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Repetitive Transcranial Magnetic Stimulation as a Treatment for Veterans with Cognitive Impairment and Multiple Comorbidities

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Abstract.
Background: Despite decades of research efforts, current treatments for Alzheimer's disease (AD) are of limited effectiveness and do not halt the progression of the disease and associated cognitive decline. Studies have shown that repetitive transcranial magnetic stimulation (rTMS) may improve cognition.
Objective: We conducted a pilot study to investigate the effect of rTMS on cognitive function in Veterans with numerous medical comorbidities.
Methods: Participants underwent 20 sessions, over the course of approximately 4 weeks, of 10 Hz rTMS at the left dorsolateral prefrontal cortex with intensity of 120% resting motor threshold. Outcome measures including memory, language, verbal fluency, and executive functions were acquired at baseline, end of treatment, and 4 months after the last rTMS session. Twenty-six Veterans completed the study (13 in the active rTMS group, 13 in the sham rTMS group).
Results: The study protocol was well-tolerated. Active, compared to sham, rTMS showed improved auditory-verbal memory at the end of treatment and at 4-month follow-up. However, the active rTMS group demonstrated a trend in decreased semantic verbal fluency at the end of treatment and at 4-month follow up.
Conclusion: These preliminary results show rTMS is safe in general in this elderly Veteran population with multiple comorbidities. Patients in the sham group showed an expected, slight decline in the California Verbal Learning Test scores over the course of the study, whereas the active treatment group showed a slight improvement at the 4-month post-treatment follow up. These effects need to be confirmed by studies of larger sample sizes.

Keywords: Brain stimulation, california verbal learning test, repetitive transcranial magnetic stimulation, veterans

INTRODUCTION

Despite decades of research efforts, current treatments for Alzheimer's disease (AD) are of limited effectiveness and do not halt the progression of

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Table 1
Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Veterans aged 55 or older	Prior exposure to repetitive transcranial magnetic stimulation or electroconvulsive therapy
Diagnosis of mild or major neurocognitive disorder, and exclusion of other causes of dementia	Unable to safely withdraw from medications that increase seizure risk
Ability to obtain Motor Threshold	Cardiac pacemaker or cochlear implant
Stable condition and living environment	Implanted device or metal in the brain
If on cognitive medication (donepezil, galantamine, rivastigmine, or memantine), stable dose for at least 4 weeks prior to randomization	Current substance abuse, suicidal intent or plan, psychosis
	Current or prior history of seizure disorder
Able to provide informed consent	Traumatic brain injury within past two months
	Participation in concurrent clinical trial
	Current or prior history of mass lesion, cerebral infarct, or other non-cogitative active CNS disease that would increase risk for seizures
	Unable to complete neuropsychological assessments

the disease and associated cognitive decline. FDA-approved medications for AD management (e.g., donepezil, galantamine, rivastigmine, and memantine) are problematic, as they are only effective in decreasing cognitive decline in a subset of patients, for a relatively brief period of time, with significant side effects and substantial financial costs [1].

Recently, a non-pharmacological form of non-invasive brain stimulation, repetitive transcranial magnetic stimulation (rTMS), has emerged as a possible treatment to improve cognition in patients with AD. rTMS uses a strong, pulsating magnetic field to stimulate relatively localized brain regions. rTMS was initially approved by the FDA for treating treatment-resistant depression in 2008 and has been investigated for its potential benefits on several neurological conditions, such as seizures, traumatic brain injury, pain, Parkinson's disease, AD, and mild cognitive impairment (MCI). At least eight studies have been conducted to explore the possibility of using rTMS as a treatment for AD [2–9]. A meta-analysis of results pooled from several randomized controlled trials suggests that high frequency rTMS (10–20 Hz) may be associated with improved global cognitive function in patients with AD [10]. The mean difference in Alzheimer's Disease Cognitive Assessment Scale, Cognitive subscale (ADAS-cog) [11] scores between active and sham: (–3.65; 95% CI: –5.82 to –1.48; $p = 0.001$), with no between-study heterogeneity. Despite these encouraging results, these studies were not conducted in typical elderly populations with multiple medical co-morbidities, such as those seen in Veterans. Given that the treatment efficacy of rTMS for AD patients with comorbidities, especially depression, is largely unclear [12], it is imperative to further investigate this in a representative population. Hence, we conducted a pilot study in Veterans to explore the effect of rTMS on cognitive function in this challenging population.

