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Treatment of Alzheimer's Disease with Repetitive Transcranial Magnetic Stimulation Combined with Cognitive Training: A Prospective, Randomized, Double-Blind, Placebo-Controlled Study

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Background and Purpose Repetitive transcranial magnetic stimulation (rTMS) has been examined as a potential treatment for many neurological disorders. High-frequency rTMS in particular improves cognitive functions such as verbal fluency and memory. This study explored the effect of rTMS combined with cognitive training (rTMS-COG) on patients with Alzheimer's disease (AD).

Methods A prospective, randomized, double-blind, placebo-controlled study was performed with 27 AD patients (18 and 8 in the treatment and sham groups, respectively, and 1 drop-out). The participants were categorized into mild [Mini-Mental State Examination (MMSE) score=21−26] and moderate (MMSE score=18−20) AD groups. The rTMS protocols were configured for six cortical areas (both dorsolateral prefrontal and parietal somatosensory associated cortices and Broca's and Wernicke's areas; 10 Hz, 90−110% intensity, and 5 days/week for 6 weeks). Neuropsychological assessments were performed using the AD Assessment Scale-cognitive subscale (ADAS-cog), Clinical Global Impression of Change (CGIC), and MMSE before, immediately after, and 6 weeks after the end of rTMS-COG treatment.

Results Data from 26 AD patients were analyzed in this study. There was no significant interactive effect of time between the groups. The ADAS-cog score in the treatment group was significantly improved compared to the sham group (4.28 and 5.39 in the treatment group vs. 1.75 and 2.88 in the sham group at immediately and 6 weeks after treatment, respectively). The MMSE and CGIC scores were also improved in the treatment group. Based on subgroup analysis, the effect of rTMS-COG was superior for the mild group compared to the total patients, especially in the domains of memory and language.

Conclusions The present results suggest that rTMS-COG represents a useful adjuvant therapy with cholinesterase inhibitors, particularly during the mild stage of AD. The effect of rTMS-COG was remarkable in the memory and language domains, which are severely affected by AD.

Key Words repetitive transcranial magnetic stimulation, Alzheimer's disease, cognitive therapy.

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INTRODUCTION

Alzheimer's disease (AD) is the most common type of dementia among the elderly and its prevalence increases steeply with age.[1] Most current treatments for AD are focused on delaying cognitive decline using medications, and many clinical trials aiming to reverse or affect the disease course have failed.[2,3] The narrow selectivity for the treatment of AD has resulted in

an increased interest in alternative therapeutic strategies and nonpharmacological interventions.[4,5] One of the available therapeutic interventions, transcranial magnetic stimulation (TMS), has been explored as an alternative noninvasive AD treatment.

The advantages of TMS include its safety, its utility for noninvasive stimulation of the brain,[6,7] and the ease of applying various combinations of stimuli. Repetitive TMS (rTMS) generates electric currents to produce magnetic fields that surround cortical neurons so as to modulate the synaptic activities of focal neuronal circuits and corticosubcortical networks in the brain.[8-11] High-frequency rTMS has been used for various psychiatric and neurological diseases, including depression, schizophrenia, and Parkinson's disease.[10,12,13] However, a few studies have found that using rTMS improves cognitive functions in AD.[14,15]

Cotelli et al.[16,17] stimulated the dorsolateral prefrontal cortex (dlPFC) bilaterally with high-frequency rTMS and reported an improvement of action-naming and object-naming accuracy in moderate-to-severe AD. Haffen et al.[18] reported that episodic memory and the information processing speed improved in AD subjects following application of trains of high-frequency rTMS to the left dlPFC. Improvement in not only general cognitive performance [as evaluated by Mini-Mental State Examination (MMSE) score], but also specific cognitive tasks were demonstrated in the aforementioned studies.[19,20] Although Rabey et al.[21,22] revealed significant cognitive improvement in AD patients using rTMS combined with cognitive training (rTMS-COG), the number of participants studied was relatively small and the effects of rTMS-COG on different stages of AD were unclear.

