Results of Utilizing rTMS with Cognitive Training in Alzheimer Patients: A Pilot Study and Literature Review

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Abstract

Introduction : Repetitive transcranial magnetic stimulation (rTMS) has shown potential in enhancing brain plasticity and cognition, particularly when combined with cognitive training. This study evaluated the effects of rTMS with cognitive training on cognition and gait in patients with mild to moderate Alzheimer's disease (AD).

Methods : This retrospective chart review analyzed data from a previous pilot study. Nine AD patients underwent rTMS targeting six cortical areas (Broca's area, Wernicke's area, dorsolateral prefrontal, and parietal somatosensory cortices) using 10 Hz stimulation, 20 trains per session, five days per week for six weeks. Cognitive and functional assessments, including TMSE, MOCA, NPT, dual-task gait performance, and Thai-ADL scores, were conducted at baseline and six months post-stimulation. The primary outcome was cognitive improvement, while secondary outcomes included Thai-ADL, Neuropsychiatric Inventory (NPI), and gait performance.

Results : TMSE and MOCA scores showed a trend toward improvement at six months post-treatment (22 vs. 12 and 24 vs. 16.5, respectively), though statistical significance was not reached (P = 0.059, P = 0.058). Significant improvements were observed in logical and visual memory, VOSP, and BNT. Dual-task gait performance showed increased step length in both feet, while Thai-ADL scores remained unchanged.

Conclusion : These findings suggests that rTMS combined with cognitive training is a safe and promising medical intervention for treating AD,

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particularly during the mild stages of the disease.

Keywords: Repetitive Transcranial Magnetic Stimulation (rTMS), Alzheimer's Disease, Cognitive Training

Introduction

Alzheimer's disease, the leading type of dementia globally, is marked by gradual memory loss and deterioration in various cognitive functions, including gait, especially dual-task gait.[1] At present, pharmacological therapies are the most common treatments for Alzheimer's disease, especially acetylcholinesterase inhibitors (AchEI), which reduce the degradation of acetylcholine, an essential neurotransmitter associated with memory functions. However, these medications provide only limited symptom relief and may cause adverse effects. Accordingly, non-pharmacological interventions have gained increasing attention for their potential to treat, maintain and improve both cognition and behavioral problems in AD. One such approach is rTMS, a non-invasive neuromodulation technique, which is considered to be a safe and painless modality for AD treatment. rTMS generates electric currents to produce magnetic fields that surround the cortical neurons, modulating synaptic activity in focal neuronal circuits and cortico-subcortical networks when applied repetitively.[2,3]

Currently, the USFDA has approved rTMS for the treatment of various psychiatric and neurological disorders, such as MDD, Parkinson's disease and chronic pain. rTMS functions by delivering an electrical current through a figure-of-eight shaped coil positioned on the scalp. The effects of rTMS depend on factors such as frequency, pulse waveforms, and direction of the current,[4] likely due to the activation of different groups of cortical fibers[5].

Several previous studies have demonstrated the positive effects of high-frequency rTMS on cognition in patients with mild to moderate AD patients.[6-11] However, these studies involved relatively small sample sizes, leaving significant knowledge gaps about this treatment. Given these limitations, the present study was conducted to evaluate the efficacy and safety of rTMS in Thai patients with AD.

Objectives

1. Evaluate the cognitive outcomes (TMSE, MOCA, NPI, THAI-ADL scores, and dual-task gait) of high-frequency rTMS combined with cognitive training (rTMS-COG) compared to sham treatment in Thai patients with mild to moderate AD, based on a pilot study conducted from 2013 to 2017.

2. Review existing literature on previous case-controlled trials of rTMS in AD from 2006 to 2023.

Methods

Study population

This study was a retrospective chart review using data from a previous study titled "New Treatment for Alzheimer Patients Using Repetitive e Transcranial Magnetic Stimulation with Cognitive Training (rTMS-COG): A Pilot Study", conducted between 2013 and 2017. The inclusion and exclusion criteria for this study were based on those of the original study.