METHODS

Participants and procedures

Study participants were Veterans, recruited from outpatient and specialty care clinics within the VA Palo Alto Health Care System. All participants met DSM-V criteria for having mild neurocognitive disorder or major neurocognitive disorder [13] likely due to AD. Chart review, neurological examination, and, if necessary, laboratory studies and brain MRI were performed prior to enrollment to exclude other causes of cognitive impairment. Inclusion and exclusion criteria are in Table 1. Psychoactive medications (including medications approved by FDA for treating cognitive impairment) were allowed, and we requested the participant to stay on the same dose of medication during the study and follow up period. Participants were recruited from outpatient and specialty care clinics in a VA hospital setting. All study procedures were approved by institutional review boards.

Participants were randomized to active or sham rTMS treatment. 10 Hz rTMS powered at 120% of motor threshold was delivered to the left dorsolateral prefrontal cortex, following a 4 s on, 10 s off pattern. The pattern was repeated for about 30–45 min (allowing pauses for cooling of the coil) to deliver a total of

4000 stimuli per treatment session. Sham (Control) treatment was accomplished by using the Cool-B65-A/P coil that functions both as an active (A) and placebo (P) coil. It has a symmetrical mechanical design and no labeling on the coil indicates the active or placebo side. Consequently, it is not possible for the rTMS administrator to see or hear which side is used. Additionally, for each treatment session, whether sham or active, each participant wore scalp electrodes on the forehead through which, in the case of sham treatments, a low-voltage, low electric current (2–20 mA at no more than 100V) was passed in order to provide cutaneous stimulation that mimics the sensation of actual rTMS. Participants in both groups attended daily rTMS treatments for four weeks for a total of 20 rTMS sessions. To blind the rTMS operator and maintain balance between treatment and sham cases, participant assignment was performed by randomizing the rTMS machine subject codes by pairs, where one of each pair is treatment and the other is sham. Study staff and participants were blinded to group assignment. In the prior work [14], the blinding procedure has been evaluated and was shown to be highly successful.

Outcome measures

The primary outcome for this study was change in episodic memory function from study entry to the end of treatment. Auditory-verbal episodic memory was assessed with the Long Delay portion of the California Verbal Learning Test (CVLT-II) [15, 16]. To reduce learning effects from repeated administration of the same measure, alternate forms of CVLT were applied at end of treatment (ET) and 4-month follow up (4M). Secondary outcome measures included assessment of visuospatial memory (Brief Visuospatial Memory Test-Revised (BVMT-R) [17], language (Boston Naming Test) [18], semantic verbal fluency (Animal Fluency) [19], and executive function (Trail Making Test) [20]. Similar to what was done with the primary outcome measure, alternate forms of testing materials were used when available to reduce learning effects.

Depression was assessed with the Geriatric Depression Scale (GDS) [21]. Cognitive outcome measures were assessed at baseline (BL), ET, and 4M. Biological assessments included examination of brain-derived neurotrophic factor (BDNF) plasma levels as well as *APOE* genotype. Demographic variables included age, education, gender, ethnicity, race, and medical and mental health comorbidities. Demographics and *APOE* were assessed at BL, while plasma level BDNF was assessed at BL and ET.

Statistical analyses

All analyses were performed using SAS v9.4 (SAS Inc., Cary, NC). Differences in baseline characteristics for active and sham subjects were evaluated using two sample *t*-tests and chi-square tests. Cohen's d and two sample *t*-tests were computed to measure effect sizes and differences between BL and ET, as well as BL and 4M. The bootstrap percentile-based confidence intervals are each based on 10,000 randomly resampled data sets. Change scores at ET minus BL, and 4M minus BL were computed for the CVLT-II measures, GDS, and Pearson correlations (r).