The present study tested the hypotheses that high-frequency rTMS-COG enhances the effect of using rTMS alone, and is more effective during the early stage of AD in which the cognitive reservoir is preserved. The aims of this study were twofold: 1) to determine the effect of rTMS-COG on AD between treated and sham groups, and 2) to determine the stages of AD and cognitive domains that rTMS-COG is more useful in.

METHODS

Study population

Inclusion criteria

Twenty-seven patients (18 patients receiving rTMS-COG treatment and 9 receiving sham treatment) diagnosed with probable AD based on the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition were recruited for this study. Their MMSE score was 18−26 and their global Clinical Dementia Rating scale score was 1 or 2. All of the participants in this study were required to be accompanied by a caregiver or a family member who spent more than 72 hours per week with the patient to provide daily information about them. All patients could read and write Korean proficiently, and brain MRI was performed to exclude any organic brain lesions that might have affected cognitive function. The patients were required to maintain their drugs without changes from at least 2 months before the start of the study and throughout its duration.

Exclusion criteria

Patients with a history of alcohol abuse or who had taken psychoactive medications within the past month were excluded. Patients who were not capable of touching a computer screen, who were unable to cooperate with the technician because of vision or hearing difficulty, or who had contraindications for rTMS were also excluded, as were patients who were not available for general TMS treatment.

Approval of the standard protocol

This study was conducted at Chungnam National University Hospital using a protocol approved by the hospital ethics committee. All participants in the study or their legal family members understood and signed the informed consent.

Study design

This was a prospective, randomized, double-blind, placebo-controlled study that was conducted from February 2013 to February 2014. The patients were randomly assigned to the treatment or sham-treated group at a ratio of 2:1. The patients in the treatment group received daily treatment sessions for 6 weeks (1 session/day and 5 days/week for total of 30 sessions), while the sham-treated group received regular sham management without either stimulation or cognitive training. Neuropsychological assessments were performed before the treatment and immediately after and 6 weeks after the end of rTMS-COG. The primary outcomes included differences in the AD Assessment Scale-cognitive subscale (ADAS-cog) scores between the groups and between pre- and posttreatment. Secondary outcomes included the differences in the Clinical Global Impression of Change (CGIC), MMSE, and the Geriatric Depression Scale (GDS) scores.

rTMS-COG protocols

Brain mapping and stimulation protocol

Every patient submitted to brain MRI (3.0-T MRI scanner, HD excite, GE, USA). Two neurologists and one neuroradiologist evaluated the MRI images to mark six cortical areas for stimulation. The rTMS system (Neuronix, Yokneam, Israel)

superimposed the anatomical location of each stimulated brain area on the MRI images, such that the position of each cortical area could be identified for applying rTMS. These six brain areas represented the location of the primary centers involved in the manifestation of the clinical symptoms of AD, including the right and left dlPFC, Broca's and Wernicke's areas, and the right and left parietal somatosensory association cortex (pSAC). rTMS was applied to the six areas in conjunction with active cognitive training that were associated with the function of each cortical area.

A motor threshold was determined by placing the magnetic coil over the motor cortex and adjusting the stimulation intensity to elicit visible contraction of the patient's hand. The intensity was adjusted to 90% of the motor threshold in Broca's area and the dlPFC, and to 110% of the motor threshold in Wernicke's area and the pSAC. Broca's area, Wernicke's area, and the right dlPFC were treated during the same daily session (days 1, 3, and 5), and the left dlPFC and both pSAC areas were treated on the alternate days (days 2 and 4). Each area was stimulated with 20 trains (10 Hz for 2 s at 20 pulses/train), and so 1,200 pulses were applied per day, which was in accordance with the safety limitation of a maximum number of 1,500 pulses/day.[23] The sham group received the same recording sounds but without magnetic stimulation.