Inclusion criteria

Nine patients diagnosed with probable AD were included based on the diagnostic criteria set by the Diagnostic Manual of Mental Disorders, 4th Edition (six patients received rTMS COG treatment and three received sham treatment), along with MRI findings consistent with AD. The severity of AD was

categorized as mild to moderate based on assessments using the TMSE, CDR, ADL and NPI. Additional inclusion criteria included requirements that each participant be accompanied by a caregiver or family member who spent more than 10 hours per week with them and could provide daily information. All patients also had to be proficient in reading and writing Thai language and have at least completed Grade 6 education. Brain MRIs were performed to confirm AD-related brain atrophy and exclude other organic brain lesions. Patients were also required to maintain a stable dose of AChEI without changes for at least two months prior to the study and throughout its duration.

Exclusion criteria

Patients were excluded from the study if they had a history of alcohol or drug abuse, had taken psychoactive medications and antiepileptic drugs, had a history of seizures, metal implants in the head or implanted cranial or thoracic devices, or any other contraindications for rTMS.

Study approval This study was conducted at Siriraj Hospital, Mahidol University following a protocol approved by the Siriraj Institutional Review Board Committee. All participant information was handled confidentially.

Study design

The study followed a retrospective chart review design, based on the protocol of a previous prospective cohort study. Patients in the treatment group underwent rTMS sessions for six weeks (one session per day, five days per week, totaling 30 sessions), combined with cognitive training. The sham group received only cognitive training without magnetic stimulation. Neuropsychological assessments were conducted before treatment and six months after the completion of rTMS-COG.

rTMS-COG protocols

Brain mapping and stimulation protocol

Six patients in the treatment group underwent brain MRIs (3.0T MRI scanner). A neurologist evaluated MRI images to identify and mark six cortical areas for stimulation. The rTMS system (Neuronix, Yokneam, Israel) superimposed the anatomical locations of these targeted brain regions onto the MRI images, allowing precise positioning of each cortical area for rTMS application. The six brain regions included Broca's area, Wernicke's area, the left and right dorsolateral prefrontal cortices (dlPFC), and the left and right parietal somatosensory cortices (pSAC), all of which are known to be affected in AD. rTMS was applied to these six areas in combination with cognitive training, targeting the specific functions associated with each cortical area. The rTMS intensity was set at 90% of the motor threshold for Broca's area and the bilateral dlPFC, while for Wernicke's area and the bilateral pSAC, the intensity was set at 110%. Patients in the sham group did not receive any brain stimulation.

Cognitive training

The NeuroAD system provided cognitive training paradigms tailored to the brain regions implicated in AD. While rTMS was applied to the six targeted brain areas, patients simultaneously performed cognitive tasks designed to engage the high-order cortical functions of each respective region. The cognitive paradigms included: syntax and grammar tasks for Broca's area;[12-14] comprehension of lexical meaning and categorization tasks for Wernicke's area;[15,16] action naming, object naming and spatial memory tasks (shapes, colors and letters) tasks for both dlPFC areas; and spatial attention tasks for shapes and letters. .

The cognitive tasks in this study were customized for each patient, with difficulty levels adjusted weekly based on their performance in previous tasks. These tasks were presented on a computer touchscreen as part of the Neuronix system, which was specifically designed in the Thai language. Participants interacted with the tasks by selecting answers through touchscreen icons. Patients in the sham group completed the same cognitive tasks but without brain stimulation.

rTMS procedure

Patients in the treatment group received daily rTMS sessions, five days per week, for six weeks (total of 30 sessions). Each session lasted about one hour. Treatment for each targeted brain region consisted of 20 trains of rTMS, with each train delivering 2 seconds of 10 Hz simulation (20 pulses per train). This was followed by two to four cognitive tasks administered over a 20 to 40-second period, resulting in a total of 400 pulses per session within seven to 15 minutes. The procedure was conducted by a trained technician.