To further enable the interpretation of these results, we conducted a confirmatory analysis fitting a comprehensive mixed effects model that encompassed all three timepoints in the same model, with a random effect for subject. We used a piecewise regression model over time, with changepoint at end of treatment, to avoid assumptions about the relationship between treatment effects prior to and following the end of the treatment protocol. This model uses the variability across all three timepoints to estimate standard errors and infer statistical significance and includes a time by group interaction to examine effects of treatment. Please see Supplementary Table 1.

RESULTS

Thirty-two Veterans with mild neurocognitive disorder or major neurocognitive disorder likely due to AD were enrolled; 29 completed the treatment phase of the study, and 26 completed all phases of the study and were assessed for the primary outcome measures. Subjects with missing secondary outcome measures were excluded from all time points. The information on demographics, Montreal Cognitive Assessment (to contrast the severity of cognitive impairment between the two groups), GDS, and comorbidities are presented in Table 2. As shown in Table 2, AD risk factors common for the general population, such as diabetes, hypertension, hyperlipidemia, obstructive sleep apnea, depression, and risk factors more specific for Veterans (traumatic brain injury, post-traumatic stress disorder) are prevalent [22, 23]. We note that there were higher percentages of Veterans with hyperlipidemia and diabetes in the active group.

Table 2
Demographics, GDS, MoCA scores, and medical comorbidities of the study participants

	Sham ($n = 13$)	Active ($n = 13$)	Statistic
Diagnosis and Duration:			
MCI duration, y (n, mean sd)	12, 1.6 (1.9)	12, 2.0 (3.1)	
Major Neurocognitive Disorder Duration, y (n, mean, sd)	1, 2.6 (N/A)	1, 3.0 (N/A)	
Age, y (mean, sd)	70.2 (7.6)	71.3 (7.6)	$t(24) = –0.39$, $p = 0.70$
Education, y (mean, sd)	15.9 (2.6)	16.2 (3.2)	$t(24) = –0.27$, $p = 0.79$
GDS, total score (mean, sd)	5.0 (4.7)	3.8 (3.7)	$t(24) = 0.70$, $p = 0.49$
MoCA, total score (mean, sd)	24.3 (3.0)	22.4 (6.1)	$t(24) = 1.02$, $p = 0.32$
Gender Male (n, %)	12 (92.3%)	13 (100.0%)	$\chi^2(1) = 1.04$, $p = 0.31$
Ethnicity: Hispanic (n, %)	2 (15.4%)	2 (15.4%)	$\chi^2(1) = 0.00$, $p = 1.00$
Race:			$\chi^2(5) = 4.95$, $p = 0.42$
White (n, %)	6 (46.2%)	8 (61.5%)	
Black (n, %)	3 (23.1%)	0 (0.0%)	
Asian (n, %)	1 (7.7%)	2 (15.4%)	
Native Hawaiian (n, %)	0 (0.0%)	1 (7.7%)	
More than One Race (n, %)	2 (15.4%)	1 (7.7%)	
Unknown (n, %)	1 (7.7%)	1 (7.7%)	
Medical and Mental Health Comorbidities			
Hyperlipidemia (n, %)	2 (15.4%)	7 (53.9%)	$\chi^2(1) = 4.95$, $p = 0.04$
Hypertension (n, %)	7 (53.9%)	8 (61.5%)	$\chi^2(1) = 0.16$, $p = 0.69$
Type 2 Diabetes (n, %)	7 (53.9%)	12 (92.3%)	$\chi^2(1) = 4.89$, $p = 0.03$
Obstructive sleep apnea (n, %)	3 (23.1%)	5 (38.5%)	$\chi^2(1) = 0.77$, $p = 0.40$
Anxiety (n, %)	1 (7.7%)	3 (23.1%)	$\chi^2(1) = 1.18$, $p = 0.28$
Depression (n, %)	5 (38.5%)	3 (23.1%)	$\chi^2(1) = 0.72$, $p = 0.40$
PTSD (n, %)	5 (38.5%)	4 (30.8%)	$\chi^2(1) = 0.17$, $p = 0.68$
TBI (n, %)	4 (30.8%)	1 (7.7%)	$\chi^2(1) = 2.23$, $p = 0.14$
APOE4 Carrier	2 (15.4%)	1 (7.7%)	$\chi^2(1) = 0.38$, $p = 0.54$

MCI, mild cognitive impairment; GDS, Geriatric Depression Scale; MoCA, Montreal Cognitive Assessment; PTSD, Post-traumatic stress disorder; TBI, traumatic brain injury.