Cognitive training

Magnetic stimulation of cortical brain areas was performed using a NeuroAD system, which provided patients with specific cognitive paradigms. The cognitive tasks were matched to the high-order cortical functions corresponding to each of the six selected areas. The patients performed these tasks in conjunction with the cortical stimulation with rTMS: syntax and grammar tasks for Broca's area; comprehension of lexical meaning and categorization tasks for Wernicke's area; action naming, object naming, and spatial memory of shapes, colors, and letters tasks for both dlPFC areas; and spatial attention for shapes and letters tasks for both pSAC areas.

The cognitive tasks were displayed on a touch screen in front of the patient, who selected the answers by touching the icons on the screen. The difficulty level of the cognitive tasks was assigned according to patient's cognitive performance and was adjusted according to the prior results for the cognitive task performance. All cognitive tasks and related commands on the screen were translated into Korean by a bilingual professor in the Department of English Literature and were checked by two neuropsychologists. For the patients in the sham group, the screen presented simple objects (e.g., a flower or a landscape) unrelated to cognitive function, and they simply chose whether or not they liked them.

Treatment procedure

The patients in the treatment group received daily treatment sessions for 6 weeks (1 session/day and 5 days/week for total of 30 sessions in 6 weeks). Each session lasted 1 hour, including preparation, and three brain areas were targeted and stimulated separately. Twenty trains of rTMS (2 s of 10 Hz/train and 20 pulses/train) followed by two to four cognitive tasks were administered over the course of 20−40 s for each brain area, resulting in 400 pulses in 7−15 min. For patients in the sham group, the same coil was positioned for stimulating the same selected brain areas but without applying any magnetic stimulation, and the patients heard the same sounds that had been recorded for when stimulation was applied to the other patients.

Clinical assessments and analyzed variables

All measurements of clinical assessments were repeated three times: at baseline and then immediately and 6 weeks after the end of rTMS-COG treatment. The initial evaluation was performed 2 weeks before starting rTMS-COG treatment. The second evaluation was performed at the time that the 6-weeks stimulation period was completed, and the final evaluation was performed 6 weeks after the end of rTMS-COG treatment. Patients were also divided into two groups according to the severity of AD using the cutoff MMSE score of 21: mild group, 21−26; and moderate group, <20. All cognitive assessments were performed by a trained neuropsychologist who was blinded to the treatment status of the participants (i.e., treated or sham-treated) throughout the study.

Primary outcome measures

The primary outcome measure of this study was the change in ADAS-cog score between the treatment and sham groups. The total possible ADAS-cog score was 70, and the average ADAS-cog score was compared between baseline and immediately and 6 weeks after the end of rTMS-COG treatment between the treatment and sham groups. These analyses were replicated to compare the groups with mild and moderate cognitive impairments.

Secondary outcome measures

The MMSE and GDS scores were assessed for all participants at baseline and then immediately and 6 weeks after the end of rTMS-COG treatment. CGIC was assessed for all participants immediately and 6 weeks after the end of treatment. The scores for memory, language, and executive function on the ADAS-cog were compared between pre- and posttreatment (immediately and 6 weeks after). The memory subdomain of the ADAS-cog scales includes orientation, word recall, word recognition, and remembering test instruction. The language subdomain consists of commands, naming objects, spoken

Table 1. Baseline characteristics of the participants

Variables	Total (*n*=26)	Real treatment (*n*=18)	Sham (*n*=8)	*p*-value
Age (years)	71.6±6.8	72.1±7.6	70.3±4.8	0.531
Females (%)	57.7	55.6	62.5	1.000
Education (years)	9.9±3.9	9.9±4.8	9.9±3.7	0.978
Donepezil (mg)	8.1±2.5	7.8±2.6	8.8±2.3	0.461
ADAS-cog	23.4±6.2	23.7±6.4	22.9±6.2	0.892
MMSE	22.5±2.7	22.4±2.9	22.8±2.5	0.807
GDS	10.9±6.9	10.5±6.2	11.6±8.9	0.807

Values denote means±SD unless specified otherwise.
ADAS-cog: Alzheimer's disease assessment scale-cognitive subscale, GDS: Geriatric Depression Scale, MMSE: Mini-Mental Statue Examination.

language ability, word-finding difficulty, and comprehension. Constructional praxis and ideational praxis are included in executive function.