Cognitive function assessment

Clinical outcomes were assessed for all participants within one month prior to treatment, serving as the baseline measurement .The follow-up assessment was conducted six months after treatment completion by a trained neuropsychologist who remained unaware of the patients' treatment conditions (treated or sham group) during the entire study.

Gait assessment

Spatiotemporal gait variables were recorded at 100 Hz using the Force Distribution Measurement (FDM) platform (Zebris Medical GmbH, Germany), which measured 307 cm in length and 60.5 cm in width. Gait evaluations were performed at the beginning of the study and six months following treatment completion, utilizing the Zebris FDM plantar pressure measurement system. For the dual-task condition, participants were instructed to count backward by one out loud while walking at their usual pace along a six meter mat, which was a part of the system. All gait parameters, including step length and stance phase (measured in centimeters), foot rotation angle (measured in degrees), were calculated using the Zebris FDM plantar pressure measurement program.

Primary outcomes

The primary outcome measure of this study was the change in average TMSE and MOCA scores between the treatment and sham groups.

Secondary outcomes

The secondary outcomes included changes in the Thai ADL scores (covering both basic and instrumental ADL), NP test scores, and dual-task gait performance at baseline and six months after treatment. All outcome measures were conducted by trained neuropsychologists.

Literature review

Literature search strategy

We conducted a literature search on Pub Med, MEDLINE, Embase and Cochrane library for relevant studies published from 2006 to January 2023 using the following keywords: "repetitive transcranial magnetic stimulation", "brain stimulation", "Alzheimer disease", "Alzheimer dementia", "cognition" and "randomized controlled trial", "controlled clinical trial", "cross-section". In addition, the reference lists of pertinent articles were manually reviewed.

Eligibility criteria

The inclusion criteria for the literature review were as follows: (1) rTMS performed on patients with Alzheimer's disease; (2) rTMS conducted either

alone or in combination with cognitive training; (3) cross-sectional, or case series without control groups, RCT studies with control groups, or meta-analyses; (4) control group receiving sham treatment, cognitive training or other treatments; and (5) outcome measurements focused on language or global cognition. The exclusion criteria were: (1) animal studies; (2) studies that included patients with neurological disorders other than Alzheimer's disease; (3) review, letters, comments, unpublished reports; and (4) non-English articles.

Statistical analysis

Demographic data were analyzed using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. The IBM SPSS software (Ver.29) was used to conduct repeated measures analysis of variance (ANOVA) for all assessed measures, including TMSE, MOCA, NPI, Thai-ADL and dual-task gait assessment. The Wilcoxon Signed Ranks test was used to compare scores between pre- and post-treatment. A p-value <0.05 was considered statistically significant.

Results

Participants

All nine participants were diagnosed with probable AD and had been treated with AD medication for more than two months prior to study recruitment, continuing the same medication regimen throughout the study without any change in dosage. All participants remained in the study for the full six-month duration, with no side effects reported during the study period. There were no significant differences in baseline characteristics, including age, gender, education duration, and neuropsychological assessments (TMSE, MOCA, ADL, FAQ and NPI) between the two groups (Table 1).

Table 1 Baseline characteristics of participants

Gr	Experiment(n=6)	Control(n=3)	P value
Age (yrs.)	75.7±7.8	75.7±10.2	1
Gender			
Male:Female	3:3	1:2	0.635
Education (yrs.)	10.3±5.1	12.3±3.5	0.586
TMSE total	22.8±3.8)	18.7±8.1	0.311
ADL m0 :	3(0-8)	13(0-18)	0.362
Median(min-max)			
FAQ m0	10.2±9.6	14±11.3	0.603
NPI (y/n) :	0.5(0-3)	1(1-3)	0.683
Median(min-max)			
SBP	154.2±15.6	133.3±14.2	0.094
DBP	85.3+14.5	85.7+22.7	0.975
pulse	70+5.6	69.3+13.2	0.915
Body height (cm.)	158.7+5.6	155.3+10.5	0.543
Body weight (Kg.)	60.7+10.2	60.5+5.8	0.962

