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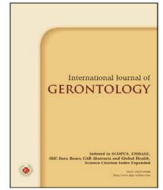
Original Article

Cognitive Effect of Repetitive Transcranial Magnetic Stimulation with Cognitive Training: Long-Term Mitigation Neurodegenerative Effects of Mild Alzheimer's Disease

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A R T I C L E   I N F O

S U M M A R Y

Background: Despite several studies having reported on the cognitive effects of repetitive transcranial magnetic stimulation (rTMS) in Alzheimer's disease (AD), no studies, to date have addressed the long-term effects of rTMS with cognitive training (CT). This study was aimed to investigate the long-term effects of rTMS-CT in mild AD.
Methods: Patients with mild AD (Mini-mental Status Examination [MMSE] score of 21–26), diagnosed based on the diagnostic and statistical manual of mental disorders-IV, were recruited and randomly allocated to two groups, treatment and sham, in a 2:1 ratio. We matched the acetylcholinesterase inhibitor (AChEI)-only group to the treatment group to comparing the long-term effect of rTMS-CT. Treatment group was treated for 6 weeks with high-frequency (10 Hz) rTMS-CT, whereas the other group received 6 weeks of the sham management. These groups underwent neuropsychological tests at baseline, immediately after rTMS-CT, and 6 weeks after the last rTMS-CT. Data of AChEI-only and treatment groups were analyzed changes of cognitive scores (MMSE, and clinical dementia rating-sum of boxes scales) over 3 years.
Results: Among the 44 enrolled mild AD (mean age, 72.5 years; females, 36.4%), the rTMS-CT group (n = 30) showed improvement on the ADAS-Cog score for 12 weeks compared with the sham group (n = 14). The rTMS-CT group showed slower rates of neurodegeneration than those in the AChEI-only group (n = 60) during the 3 years of follow-up.
Conclusions: Compared to the administration of AChEI only, the use of rTMS-CT might be a useful supplementary interventional strategy in mild AD for long-term mitigation of neurodegeneration.

1. Introduction

Alzheimer's disease (AD) is the most common type of dementia (60–70%), affecting an estimated 47 million people in the world.[1] Although many studies have investigated on the prevention and treatment of AD, effective strategies have remained elusive.[2] Therefore, the current research on AD is not limited to drug discovery but also includes various non-pharmacological interventions, such as physical activities, cognitive intervention, non-invasive brain stimulation, etc.

Transcranial magnetic stimulation (TMS) is a non-invasive, safe, and painless intervention which induces electrical currents under the skull by application of an external magnetic stimulation to change the brain function. In previous studies, the use of high-frequency repetitive TMS (rTMS) in AD[3,4] and cognitive normal participants[5] showed improvement of general cognition, naming accuracy, episodic memory, and processing speed. Although the underlying mechanism remains unclear, rTMS was demonstrated to affect the cortical excitability[6] and synaptic plasticity,[7] which in turn enhanced learning and memory.[8]

Cognitive training (CT) is defined as the guided cognitive exercises, designed to improve specific cognitive functions. While the favorable cognitive effects of CT have been reported in healthy elderly and mild cognitive impairment, the evidence of its for AD has been limited.[9] However, combining rTMS with CT (rTMS-CT) demonstrated a favorable cognitive effect in AD.[10–12] We had previously conducted a randomized controlled study to investigate the effects of rTMS-CT with mild to moderate AD, and found rTMS-CT to confer a therapeutic effect in the mild AD as compared to those who received sham management.[10] Therefore, we selected mild AD patients as the candidates for receiving rTMS-CT in this study.

Abundant evidence on the cognitive effect of rTMS is available, but the duration till which its effects last has not been ascertained yet. Therefore, this study aimed to investigate the long-term (3 years) cognitive effects of undergoing 30 consecutive sessions of rTMS-CT in mild AD as compared to those treated with only AChEI, and moreover, we confirmed the short-term (12 weeks) cognitive effect of rTMS-CT compared to sham in mild AD.