All medications were stable throughout the protocol. Regarding medications with potential anti-dementia effects: Two subjects were diagnosed with dementia before enrollment. One subject (received active rTMS) had a three-year history of dementia, was on stable combination of memantine and donepezil. One subject (received sham rTMS) had a 2.6-year history of dementia, was on stable dose of donepezil. There was only one MCI subject (who received sham rTMS) who was on medication for cognitive impairment (donepezil) during the study. Thus, the number of subjects on cognitive medication were too small for subgroup analysis.

Cognitive testing results

In Table 3 below, we present the results of commonly calculated CVLT parameters, Long Delay Cued Recall and Long Delay Free Recall, as well as results of all secondary outcome measures. The Long Delay Cued Recall and Free Recall are the most relevant parameters in assessing the effect of the intervention on auditory-verbal learning and memory. We note that there may be baseline differences in outcome measures between the active and sham groups. Change scores were used to account for baseline differences.

Statistical analysis of the primary outcome suggests a moderate effect size of rTMS on the Long Delay Cued Recall and Free Recall as measured by Cohen's d at the end of the treatment. Further analysis of the primary and secondary outcome measures suggests that: 1) the positive effect of rTMS on auditory-verbal Cued Recall and Free Recall appears to be even more pronounced at 4M, and 2) rTMS might have a negative effect on animal (verbal) fluency at ET and 4M. We note that due to small sample size and large number of outcome measures, results of statistical analysis are less reliable and need to be confirmed by studies of larger size.

Confirmatory analyses

We also fit a piecewise, mixed effects regression model to further enable interpretation of the results, including a time by group interaction to examine treatment effects. This model uses variability across all three timepoints to estimate standard errors. Thus, point estimates for the treatment effect interactions for ET-BL, 4M-BL, and 4M-ET are identical to point

Table 3
Cognitive Outcomes and BDNF Mean Scores

	Treat	*n*	BL	ET	4M	Cohen's d 95% CI (lower, upper)		2 Sample *T*-Test [t(df); p]	
			mean, (std. dev.)			ET-BL	4M-BL	ET-BL	4M-BL
Primary									
CVLT Long Del. Cued Recall (Total)	Sham	11	11.5 (2.4)	10.1 (2.5)	10.5 (3.2)	0.66 (–0.13, 1.35)	1.51 (0.97, 2.70)	$t(21) = -1.56$ $p = 0.13$	$t(21) = -3.60$ $p = 0.002$
	Active	12	9.6 (3.6)	9.6 (4.4)	11.2 (4.4)				
CVLT Long Del. Free Recall (Total)	Sham	12	9.4 (3.8)	8.3 (3.7)	9.2 (4.2)	0.52 (–0.45, 1.44)	0.77 (0.00, 1.72)	$t(22) = -1.26$ $p = 0.22$	$t(22) = -1.89$ $p = 0.07$
	Active	12	8.2 (4.6)	8.6 (4.3)	10.1 (4.1)				
Secondary									
Brief Visual Memory (Total)	Sham	12	16.3 (5.2)	16.3 (6.6)	16.6 (7.0)	0.10 (–0.88, 1.02)	–0.25 (–1.14, 0.57)	$t(22) = -0.24$ $p = 0.81$	$t(22) = 0.62$ $p = 0.54$
	Active	12	19.8 (8.7)	20.3 (8.4)	18.8 (7.5)				
Boston Naming (Total)	Sham	12	53.3 (8.6)	56.3 (3.6)	55.0 (5.3)	–0.56 (–1.27, –0.19)	–0.22 (–0.68, 0.47)	$t(22) = 1.37$ $p = 0.20$	$t(22) = 0.54$ $p = 0.60$
	Active	12	53.4 (12.6)	53.9 (13.0)	54.4 (13.1)				
Animal Fluency Test (Total)	Sham	12	15.6 (3.5)	16.5 (2.8)	16.9 (5.1)	–0.66 (–1.27, –0.01)	–1.13 (–2.48, –0.43)	$t(21) = 1.54$ $p = 0.15$	$t(21) = 2.69$ $p = 0.01$
	Active	11	17.5 (6.6)	15.9 (5.0)	15.4 (5.4)				
Trail Making A (s)	Sham	12	36.8 (13.5)	44.1 (23.3)	47.5 (32.1)	0.52 (–0.32, 1.06)	0.51 (–0.37, 1.06)	$t(22) = -1.27$ $p = 0.22$	$t(22) = -1.24$ $p = 0.23$
	Active	12	57.7 (85.5)	49.2 (56.1)	50.7 (54.7)				
Trail Making B (s)	Sham	12	174.5 (98.8)	150.8 (67.8)	197.6 (204.9)	–0.23 (–1.01, 0.66)	0.22 (–0.82, 1.05)	$t(22) = 0.57$ $p = 0.58$	$t(22) = -0.55$ $p = 0.59$
	Active	12	190.0 (231.9)	178.1 (216.8)	185.8 (237.8)				
BDNF (ng/ml)	Sham	11	4.4 (3.3)	5.3 (5.0)	N/A	–0.28 (–1.21, 0.95)	N/A	$t(21) = 0.68$ $p = 0.51$	N/A
	Active	12	5.1 (3.5)	5.2 (3.7)					