Primary outcomes

A trend toward improvement in TMSE and MOCA scores was observed at six months (M6) from baseline (M0) in the treatment group, although the differences were not statistically significant (Table 2). The TMSE score in the treatment group increased by two points at M6 compared to baseline (P = 0.059). Similarly, the MOCA score improved by 4.5 points in the treatment group at M6 compared to the baseline (P = 0.059). In the sham group, TMSE scores also showed improvement, but the change was not statistically significant (P = 0.18). Notably, one patient in the sham group exhibited a marked TMSE improvement of 6 points while others showed only slight increases of 0 or 1 point. In contrast, the MOCA score in the sham group remained unchanged at M6 compared to the baseline (10 vs 9, respectively).

Secondary outcomes

ADL score

The total ADL score in the treatment group increased from 3.0 at baseline to 3.5 at six months post-treatment. In the sham group, the average total ADL score was 13 at baseline and 15 at M6. However, these changes were not statistically significant in either group (Table 3).

Table 2 TMSE and MOCA scores at baseline and 6 months

	Experiment (n=6)	Control (n=3)	P-value
TMSE total			
M0	22(19-30)	15(13-28)	0.3
M6	24(22-30)	21(15-30)	0.362
P-value	0.059	0.180	
M0-M6:Improve	4/6	2/3	1
MOCA total			
M0	12(9-26)	10(9-23)	0.60
M6	16.5(12-27)	9(8-26)	0.30
P-value	0.058	0.655	
M0-M6:Improve	5/6	1/3	0.22

Values denote median(min-max) unless specified otherwise.

Neuropsychological Test (NPT)

A statistically significant improvement was observed in the treatment group at M6 compared to M0 in the following tests: VOSP (P = 0.026), BNT (P = 0.027), logical memory (LM 1 & LM 2; P = 0.026 and 0.027 respectively) and visual memory (ray copy, ray immediate and ray recall; P = 0.042,0.027 and 0.042, respectively). In contrast, no significant improvement was detected in the sham group (Table 4).

Dual-task gait analysis

The treatment group showed a significant improvement in step length for both feet in the treatment group (P = 0.001). However, changes in foot rotation, step time and stance phase were not statistically significant. No improvement in gait parameters were detected in the sham group (Table 5).

Table 3 Functional assessment of CDR and ADL

	Experiment (n=6)	Control (n=3)	P-value Mann-Whitney
CDR sum box			
M0	3.75(0.5-8.0)	5(1.0-7.0)	0.897
M6	2.5(0.5-6.0)	8.0(0.5-13.0)	0.364
P-value (Wilcoxon)	0.068	0.285	
M0-M6:Improve (Fisher's test)	4/6	1/3	0.523
BADL			
M0	0.0(0-1)	4(0-6)	0.155
P-value	1	0.655	
M0-M6:Improve	1/6	1/3	1
iADL			
M0	3(0-7)	7(0-14)	0.433
P-value	0.414	0.655	
M0-M6:Improve	2/6	1/3	1
ADL total			
M0	3(0-8)	13(0-18)	0.362
P-value	0.414	0.655	
M0-M6:Improve	2/6	1/3	1

Values denote median(min-max) unless specified otherwise.