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2. Methods

2.1. Study population

Between February 2013 to August 2017, we prospectively re-cruited mild AD patients, who met the Diagnostic and Statistical Manual of Mental Disorders-IV criteria. Mild AD was defined as the Mini-Mental State Examination (MMSE) score of 21–26, Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog) score of 17–30, and Clinical Dementia Rating (CDR) score of 1. All participants could read and write Korean. The patients took acetylcholinesterase inhibitor (AChEI) since at least 2 months before their recruitment, without any changes in dosage. Patients with a history of psychiatric or neurologic disorders affecting cognition, seizure, alcohol, or drug abuse were excluded. Additionally, patients on medications known to affect cognition or lower the seizure threshold, for the past several months, were excluded. Those with severe impairment of vision or hearing were excluded. The included patients were ran-domly assigned to the treatment (rTMS-CT) or sham groups in a 2:1 ratio (Figure 1A). The purpose of this randomization was to clarify the effects of rTMS-CT and to give more treatment opportunities to the AD patients. Patients in the treatment group received rTMS-CT for six weeks, whereas, those in the sham group received sham man-agement during the same period.

For further analysis, we reviewed the medical charts, and re-trospectively recruited mild AD patients who consumed AChEI, and performed MMSE, annually, and categorized them as belonging to the AChEI-only group. The patients in the AChEI-only group were matched with those from the rTMS-CT group according to age, sex, education, MMSE score, CDR score, and disease duration. These subjects enrolled twice as many as the rTMS-CT group.

All participants and their legal family members signed a consent form of their own free will. The study was approved by the Institu-tional Review Board of the Chungnam National University Hospital (IRB file No.2012-12-013 / 2015-04-030).

2.2. Brain stimulation and cognitive training protocol

rTMS was performed using a figure-of-eight coil connected to a generator (NeuroAD, Neuronix Ltd., Yognea'm, Israel). Each session of stimulation consisted of a series of 20 trains with 20 pulses at 10 Hz (a total of 400 pulses). A total of 30 sessions of rTMS-CT was per-formed, 5 days a week, for 6 weeks. The total of 1,200 pulses were applied each day, and was below the published safety limit of 1,500 pulses/day.[13] During the inter-train intervals (30 s), 2–4 cognitive tasks were given. The intensity of the stimulation was adjusted to 90–110% of the resting motor threshold, depending on the stimu-lated region. Six brain areas, which are well-known to be affected in AD,[14] were targeted, such as: the left and right dorsolateral pre-frontal cortices (dlPFCs), left and right parietal somatosensory association cortices (pSACs), and Broca's and Wernicke's areas. Three different cortical regions per day were stimulated following the protocol (Figure 1B).

Computer-based CT, appropriate for the target area was un-dertaken with rTMS. A NeuroAD system provided the CT programs with specific cognitive paradigms such as: 1) syntax and grammar tasks for Broca's area,[15] 2) comprehension of lexical meaning and categorization tasks for Wernicke's area,[16] 3) naming of actions and objects, word recall, and spatial memory tasks for the bilateral dlPFC,[17] and 4) spatial attention tasks for the bilateral pSAC.[18] Al-though the CT undertaken was newly devised for use in the NeuroAD system and was not validated, it provided sufficient evi-dence of relation between the use of CT and stimulated brain re-gion. All CT tasks were translated to Korean by a bilingual linguist and a neurologist.