Statistical analysis

Demographics were analyzed using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. All of the assessments (ADAS-cog, MMSE, GDS, and CGIC) were analyzed via repeated-measures analysis of covariance, including age, gender, and duration of education as covariates to evaluate the consecutive changes in each score from baseline to after rTMS-COG treatment between the treatment and sham groups. The scores obtained immediately and 6 weeks after the end of rTMS-COG treatment were compared with those obtained at baseline by multiple comparisons with Bonferroni correction. Given that the CGIC is a comparative analysis tool, a score of "4" ("unchanged") was assigned to all participants at the pretreatment level to compare with the posttreatment score as a baseline. All of these statistics were applied identically in the subgroup analysis. All analyses were performed using SPSS software (Windows version 21.0, SPSS Inc., Chicago, IL, USA). Two-sided probability values of $p<0.05$ were considered statistically significant.

RESULTS

Participants

Twenty-seven patients were enrolled in this study. Eighteen patients were randomly assigned to the treatment group and the others were assigned to the sham group at a 2:1 ratio. The only adverse effect in any participant during the follow-up period occurred in one patient in the sham group who complained of mild headache and fatigability at the first visit. That patient withdrew, and so 26 patients completed this study. No significant differences in the baseline characteristics such as age, gender, duration of education, and neuropsychological assessments (ADAS-cog, MMSE, and GDS scores) were detected between these two groups (Table 1).

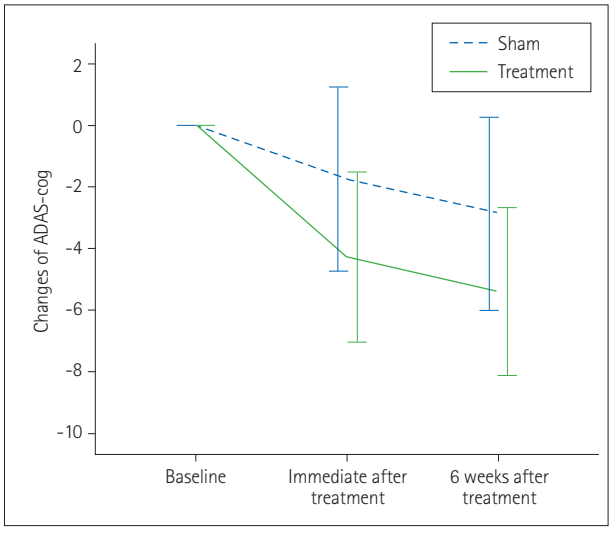

Fig. 1. Differences in ADAS-cog score at each measurement time point (immediate after, 6 weeks after treatment) from baseline. There was no significant time×group interaction, although significant improvements were found in the treatment group. The solid and dotted lines indicate the treatment and sham-treated groups, respectively. ADAS-cog: Alzheimer's disease Assessment Scale-cognitive subscale.

Primary outcomes

Comparison of the changes in ADAS-cog score between groups revealed no significant group-by-time interaction (p=0.208), although the improvement in the ADAS-cog score was much greater in the treatment group than in the sham group (Fig. 1). The patients in the treatment group exhibited an improvement of 4.28 points on the ADAS-cog score immediately after the end of rTMS-COG treatment (6 weeks) from baseline (p=0.018). The effect of rTMS-COG treatment remained steady or was even enhanced at 6 weeks after the end of rTMS-COG treatment (12 weeks), as demonstrated the 5.39-point improvement in ADAS-cog score in the treatment group from baseline at that time point (p=0.002). The patients in the sham group also improved slightly, by 1.75 and 2.88 points immediately and 6 weeks after treatment, respectively, although difference in interactions follow-up and two group (treatment and sham group) was not statistically significant (Fig. 2, Table

2). The ADAS-cog score improved much more significantly from baseline in the mild group (MMSE score=21–26) than in the moderate group (Fig. 3).