estimates for mean differences calculated using the *t*-test, but the confidence intervals and *p*-values differ somewhat. Specifically, the 4M-BL difference for CVLT Long Delay Free Recall is significant ($p = 0.04$) under the mixed effects model, but not ($p = 0.07$) using the *t*-test. In contrast, the 4M-ET difference for the Boston Naming Test was borderline significant ($p = 0.05$) using the *t*-test, but not under the mixed effects model ($p = 0.20$). It is notable that the point estimates for the Boston Naming Test for the first and second time intervals reverse direction, which may suggest a spurious result. Results for the CVLT Long Delay Cued Recall and for Animal Fluency for the total study period, 4M-BL, retained significance under both statistical models.

Biochemical testing results

To explore the mechanism of action of rTMS, we examined plasma BDNF via ELISA (R&D Systems) at BL and ET. Table 3 also details the mean BDNF levels on the two groups at BL and ET.

Adverse events

The rTMS procedure was well-tolerated as most of the participants were able to complete all treatment sessions. There were eight reported adverse events. Three of these events were seizures. These events occurred 6 to 12 months after the end of treatment. Two seizures occurred in subjects receiving sham treatment, and one seizure occurred in a participant six months after completing the active treatment. Investigation of the possible causes of the seizures was conducted under the supervision of the IRB and Data Safety Monitoring Board. It was concluded that the increased seizure rate was not due to rTMS treatment. Other adverse events were: Two had self-limiting headache at the site of stimulation; one had vertigo which was found to be related to sinusitis; one had rectal bleeding unrelated to rTMS; and one had subacute onset of left arm weakness which was later determined to be caused by idiopathic brachial neuritis, an inflammatory condition unrelated to rTMS.

DISCUSSION

As shown in Table 3, participants in the active group tended to perform better on memory performance at ET than those in the sham group, which has been reported previously. What is novel in this study

is that the result was seen in a population with a high level of medical co-morbidities and that the trend of improvement appears more pronounced at 4M. These results imply that the effect of rTMS may not become fully manifest until months after the treatment is completed. This trend is consistent with the recent observation that certain effects of rTMS only manifest several weeks after active treatment [24–27]. Delayed effects of rTMS have also been observed in studies on major depression [26] and negative symptoms or cognitive function of patients with psychosis [24, 25, 27]. The exact mechanism for such a delayed effect in humans is unknown. However, animal studies have found that over time rTMS may increase the number of N-methyl-d-aspartate (NMDA) receptors, activate BDNF signaling pathways, or alter receptors binding [28, 29].