Patients in the sham group were mock-treated with a coil on the scalp and pre-recorded sound, without any magnetic stimulation. Simple objects (e.g., a flower or landscape) were displayed on the screen, and irrespective of their choice, the participants selected the figures as a mock-training with mock-stimulation. This sham man-agement lasted an hour.
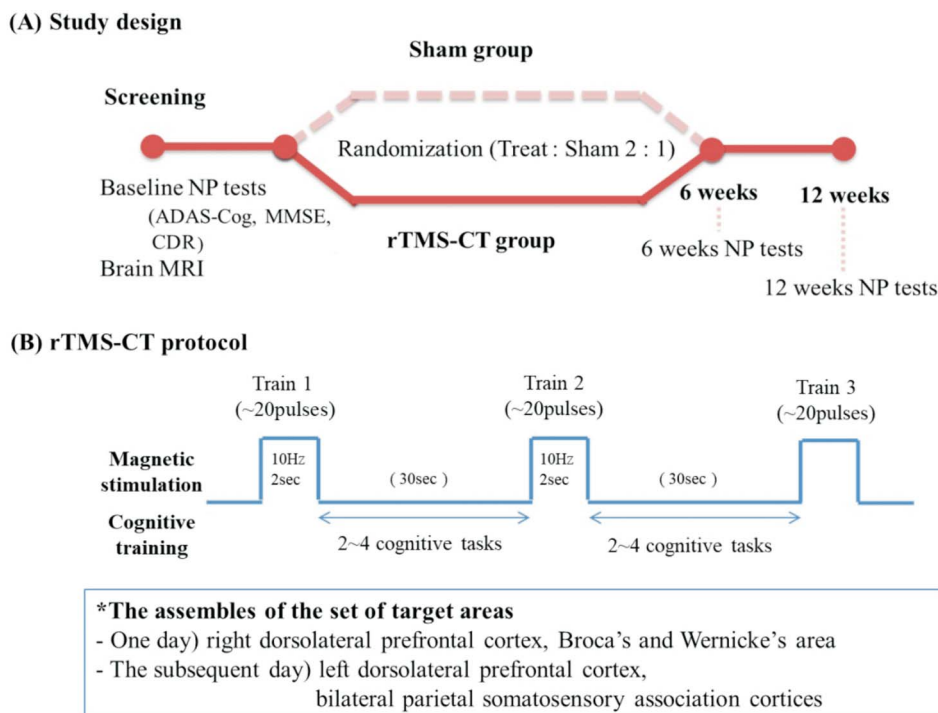

Figure 1. Study design and rTMS-CT protocols. ADAS-cog, Alzheimer's Disease Assessment Scale-cognitive subscale; CDR, clinical dementia rating; MRI, magnetic resonance image; NP, neuropsychological; rTMS-CT, repetitive transcranial magnetic stimulation with cognitive training.

2.3. Magnetic resonance imaging (MRI) and navigation system

All participants underwent a brain MRI scanning, which consisted of T2-weighted images, fluid-attenuated inversion recovery, gradient echo, and sagittal and coronal T1-weighted images, with 1-mm slice thickness without spacing (3.0-T MRI scanner, HD excite, GE, USA).

Two neurologists and one neuro-radiologist manually specified the six cortical area coordinates on the MRI scans using multi-image analysis graphical user interface. The coordinates were loaded onto the navigation control of the NeuroAD system to stimulate the exact location.

2.4. Neuropsychological assessments

The cognitive effects of rTMS-CT were evaluated by neuropsychological assessments, including ADAS-Cog, MMSE, and CDR, conducted three times repeatedly at baseline, immediately after rTMS-CT (6 weeks), and 6 weeks after the last rTMS-CT (12 weeks) (Figure 1A). ADAS-Cog is frequently used to evaluate the cognitive status of AD patients and to measure the therapeutic efficacy of the intervention in clinical trials.

The annual MMSE and CDR-Sum of Boxes (CDR-SB) scores were retrospectively collected in the rTMS-CT and AChEI-only groups to investigate the long-term (3 years) effects of rTMS-CT.

2.5. Statistical analyses

The demographic data were analyzed using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. A linear mixed model was used to compare the longitudinal changes in the neuropsychological test scores between the rTMS-CT and AChEI-only groups over 3 years of follow-up, and it was used to compare between the rTMS-CT and sham groups over 12 weeks. In the linear mixed model, age, sex, education, group, time, and the time-group interaction were used as the fixed effects, and the subjects were used as random effects.

Changes in the neuropsychological test scores at each time point were evaluated with the Wilcoxon's signed rank test. All analyses were performed using the SPSS® version 21 (IBM Corporation, Armonk NY, USA) for Windows®. Values of $p < 0.05$ were considered statistically significant.