Table 4 Neuropsychological assessment

	Experiment (n=6) median(min-max)	Control (n=3) median(min-max)	P-value
VOSP : median(min-max)			
M0	115(92-127)	119(105-135)	0.437
M6	120(97-132)	119(105-135)	0.795
P-value	0.026	1	
M0-M6:Improve	6/6	0/3	0.01
Ray copy : median(min-max)			
M0	28.5(2-36)	0.0(0-32)	0.195
M6	32(5-36)	0.0(0-34)	0.191
P-value	0.042	0.317	
M0-M6:Improve	5/6	1/3	0.22
Ray immediate			
M0	5.5(0-25)	0(0-23)	0.59
M6	5.5(0-30)	0(0-26.5)	0.298
P-value	0.027	0.317	
M0-M6:Improve	6/6	1/3	0.083
Ray recall			
M0	0(0-25)	0(0-19)	1
M6	0(0-19)	9(8-26)	0.431
P-value	0.042	0.317	
M0-M6:Improve	5/6	1/3	0.22
Construction praxis			
M0	3(0-4)	3(2-4)	0.887
M6	3(3-4)	3(2-4)	0.758
P-value	0.317	1	
M0-M6:Improve	1/6	0/3	1

Values denote median(min-max) unless specified otherwise.

Table 4 Neuropsychological assessment (continued)

	Experiment (n=6) median(min-max)	Control (n=3) median(min-max)	P-value
Color trail I			
M0	170.5(54-350)	180(57-247)	0.795
M6	200(37-350)	180(49-250)	0.604
P-value	0.5	0.655	
M0-M6:Improve	4/6	1/3	0.52
Color trail II			
M0	350(89-350)	350(107-350)	1
M6	320(97-350)	350(119-350)	0.777
P-value	0.285	0.317	
M0-M6:Improve	2/6	1/3	1
Clock drawing			
M0	10(9-10)	5(5-8)	0.011
M6	10(6-10)	5(5-9)	0.023
P-value	0.655	0.317	
M0-M6:Improve	1/6	1/3	1
LM I			
M0	1.5(0-12)	0.0(0-11)	0.429
M6	6(3-17)	0.0(0-8)	0.296
P-value	0.026	0.317	
M0-M6:Improve	5/6	0/3	0.04
LM II			
M0	0(0-4)	0(0-3)	0.724
M6	3(1-14)	0(0-5)	0.296
P-value	0.027	0.317	
M0-M6:Improve	6/6	1/3	0.08

Values denote median(min-max) unless specified otherwise.

Table 4 Neuropsychological assessment (continued)

	Experiment (n=6) median(min-max)	Control (n=3) median(min-max)	P-value
Word list recall			
M0	1.5(0-5)	0(0-1)	0.396
M6	4.5(3-6)	0(0-5)	0.185
P-value	0.066	0.317	
M0-M6:Improve	4/6	1/3	0.523
Animal			
M0	12.5(2-17)	17(5-21)	0.364
M6	15.5(8-21)	17(5-20)	0.897
P-value	0.435	0.317	
M0-M6:Improve	5/6	0/3	0.047
กฉป			
M0	11.5(3-25)	9(5-18)	0.606
M6	14(6-33)	9(5-25)	0.604
P-value	0.176	0.317	
M0-M6:Improve	4/6	1/3	0.523
BNT			
M0	22.5(12-26)	19(10-26)	0.697
M6	24.5(20-28)	19(10-30)	0.439
P-value	0.027	0.317	
M0-M6:Improve	6/6	1/3	0.08
Codding			
M0	11.5(0-43)	25(10-41)	0.517
M6	20(12-45)	25(10-42)	0.696
P-value	0.042	0.317	
M0-M6:Improve	5/6	1/3	0.22

Values denotemedian(min-max) unless specified otherwise.