Although animal work based on brain samples shows that rTMS increased expression of BDNF [30], variance in human plasma levels may be too large to detect a change in plasma levels that are far removed from the brain, especially in small samples. We recognize that multiple factors may affect plasma BDNF levels and also contribute to the large variability of our pilot data [31]. Furthermore, the response to rTMS may be affected by a BDNF polymorphism [32] and that *APOE4* carrier status may modulate the changes in network connectivity induced by brain stimulation in non-demented elders [33]. To quantify the potential impact of these genetic factors, study subjects might need to be tested for and stratified by these factors accordingly.

Many other mechanisms have been proposed to explain how rTMS applied to the left dorsolateral prefrontal cortex may improve verbal memory. Previously, studies have shown that the effects of rTMS on cognitive performance are dependent on cognitive domain, experimental design, cortical target, stimulation frequency, timing, and duration of rTMS application (see review by Preston et al. [34]). More recently, Rosenblum et al. [35] proposed that prefrontal stimulation leads to enhanced functional connectivity between frontal and posterior regions and, as a consequence, enhanced stimulus processing and improved memory performance. Locally, repetitive activation of neurons in the prefrontal cortex may stimulate local connections and projections, strengthen existing synapses or produce new synapses. At the neuronal network level, functional MRI and PET scan studies have shown that rTMS may alter metabolic activities in deep brain structures functionally connected to the areas directly stimulated by rTMS, suggesting that in addition to local activation, rTMS modifies neuronal network activities distant from the site of stimulation [36, 37], thus effecting neuroplasticity. At the molecular level, it is known that repetitive activation of the BDNF-TrkB signal pathway can cause modification of synaptic connections [38–40]. Additionally, repetitive activation of the Ca-Calmodulin-dependent protein kinase II (CaMKII) signaling pathway can cause phosphorylation of CaMKII and promote a sustained remodeling of the synaptic structure at the dendritic spine [41]. Another well-studied system involves glutamate, NMDA receptors, and cAMP-activated Protein Kinase A (PKA). When repeatedly activated, a cascade of action may modify the synaptic structure thereby mediating neuroplasticity [42, 43]. Thus, there are many mechanisms of action proposed for the effects of rTMS.

One limitation of this small pilot study is that it did not repeat a formal evaluation of the successfulness of the sham. This was performed using the same equipment that used in a formal extensive evaluation of the sham in preparation for a large multi-centered trial [44]. Future large-scale work attempting to replicate this small pilot study should perform another formal double-blind evaluation of the sham. Thus, the sham used in this study might not have been the equivalent of the sham used in the multi-centered trial.

Finally, an unexpected observation is that participants receiving active treatment tended to perform worse on one of the secondary outcome measures, namely, the animal fluency test. Previously, it has been reported that high frequency rTMS may improve verbal fluency, although the areas of stimulation were often different from the left dorsolateral prefrontal cortex (see review by Guse [45]). rTMS has also been extensively studied in aphasic stroke patients where a meta-analysis of 7 studies shows a positive effect on improvement of language impairment without significant side effects [46]. Thus, the subject of rTMS effects on aphasia is a major area of study unto itself and additional data are needed to confirm the current study's findings and better place them in the context of this extensive aphasia work.

Conclusion

These preliminary results show rTMS is safe in general in this elderly Veteran population with multiple co-morbidities. Although analysis of the primary cognitive outcome data suggests that prior findings

of a cognitive effect of rTMS can also be seen in older adults with multiple medical comorbidities, the potential decline of active rTMS on semantic verbal fluency needs to be further investigated; incorporating measures of phonemic fluency is necessary to better understand the potential effects of rTMS on verbal fluency in this population. rTMS was well-tolerated in this frail population and most of the participants were able to complete all treatment sessions. Although the anticipated biochemical effect on BDNF was not seen in this small sample, these subtle effects may need larger study populations to discern. We also noted that patients in the sham group showed an expected, slight decline in the CVLT scores over the course of the study, whereas the active treatment group showed a slight improvement at the 4-months post-treatment follow up. These results suggest the need for larger long-duration clinical trials of rTMS in such patients.

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The study is registered with clinicaltrials.gov, identified as NCT02621424.

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SUPPLEMENTARY MATERIAL

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