3. Results

3.1. Short- and long-term effects of rTMS-CT in mild AD

A total of 45 patients were recruited for this study. Thirty patients were allocated to the rTMS-CT group, and fifteen to the sham group. No significant adverse effects were observed during the study, except tolerable sensations of pain during the stimulation of the dlPFC or Broca's area. One patient in the sham group, complained of fatigue and withdrew his consent on the first day of management; the data of the remaining 44 participants were used in the analyses. There were no significant differences in the clinical and cognitive baseline characteristics of patients between the two groups (Table 1).

The rTMS-CT group showed more significant improvement than the sham group for ADAS-Cog score for 12 weeks ($p = 0.04$) (Figure 2). Within the rTMS-CT group, the ADAS-Cog score improved by 4.3
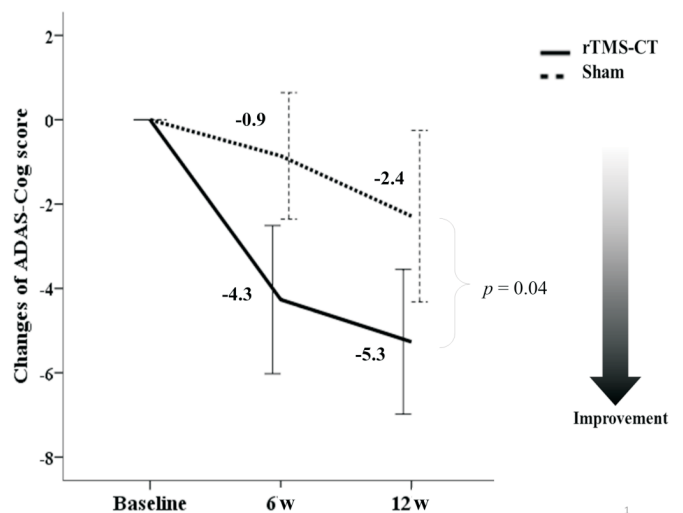
Figure 2. Comparison of the ADAS-Cog scores between rTMS-CT and sham groups. The ADAS-Cog score in the rTMS-CT group showed significantly greater improvement over time compared to that in the sham group (β = -1.47, $p = 0.04$). ADAS-cog, Alzheimer's Disease Assessment Scale-cognitive subscale; rTMS-CT, repetitive transcranial magnetic stimulation with cognitive training.

Table 1
Baseline characteristics of participants in the prospective study.

Characteristics	Total n = 44	rTMS-CT n = 30	Sham n = 14	U	p value
Age (years)	72.5 ± 7.4	72.1 ± 7.1	73.5 ± 8.1	184.0	0.51
Female	16 (36.4%)	12 (40.0%)	4 (28.6 %)	NA	0.35
Education (years)	11.9 ± 4.6	11.6 ± 4.8	12.6 ± 4.3	182.0	0.47
Family history of AD	11 (25.0%)	5 (16.7%)	6 (42.9%)	NA	0.07
APOE4 carrier	10 (38.5%)	5 (31.3%)	5 (50.0%)	NA	0.29
Dosage of AchEI (mg)	6.8 ± 2.4	6.6 ± 2.4	7.1 ± 2.6	190.0	0.55
Disease duration (years)	11.1 ± 15.2	10.9 ± 17.2	11.6 ± 9.9	169.0	0.30
Hypertension	15 (34.1%)	12 (40.0%)	3 (21.4%)	NA	0.31
Diabetes mellitus	7 (15.9%)	6 (20.0%)	1 (7.1%)	NA	0.40
Dyslipidemia	2 (4.5%)	1 (3.3%)	1 (7.1%)	NA	0.54
ADAS-Cog	19.9 ± 4.0	20.4 ± 4.4	18.7 ± 2.5	156.5	0.16
MMSE	24.1 ± 1.7	24.0 ± 1.7	24.4 ± 1.7	173.0	0.34
CDR-SB	4.7 ± 1.2	4.7 ± 1.4	4.8 ± 0.6	210.0	0.46

AChEI, acetylcholinesterase inhibitor; AD, Alzheimer's Disease; ADAS-Cog, Alzheimer's Disease Assessment Scale-cognitive subscale; APOE, Apo lipoprotein ε; CDR-SB, Clinical Dementia Rating-Sum of Boxes; MMSE, Mini-Mental State Examination; NA, non-applicable; rTMS-CT, repetitive transcranial magnetic stimulation with cognitive training.