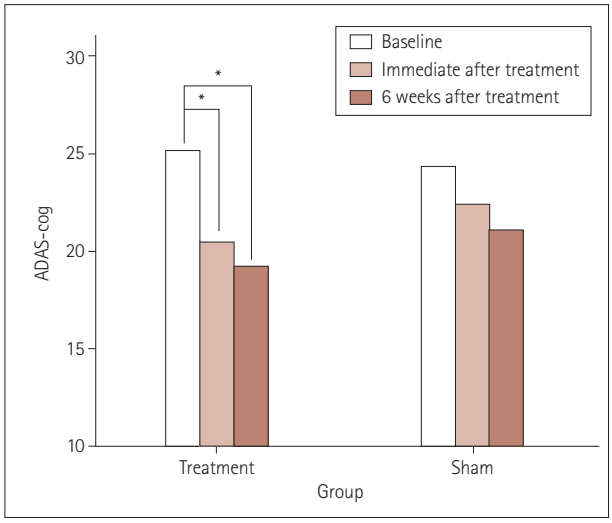

Fig. 2. Significantly improved ADAS-cog scores were found following treatment compared with baseline (immediately after treatment, improved by 4.28 points, p=0.014; 6 weeks after treatment, improved by 5.39 points, p=0.002). *p<0.05. ADAS-cog: Alzheimer's disease Assessment Scale-cognitive subscale.

Secondary outcomes

MMSE score

The average MMSE score improved from 22.39 (baseline) to 23.89 (immediate after) and 24.39 (6 weeks after) in the treatment group as a whole; these differences were not statistically significant. However, the score improved significantly between baseline and 6 weeks after treatment in the mild AD group (p=0.015) (Table 2).

GDS score

The GDS score did not improve significantly in the treatment group; however, a significant improvement at the end of the study was observed in the sham group (p=0.02) (Table 2).

CGIC score

The average CGIC scores in the treatment and sham groups were 2.4 and 3.5 immediately after treatment, respectively (p=0.009), and 2.6 and 3.3 at 6 weeks after the end of treatment (p=0.196).

Cognitive domains

Improvements in the memory and language cognitive domains were observed following rTMS-COG treatment; these

Table 2. Neuropsychological test scores at each time points with all participants and in each mild and moderate group

Neuropsychological assessments	Group (*n*)	Scores (mean±SD)			*p* value		
		Baseline [B]	Immediate after [6]	6 weeks after [12]	[B] vs. [6]	[B] vs. [12]	Time* group
ADAS	Treatment (18)	23.61 (6.40)	19.33 (8.30)	18.22 (8.85)	0.018*	0.002*	0.208
	Sham (8)	22.88 (6.20)	21.12 (7.66)	20.00 (9.49)	0.238	0.46	
	Mild treatment (13)	21.77 (5.09)	16.31 (6.40)	14.92 (7.43)	0.035*	0.005*	0.111
	Mild sham (6)	20.83 (3.76)	18.17 (4.54)	17.33 (4.93)	0.396	0.056	
	Moderate treatment (5)	28.4 (7.54)	27.2 (7.95)	26.8 (6.30)	1	0.264	0.966
	Moderate sham (2)	29.0 (9.90)	30.0 (9.90)	28.0 (18.39)	NA	NA	
MMSE	Treatment (18)	22.39±2.87	23.89±4.44	24.39±4.57	0.139	0.058	0.729
	Sham (8)	22.75±2.49	24.50±4.90	25.75±4.56	0.769	0.213	
	Mild treatment (13)	23.77±2.01	25.62±3.33	26.46±2.93	0.058	0.015*	0.785
	Mild sham (6)	23.83±1.72	26.67±2.16	27.5±2.51	0.461	0.204	
	Moderate treatment (5)	8.8±0.84	19.4±3.98	19.0±3.54	1	1	0.784
	Moderate sham (2)	19.5±0.71	18.0±5.66	20.5±6.36	NA	NA	
GDS	Treatment (18)	10.50±6.14	7.89±5.71	7.50±6.44	0.635	0.452	0.77
	Sham (8)	11.63±8.93	9.38±6.99	8.00±6.97	0.656	0.020*	
	Mild treatment (13)	11.62±4.82	9.92±5.25	10.00±5.85	1	1	0.754
	Mild sham (6)	11.83±8.45	9.17±6.97	7.50±6.16	1	0.148	
	Moderate treatment (5)	7.60±8.71	2.60±2.70	1.00±0.71	1	1	0.484
	Moderate sham (2)	11.00±14.14	10.00±9.90	9.50±12.02	NA	NA	