Table 5 Test DUAL task gait test

	Experiment (n=6) median(min-max)	Control (n=3) median(min-max)	P-value
Word list recall			
M0	1.5(0-5)	0(0-1)	0.396
M6	4.5(3-6)	0(0-5)	0.185
P-value	0.066	0.317	
M0-M6:Improve	4/6	1/3	0.523
Animal			
M0	12.5(2-17)	17(5-21)	0.364
M6	15.5(8-21)	17(5-20)	0.897
P-value	0.435	0.317	
M0-M6:Improve	5/6	0/3	0.047
กสป			
M0	11.5(3-25)	9(5-18)	0.606
M6	14(6-33)	9(5-25)	0.604
P-value	0.176	0.317	
M0-M6:Improve	4/6	1/3	0.523
BNT			
M0	22.5(12-26)	19(10-26)	0.697
M6	24.5(20-28)	19(10-30)	0.439
P-value	0.027	0.317	
M0-M6:Improve	6/6	1/3	0.08
Codding			
M0	11.5(0-43)	25(10-41)	0.517
M6	20(12-45)	25(10-42)	0.696
P-value	0.042	0.317	
M0-M6:Improve	5/6	1/3	0.22

Values denotemedian(min-max) unless specified otherwise.

Table 6 Review of previous results or TMS in dementia (cross-section studies and RCTs)

Authors	Samples	Methods	Stimulation site	Cognitive outcome measurements	Assessment schedule	Results
Cotelli et al.,2006[6]	15 pts with mild to moderate AD	A train of 10 pulses with a frequency of 20 Hz. rTMS during cognitive stimulation. No sham group	Lt. or Rt.dlPFC	Action naming& object naming	Baseline and during stimulation	Stimulation to the Lt & Rt.dlPFC improved accuracy in action naming.
Cotelli et al.,2008[17]	12 mild AD, 12 moderate to severe AD pts.	A train of 10 pulses with a frequency of 20 Hz. rTMS during cognitive stimulation. No sham group	Lt & Rt.dlPFC	Action naming& object naming	Baseline and during stimulation	Stimulation of the left and right dorsolateral prefrontal cortex enhanced action naming but did not affect object naming in the mild AD group, whereas in the moderate to severe group, it improved accuracy in both action and object naming.
Cotelli et al.,2010[18]	10 moderate AD pts.	2 groups: One group was received 4 weeks stimulation at dlPFC (hemisphere was not specified) while another group was received 2 placebo treatment followed by 2 weeks of stimulation. 20 Hz rTMS for 25 min/d, 5d/wk. NO sham group	dlPFC (hemisphere was not specified)	MMSE, ADL, IADL, Picture naming, SC-BADA, Aachen Aphasia Test, serial curve position, Cognitive estimation test	Baseline,2,4 and 12 weeks after stimulation onset	The group receiving 4-week stimulation showed improvement in auditory sentence comprehension, as assessed by SC-BADA, following the initial 2 weeks of stimulation. Both groups demonstrated sustained improvements in performance, lasting up to 8 weeks after treatment completion.
Bentwich et al.,2011[19]	7 mild or moderate AD pts.	A train of 20 pulses with a frequency of 10 Hz. rTMS combined with cognitive training. Intensive (daily session,5 days/wk for 6 wks) + maintenance (bi-weekly treatment for 3 mo.). No sham group	Broca, Lt.&Rt. dlPFC, Wernicke, Lt.&Rt. pSAC	ADAS-Cog, CGIC, MMSE, ADAS-ADL, Hamilton, NPI	Baseline, after intensive phase and after maintenance phase	The study showed an improvement in ADAS-Cog after 6 weeks and 4.5 months to treatment while the CGIC, MMSE, ADAS-ADL and NPI were no significant change.

