was associated with the decreased volume of the left hippocampus (Furtado et al., 2013). Another study reported that an increase in the volume of that the hippocampus on the side of that the brain targeted by HFrTMS was associated with improvement in depression (Hayasaka et al., 2017). However, when we analyzed combined results of GDS indicators of Ahmed et al. (2012) and Bagattini et al. (2020), we did not obtain positive results that rTMS treatment could improve the mood of AD patients. Given the small number of included studies and the different scales used in different studies, it is necessary to conduct high-quality larger-sample RCT studies in the future to confirm our findings.

Our meta-analysis also looked at the impact of various rTMS parameters on cognitive performance and discovered that L-DLPFC, 10 Hz rTMS, and at least 20 sessions were all helpful in enhancing cognitive abilities. Our findings corroborate earlier research regarding the effects of various rTMS stimulation frequencies, locations, and sessions on cognitive performance (Nguyen et al., 2017). The excitability of particular regions of the cerebral cortex can be increased or decreased by rTMS due to variations in the stimulation parameters (Nguyen et al., 2017; Jiang et al., 2022). The results of our study suggest that 10 Hz rTMS has a more beneficial therapeutic effect on cognitive functioning than HFrTMS, which may raise brain cell excitability with a ceiling effect. Future high-quality larger-sample RCT studies are required to reach an exclusive conclusion since the

opposite finding from a meta-analysis research by Wang et al. (2020), which asserted that 20 Hz rTMS appeared to be more effective than 10 Hz or 1 Hz rTMS, is needed. Prior to using rTMS, stimulating locations must be chosen. The L-DLPFC and the Precuneus were the two most frequently used sites for single-site stimulation (Nardone et al., 2014; Koch et al., 2018). As was already indicated, 10 Hz had better efficacy than 20 Hz, indicating a connection between the frequency of rTMS and the stimulation site. The left and right DLPFC are the most frequently used candidates for multisite stimulation. Whether bilateral DLPFC stimulation is superior to unilateral DLPFC stimulation remains controversial. In a meta-analysis published by Liao et al. (2015) involving 94 patients with mild to moderate AD, it was found that stimulation of the right or bilateral DLPFC was more superior to stimulation of the L-DLPFC alone. In contrast, meta-analysis by Drumond Marra et al. (2015) and Wu et al. (2015) found that stimulation of the L-DLPFC by HFrTMS was more effective in improving cognitive performance than multi-point stimulation. Cotelli et al. (2011) found that stimulation of the L-DLPFC significantly increased the percentage of correct response in auditory sentence comprehension, but there was no significant difference in other language abilities or memory. This study only included 10 patients. To draw a clear conclusion on the efficacy of different parameters of rTMS in improving cognitive performance in diverse domains, the long-term results of studies adopting multisite stimulation are needed.

In addition, we also conducted a subgroup analysis on the effect of cognitive training added to rTMS, and we found that cognitive training did not show additive effects when applied with rTMS. But the cognitive training varied from study to study. For example, Zhang et al. (2019) adopted cognitive training in areas of memory tasks, attention tasks, mathematical calculations, agility drills and logic thinking tasks. Rabey et al. (2013) and Vecchio et al. (2022) applied cognitive training to test the impact of Broca region, Wernicke region, R-DLPFC, L-DLPFC, R-PSAC, and the L-PSAC on cognitive performance. Cognitive training in the study by Bagattini et al. (2020) focused on episodic memory and specifically on face-name associative memory. Although the above studies separately described the positive results of rTMS combined with cognitive training, our results did not show statistical significance in our subgroup analysis (SMD = 0.48, 95%CI: –0.08 to 1.05, P = 0.09). Therefore, future studies should balance the number of AD patients receiving the combined cognitive training and those who do not receive this combined therapy, in order to better investigate whether cognitive training leads to synergistic effects.

In the study of Zhang et al. (2019), MMSE and ACE-III indicators were used to observe the effect of rTMS 4 weeks after rTMS treatment, and the results showed that patients treated with rTMS still maintained significant improvement in cognitive functions. Zhao et al. (2017) reported the effect of rTMS 6 weeks after rTMS treatment, three cognitive domains of memory, language, and executive ability were individually analyzed based on ADAS-cog, MMSE, MoCA, and WHO-UCLA AVLT indicators. The results showed that memory function improved the most, followed by language function. Ahmed et al. (2012) reported the effect of rTMS on AD patients 1 and 3 months after rTMS treatment, respectively. MMSE results showed that mild or moderate AD patients who received HFrTMS stimulation benefited the most. Positive results of long-term therapeutic effects of rTMS were reported in studies by Bagattini et al. (2020), Li et al. (2021), and Vecchio et al. (2022). Their follow-up duration was 2, 3, and 4 months, respectively. In our subgroup analysis, patients who received rTMS still maintained good cognitive function improvement within 6 weeks after the end of treatment, but the improvement effect was more apparent after over 6 weeks, evidenced by results of Ahmed et al. (2012).

This study was conducted on the basis of the study by Lin et al. (2019), apart from global cognitive functions, different cognitive domains such as language, memory, executive ability, daily living ability and emotion, as well as rTMS parameters were analyzed, and compared at different follow-up time points. The forest maps of MMSE and ADAS-cog were drawn for analysis. In terms of publication bias and sensitivity analysis, we conducted more comprehensive validation and discussion, and the results were robust. Meta-regression analysis was used to explore the source of heterogeneity, and the results suggested that there was no correlation between sample size, age, and the therapeutic effect of rTMS. Some limitations should be considered when interpreting our results. The use of different scales to measure global cognitive functions in different studies may lead to high heterogeneity. Meta-regression analysis suggested that scale selection was significantly associated with TMS treatment effect at the level of 1% and stimulus frequency at the level of 5%. Among the included studies, only 6 explored the therapeutic effect 1 to 3 months after completing the treatment, longer follow-up period is needed to examine the long-term therapeutic effect of rTMS on AD in the future.

V.   Conclusion

Patients with AD can have their everyday functioning and general cognitive abilities improved with repetitive transcranial magnetic stimulation (rTMS). rTMS significantly enhanced cognition with 20 sessions or more at a single site at high frequency, according to subgroup analysis. Furthermore, we need to focus more on the rTMS safety in AD patients with seizures. Our results should not be taken too seriously due to the limited sample size. To more accurately determine the effectiveness of rTMS in treating AD patients and the ideal type

of stimulation needed to enhance positive outcomes, additional research with bigger sample numbers and longer follow-up periods are required.

Conflict of Interest
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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