Repeatitive measures ANCOVA adjusted with age, sex, duration of education and post-hoc analysis with Bonferroni comparison. As moderate sham group included only two participants, analysis was impossible within group.
*p value<0.05.
ADAS: Alzheimer's disease Assessment Scale-cognitive subscale, GDS: Geriatric Depression Scale, MMSE: Mini-Mental State Examination, NA: not applicable.

results were more significant in the mild-AD treatment group (Table 3). ADAS-cog subdomains such as word recall, word recognition, orientation, naming objects, and fingers and commands were improved in the treatment group. No statistically significant change in cognitive function was detected among the moderate-AD treatment group (Table 3).

DISCUSSION

A significant improvement in cognition was observed among the AD patients in this study after rTMS-COG treatment, although the differences between the treatment and sham groups were not significant. In addition, the mean ADAS-cog scores among those with mild AD improved by 5.46 points after rTMS-COG treatment. These results were remarkable compared with the treatment effects of cholinesterase inhibitors, which resulted in an average improvement of 2.7 points over 6 months[4] and 1.8 points over 12 weeks.[24]

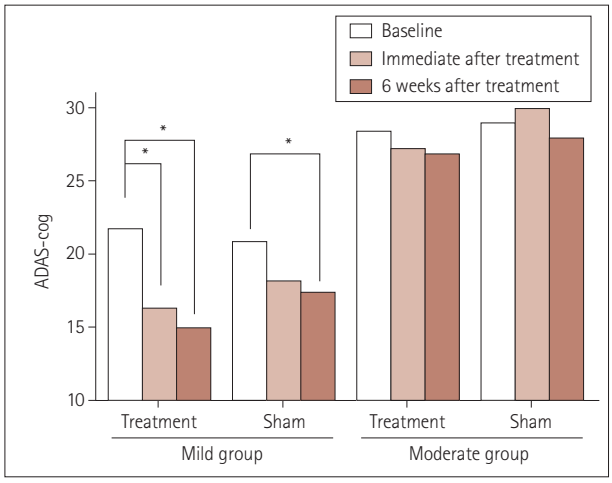

Fig. 3. Significant improvements of ADAS-cog scores compared with baseline were observed in the mild-AD treatment group. *p<0.005
AD: Alzheimer's disease, ADAS-cog: AD Assessment Scale-cognitive subscale.

While the mechanisms underlying the beneficial effects of rTMS are not fully understood, more efficient processing due to the direct modulation of cortical areas or networks has been proposed as an underlying mechanism.[25] The synaptic neuronal activities involved in long-term potentiation (LTP) might be related to memory and learning processes based on the Hebbian theory of changes in synaptic strength via coactivation of input neurons, and such neural coactivation might be facilitated by TMS.[25,26] Given the activation of Hebbian and LTP-like mechanisms, TMS has the potential to accelerate learning skill by targeting a cortical area that is essential to performing or learning the skill, especially when TMS is applied in conjunction with training or exercise of the skill.[27] High-frequency rTMS was applied to multiple cortical sites coincident with associated cognitive training in the present study. Thus, rTMS-COG may increase the probability of cortical plasticity by applying rTMS and subsequently performing cognitive training to the targeted cortical areas.