Authors	Samples	Methods	Stimulation site	Cognitive outcome measurements	Assessment schedule	Results
Ahmed et al.,2012[20]	32 mild to moderate AD, 13 severe AD pts.	3 groups: 1st group received real rTMS 20 trains of 20 Hz., 2nd group received real rTMS 2 trains of 1 Hz. Another group received sham treatment.	Lt & Rt.dlPFC	MMSE, IADL, GDS	Baseline, end of treatment, 1 and 3 months after treatment	The high-frequency (20 Hz) group showed significantly greater improvement compared to the low-frequency and sham groups across all rating scales and at every time point following treatment.
Rabey et al.,2013[7]	15 mild to moderate AD pts.	Stimulation and sham group. Stimulation group received rTMS-COG. Intensive (daily session,5 days/wk for 6 wks) + maintenance (bi-weekly treatment for 3 mo.).	Broca, Lt.&Rt. dlPFC, Wernicke, Lt.&Rt. pSAC	ADAS-Cog, CGIC, NPI	Baseline, after intensive phase and after maintenance phase	The study showed an improvement in ADAS-Cog and CGIC at the end of the intensive phase in the treatment group. the effect on cognitive score was lasted up for 4.5 months.
Rutherford et al.,2015[8]	Stage 1: 10 mild to moderate AD pts. Stage 2: 6 mild to moderate AD pts.	2 stages of treatment: Stage 1 consisted of a double-blind crossover study with real and sham treatment which consisted of 13 sessions of 20 Hz. rTMS over 4 weeks in 10 AD patients. Stage 2 applied 10 sessions of rTMS over 2 wks every 3 months in 6 participants who complete the first stage of study	Lt & Rt.dlPFC	ADAS-Cog, RMBC, MOCA	Stage 1: baseline and 4 wks after treatment. Stage 2: a few days after treatment.	No statistical significance on ADAS-Cog score comparing treatment group and sham group in stage 1 of treatment. Nevertheless, the long-term trend noted in the study's second stage indicated a generally slower cognitive decline than anticipated.
Lee et al.,2016[9]	19 mild AD, 7 moderate AD patients.	Stimulation and sham group. Stimulation group received rTMS 10 Hz., 20 trains for 2 s combined with cognitive training.	Broca, Lt.&Rt. dlPFC, Wernicke, Lt.&Rt. pSAC	ADAS-Cog, CGIC, MMSE, GDS	Baseline, end of treatment and 6 wks after end of treatment	Patients with mild Alzheimer's disease showed improvement in ADAS-Cog scores following treatment, which persisted for 6 weeks; however, this improvement was not significantly different from that of the sham group.

Authors	Samples	Methods	Stimulation site	Cognitive outcome measurements	Assessment schedule	Results
Li et al.,2021[21]	75 mild to moderate AD pts.	Stimulation and sham group. Stimulation group The treatment group received 20 Hz. of rTMS in 30 sessions over 6 weeks	Lt.dlPFC	MMSE, ADAS-Cog, cortical plasticity reflected by motor-evoked potential	Baseline, end of treatment and 3 months after end of treatment	The result revealed an improvement on MMSE at both the post-treatment and follow up time point, while ADAS-Cog score was significantly reduced in the treatment group from baseline to post-treatment but returned to baseline at 3-month follow up.
Koch et al.,2022[22]	50 mild AD pts.	Stimulation and sham group. Stimulation group received rTMS 20 Hz. with a 2-week intensive phase (1 session/d, 5 d/weeks) followed by 22-week maintenance phase (1 session/week)	Precuneus	CDR-SB, ADAS-Cog, MMSE, ADCS-ADL	Baseline, 4 and 12 weeks after stimulation onset	Patients in stimulation group presented a stable performance of the CDR-SB score and significantly better performance on MMSE, ADCS-ADL compared with sham group.
Zhang et al.,2023[23]	35 moderate to severe AD pts.	Stimulation and sham groups. Stimulation group received rTMS 10 Hz. with total of 60 sessions over 3 months	Lt.dlPFC	MMSE, MOCA, SIB, ADL, NPI, CIBIC-Plus	Baseline and end of treatment	The findings indicated that rTMS treatment enhanced cognitive function as measured by the Severe Impairment Battery, decreased psychiatric symptoms assessed by the Neuropsychiatric Inventory (NPI), and improved the Clinician's Global Impression of Change (CIBIC-Plus).