* AChEI included donepezil and rivastigmine patch (two participants, 4.6 mg/24 hr).

points at 6 weeks, and by 5.3 points at 12 weeks, relative to the baseline ($p < 0.01$ at 6 weeks; $p < 0.01$ at 12 weeks). The MMSE scores of the rTMS-CT group, at each evaluation period, showed significant improvement relative to the baseline value.

The long-term effects of rTMS-CT were evaluated for 3 years by comparing the annual changes in the MMSE and CDR-SB scores between the rTMS-CT (n = 30) and AChEI-only groups (n = 60). The rTMS-CT group showed a significantly slower rate of cognitive decline (MMSE: β = -0.93, p = 0.01; CDR-SB: β = 0.53, p = 0.03) as compared to the AChEI-only group over the 3 years of follow-up (Figure 3).

4. Discussion

Mild AD with rTMS-CT showed cognitive improvement than those in the sham group for 12 weeks. Treatment with rTMS-CT reduced the rates of cognitive deterioration in mild AD, as indicated by the MMSE and CDR-SB scores, as compared to the AChEI-only group, over three years. To our knowledge, to date, no studies using rTMS in AD have undertaken long-term follow-up (3 years) similar to this study.

The effects of simple TMS are maintained only for few seconds to several minutes, whereas those of rTMS lasts several hours.[19] However, some studies have reported on the prolonged duration of the effects of rTMS, lasting months with multiple rTMS sessions.[20,21] In an open-label study on the effect of rTMS-CT with AD, the best responder demonstrated significant improvement which sustained for 6 months;[12] in another study using a similar protocol as in this study, the effect of rTMS in AD lasted for 10 months.[11]

The long-term effects of rTMS can be explained as follows. First, rTMS may result in long-lasting modulation of brain plasticity mediated by the modulation of neurotrophic factors, neurotransmitters, neuronal excitability, synaptic plasticity, and gene expressions.[22] TMS initiates an action potential in the neurons of the targeted site and changes the neural excitability, and induces indirect trans-synaptic activation of the nearby interneurons.[23] TMS induces structural change of the synapses,[24] such as, morphology of NMDA-expressing dendritic spines, and structural plasticity of the apical dendrites of the CA1 pyramidal neurons[24,25] which mediated the functional synaptic connections and supported neuronal functions.

TMS affects the dynamics of Ca^{2+} ions, which shows spiking, enables synaptic neurotransmitter release, and regulate gene expression.[26] Second, the rTMS-CT protocol used here comprised of 30 consecutive sessions, which might be the optimal number of sessions required for long-term effects. The effect of rTMS on corticospinal excitability was higher when performed 24 hours after the initial session with the appearance of a neurophysiologic trace of the first rTMS session that conditioned the second session.[27] Such long-lasting effects were reported in studies where daily repetitive rTMS sessions were performed.[28] Third, the rTMS-CT protocol attempted at obtaining maximal effects using variables such as the high frequency, and more number of pulses, performing multiple sessions, and the use of navigation system. Participants in this study underwent 30 sessions of high-frequency rTMS (10 Hz) with 1,200 pulses per day. The number of pulses used was closer to the maximum number of pulses allowed by the safety guidelines for TMS. Moreover, it is known that the effects of rTMS are mediated by direct targeting of the brain regions, distance effect, and distributed modulation. And this study used a navigation system to directly target the brain regions and to shorten the distance between the brain regions and the magnetic coil.

Although AChEI show modest efficacy in treating AD,[29] the cognitive functions of AD with AChEI, improved by an average of 2.4 points on the ADAS-Cog with 6 months of use.[30] In this study, the use of rTMS-CT with AChEI showed a better cognitive therapeutic effect in mild AD, over 12 weeks, than that observed in previous studies which only used AChEI. Several previous studies have demonstrated the favorable cognitive effects of rTMS in AD. Patients with AD showed improvement of general cognition,[6] and specific cognitive tasks, such as action and object naming accuracy,[3] episodic memory, and information processing speed[4] after performing high-frequency rTMS on the dlPFC. Previous studies with mild to moderate AD[12,31] showed improvement in ADAS-Cog score among subjects in rTMS-CT group than the sham group. These improvements in cognitive effects might be explained by the combined, synergistic effect of external rTMS stimulation and intrinsic cognitive training.