Cotelli et al.[16,17,28] demonstrated improvements in language and auditory sentence comprehension after rTMS, and Devi et al.[29] reported improvements in certain cognitive parameters after four sessions of rTMS in AD patients, primarily in their verbal and nonverbal agility. The performance in the language and memory domains was also significantly improved in the treatment group in the present study.

The cognitive outcome in the sham group was slightly better than in previous studies, which could have been due to our presentation of peripheral auditory clicking sounds from the

Table 3. Changes of cognitive subdomains in the rTMS-COG treatment group

Group	Cognitive domains	Changes of scores, mean (SD)		*p* value		
		Δ immediate after treatment	Δ 6 weeks after treatment	[B] vs. [6]	[B] vs. [12]	Time
Treatment	Memory	2.00 (2.81)	2.56 (3.05)	0.040*	0.006*	0.054
	Language	1.28 (1.53)	1.44 (1.92)	0.004*	0.003*	0.009*
	Executive function	0.67 (1.24)	0.56 (1.50)	0.117	0.413	0.995
Mild treatment	Memory	1.77 (3.09)	2.69 (3.17)	0.275	0.031*	0.178
	Language	1.23 (1.79)	1.23 (1.96)	0.04*	0.019*	0.002*
	Executive function	0.92 (1.12)	0.92 (1.50)	0.031*	0.093	0.2
Moderate treatment	Memory	2.60 (2.07)	2.20 (3.03)	0.627	0.688	0.397
	Language	1.40 (0.55)	2.00 (1.87)	0.243	1.000	0.947
	Executive function	0.00 (1.41)	0.40 (1.14)	1.000	0.969	0.084

Repeatitive measures analysis of covariance including age, gender and duration of education as covariates with multiple comparisons with Bonferroni correction.
*p value<0.05.
rTMS-COG: repetitive transcranial magnetic stimulation with cognitive training, Δ: differences from baseline to at each point, [B]: baseline, [6]: immediately after the end of treatment, [12]: 6 weeks after the end of treatment.

rTMS coil without cortical magnetic stimulation, thereby evoking intersensory facilitation.[30] However, a definite effect of this intersensory facilitation phenomenon was not detected in previous rTMS studies. Placebo responses are psychological constructs related to treatment and expected outcomes, and the emotional valence attached to placebo responses include goal-seeking and optimism regarding the treatment.[31] However, it cannot be concluded definitively that placebo effects were the only contribution to the improvement of cognitive function in sham participants. Improvement of depression as measured by the GDS was detected exclusively in the sham group, which might have been due to the close attention of the caregivers to the patients during this study positively influencing their psychological stability.

This study was subject to some limitations. First, the number of patients was small, especially in moderate-AD sham group (n=2). Second, this study had only two arms: rTMS-COG treatment and sham treatment; it would have been beneficial to also include a group of patients who received only rTMS without cognitive training. However, the effect of rTMS has been studied previously, and the aim of the present study was to compare the effects of cognitive training with rTMS versus sham. Furthermore, it was envisaged that significant problems would be encountered when attempting to enroll sufficient participants for a three-arm design. Despite these limitations, the present findings demonstrate an effect of rTMS-COG treatment among AD patients.

This is the first study to compare rTMS-COG treatment in AD patients with a sham-treated group in Korea. Analysis of ADAS-cog subdomains and comparison of mild- and moderate-AD patients have not been performed previously in studies with similar protocols. This study provides new evidence regarding the effects of rTMS-COG on patients with AD, especially during the mild stage, which suggest that rTMS-COG represents a useful adjuvant therapy with cholinesterase inhibitors for the treatment of mild AD.

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Conflicts of Interest

The authors have no financial conflicts of interest.

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