Table 6 (continued): Review of previous results or TMS in dementia (Meta-analyses)

Authors	Samples	Inclusion criteria	Results
Dong et al., 2018[24]	5 RCTs involving 148 participants	Sham and treatment group	High-frequency rTMS resulted in significant cognitive improvement as assessed by ADAS-cog; however, there were no significant differences in mood and functional performance between the treatment and sham groups.
Cheng et al.,2018[25]	7 RCTS involving 194 participants	Sham and treatment group	High-frequency rTMS showed a benefit on cognition amongst older patients with mild to moderate AD. Subgroup analysis demonstrated that single stimulation target, mainly the dorsolateral prefrontal cortex, showed improvement in cognition after active rTMS.
Wang et al., 2020[26]	10 studies involving 240 patients	Parallel design and crossover design trials	rTMS significantly enhanced cognitive function in Alzheimer's disease. Subgroup analysis indicated greater cognitive improvement among participants receiving stimulation at multiple sites compared to a single site.
Wei et al., 2022[27]	14 studies involving 513 patients	RCT and cross-section studies	rTMS resulted in significant improvements in overall cognitive function and activities of daily living among Alzheimer's disease patients; however, it did not enhance language, memory, executive functioning, or mood.
Zhang et al., 2022[28]	9 RCT involving 361 patients	Sham and treatment group	rTMS led to significant improvements in overall cognitive function immediately after treatment, and these beneficial effects lasted for an extended period.

Discussion

This study observed improvements in global cognitive scores, specifically TMSE and MOCA, among Alzheimer's disease (AD) patients following repetitive Transcranial Magnetic Stimulation (rTMS) combined with cognitive training, although these improvements were not statistically significant. Notably, significant improvements were noted in logical memory, visual memory, VOSP, and BNT, as well as dual-task gait in the treatment arm. These findings are consistent with previous studies, including those by Bentwich,[29] Rabey,[7] and Lee,[9] which reported improvements in ADAS-Cog, MMSE, and CGIC scores following rTMS applied to six brain regions combined with cognitive training.

The absence of statistically significant differences in global cognitive scores (TMSE and MOCA) in this study may be attributed to the small sample size. While rTMS is an emerging non-pharmacological intervention for AD, evidence regarding its long-term efficacy and safety remains limited, especially in Thai patients. Despite the small sample size, this pilot study, demonstrated promising results in both efficacy and safety, prompting the need for larger-scale studies in the future.

Interestingly, the sham group demonstrated greater improvement in global cognitive outcomes than previously reported. This enhancement could be due to the combined impact of Alzheimer's medications and cognitive training. Cholinesterase inhibitors, a common pharmacological treatment for AD, have been shown to enhance global cognition in previous trials.[30] Additionally, a meta-analysis[31] highlighted the positive impact of cognitive training on global cognition, including MMSE and task-specific improvements. The combined influence of these two interventions may explain the observed cognitive enhancement in the sham group.

Regarding dual-task gait, this study found improvements in step length in both feet, further supporting the association between dual-task gait and cognitive function, suggesting a direct link between the two[18]. However, the study has several limitations, including a small sample size, single-center setting, potential selection bias, and the absence of a control group receiving rTMS without cognitive training. Despite these constraints, the findings provide evidence of the effectiveness of rTMS combined with cognitive training in Thai patients with mild to moderate AD.

In conclusion, the present study suggests that rTMS treatment may improve global cognitive function, as measured by TMSE and MOCA scores, and demonstrates significant improvements in visual and logical memory, as well as step length in dual-task gait assessment in Thai patients with mild to moderate AD patients. Notably, no side effects were observed. Therefore, rTMS-COG is a novel, safe, and effective medical device designed for the treatment of Alzheimer's disease. Nevertheless, additional research involving well-designed, larger-scale, and longer-duration trials is necessary to validate the clinical importance of the observed cognitive improvements. In the future, rTMS may be a useful tool along with cognitive exercises and pharmacologic treatments for improving the quality of life in individuals with AD.

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