Although this study was not directly compared to the effect of rTMS only and combination of rTMS with CT, there were studies that compared cognitive effects of rTMS or CT alone in patients with AD. The application of CT alone demonstrated better functional connec-
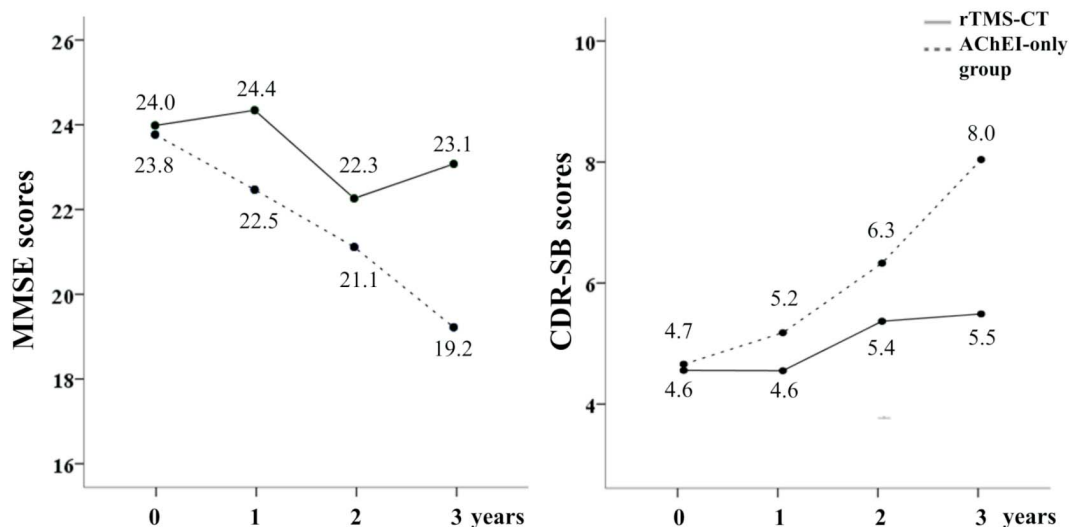

Figure 3. Comparisons of 3-year changes in the MMSE and CDR-SB scores between the rTMS-CT and AChEI-only groups. The rTMS-CT participants showed a slower decline of the MMSE (β = -0.93, p = 0.01) and CDR-SB (β = 0.53, p = 0.03) scores compared to the AChEI-only group. AChEI, acetylcholinesterase inhibitor; CDR-SB, Clinical Dementia Rating-Sum of Boxes; MMSE, Mini-mental State Examination; rTMS-CT, repetitive transcranial magnetic stimulation with cognitive training.

tivity of the posterior default mode network in amnestic mild cognitive impairment and AD.[32] Moreover, CT has been suggested to modulate the neuronal excitability and promote synaptic plasticity, thereby enhancing the learning capacity.[33] The cognitive effect of rTMS-CT is assumed to be mediated by an increase in the cortical excitability and changes in synaptic plasticity via long-term potentiation,[34] which is an essential mechanism for improving memory and learning at the neuronal level.[35] Therefore, the simultaneous use of high-frequency rTMS and CT could facilitate an improvement in the cognitive learning performance.

Our study had several limitations. First, there was a potential selection bias in the AChEI-only group because it was recruited retrospectively. Second, this study investigated the long-term effect of rTMS-CT by comparing with the AChEI-only group, but not the sham group. Nevertheless, this study demonstrated beneficial short- and long-term cognitive effects of rTMS-CT in mild AD. Therefore, the application of rTMS-CT might be a useful supplementary intervention for the long-term mitigation of neurodegeneration such as cognitive decline in mild AD patients.

Acknowledgements

Conflict of interest

None.

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