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Effects of repetitive paired associative stimulation on brain plasticity and working memory in Alzheimer's disease: a pilot randomized double-blind-controlled trial

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ABSTRACT

Design: Pilot randomized double-blind-controlled trial of repetitive paired associative stimulation (rPAS), a paradigm that combines transcranial magnetic stimulation (TMS) of the dorsolateral prefrontal cortex (DLPFC) with peripheral median nerve stimulation.

Objectives: To study the impact of rPAS on DLPFC plasticity and working memory performance in Alzheimer's disease (AD).

Methods: Thirty-two patients with AD (females = 16), mean (SD) age = 76.4 (6.3) years were randomized 1:1 to receive a 2-week (5 days/week) course of active or control rPAS. DLPFC plasticity was assessed using single session PAS combined with electroencephalography (EEG) at baseline and on days 1, 7, and 14 post-rPAS. Working memory and theta–gamma coupling were assessed at the same time points using the N-back task and EEG.

Results: There were no significant differences between the active and control rPAS groups on DLPFC plasticity or working memory performance after the rPAS intervention. There were significant main effects of time on DLPFC plasticity, working memory, and theta–gamma coupling, only for the active rPAS group. Further, on *post hoc* within-group analyses done to generate hypotheses for future research, as compared to baseline, only the rPAS group improved on post-rPAS day 1 on all three indices. Finally, there was a positive correlation between working memory performance and theta–gamma coupling.

Conclusions: This study did not show a beneficial effect of rPAS for DLPFC plasticity or working memory in AD. However, *post hoc* analyses showed promising results favoring rPAS and supporting further research on this topic. (Clinicaltrials.gov-NCT01847586)

Key words: dementia, neuroplasticity, geriatrics, transcranial magnetic stimulation, theta–gamma coupling, TMS-EEG

Introduction

Worldwide close to 50 million people are living with dementia with the numbers projected to double almost every 20 years (Prince *et al.*, 2015). Alzheimer's disease (AD) is the predominant cause of dementia and cognitive deficits including deficits in working memory are core features of the illness (Baddeley *et al.*, 1991). Current treatment of cognitive deficits in mild-to-moderate AD relies primarily on acetylcholinesterase inhibitors (AChEIs) which provide modest symptomatic benefits while causing several adverse effects (Birks, 2006). Search for novel treatments has not been successful to date with a failure rate of 99.6% for pharmacological trials (Cummings *et al.*, 2014). Studies have explored the effects of noninvasive brain stimulation on cognition in AD using transcranial magnetic stimulation (TMS) (Lee *et al.*, 2016; Sabbagh *et al.*, 2019). Still, these studies did not assess mechanisms underlying the improvement in

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cognition. Thus, there is an urgent need to advance our understanding of the physiological mechanisms underlying cognitive deficits in AD and explore novel interventions for cognitive enhancement.

Synaptic plasticity refers to the use and time-dependent alteration of synapses and is a key mechanism underlying learning and memory (Draganski *et al.*, 2004; Kim and Linden, 2007). Cortical plasticity is critically important for sustaining complex cognitive functions of higher cortical regions such as the dorsolateral prefrontal cortex (DLPFC) (Fuster *et al.*, 2000). DLPFC is important for the maintenance of executive function that includes the abilities to select, maintain, and manipulate information online, collectively referred to as working memory (Fuster *et al.*, 2000; Pasupathy and Miller, 2005; Baddeley, 1996). AD pathology involves the DLPFC early on in the course of illness, and is associated with several neurophysiological changes that cause neurodegeneration and impairment in plasticity (Kaufman *et al.*, 2012; Rowan *et al.*, 2003; Crary *et al.*, 2006). DLPFC plasticity is not only important for sustaining executive tasks, but also compensates for neuropathology and dysfunction in other regions secondary to AD pathology (Kaufman *et al.*, 2012; Voytek *et al.*, 2010; Grady *et al.*, 2003). Thus, DLPFC plasticity could be an appropriate potential target and an intermediate marker for interventions aimed at enhancing working memory in AD.

Long-term potentiation (LTP) is considered a prototype of synaptic plasticity and it can be used to assess neuroplasticity *in vitro* (Malenka and Bear, 2004; Malenka and Nicoll, 1999). Paired associative stimulation (PAS) is a TMS paradigm that can induce LTP-like activity in the human brain by simulating spike-timing-dependent plasticity protocols (Ziemann *et al.*, 2008; Vallence and Ridding, 2014). PAS-induced LTP-like activity is accomplished by combining electrical stimulation of a peripheral nerve with magnetic stimulation of the contralateral cortex (Ziemann *et al.*, 2008; Vallence and Ridding, 2014). PAS-induced LTP-like activity meets key criteria that define LTP, i.e. input specificity, associativity, cooperativity, and persistence (Stefan *et al.*, 2000). While several molecular markers of plasticity are proposed, to our knowledge, there is no evidence of change in synaptic or other molecular markers of plasticity in response to PAS in humans (Geddes *et al.*, 1990). However, there may be differential effects of brain-derived neurotrophic factor (BDNF) single-nucleotide polymorphisms on PAS-induced plasticity, with BDNF "Met" allele associated with reduced response to PAS (Cheeran *et al.*, 2008). Plasticity impairments have been shown in the motor cortex of patients with AD using single session PAS (Battaglia *et al.*, 2007; Terranova *et al.*, 2013). Further, PAS combined with electroencephalography (EEG) can be used to detect plasticity in the DLPFC (Rajji *et al.*, 2013).

We designed and conducted a randomized controlled trial (RCT) in which a 2-week course of daily repetitive PAS (rPAS) was delivered to patients with early AD and compared to control rPAS for its effect on DLPFC plasticity and working memory performance at post-intervention days 1, 7, and 14 (https://clinicaltrials.gov/ct2/show/NCT01847586). The first aim of this trial was to compare DLPFC plasticity in AD and healthy individuals at baseline and we reported the results of this comparison elsewhere (Kumar *et al.*, 2017). Here, we report the results of the RCT phase of this study. Our primary hypothesis was that active rPAS will result in better DLPFC plasticity post-intervention compared to control rPAS. Our secondary hypothesis was that active rPAS will result in better working memory performance post-intervention compared to control rPAS.

In addition, we used this RCT as a platform to study other neurophysiological mechanisms relevant to plasticity and working memory. Working memory in the DLPFC is supported by local re-entrant neuronal circuits within the DLPFC and re-entrant circuits connecting it to more posterior regions (Buzsaki, 2002; Pignatelli *et al.*, 2012). Function of these circuits has been associated with theta and gamma oscillations as measured using EEG (Gevins *et al.*, 1997; Howard *et al.*, 2003). More specifically, modulation of gamma amplitude by theta phase ("theta–gamma coupling") has been associated with working memory performance in animal and human studies (Lisman and Idiart, 1995; Rajji *et al.*, 2017). Impaired theta–gamma coupling was associated with impaired cognition in a mouse model of AD (Stoiljkovic *et al.*, 2018). In humans, theta–gamma coupling predicted impairments in working memory in patients with mild cognitive impairment (Goodman *et al.*, 2018). Thus, we also report on the impact of rPAS on theta–gamma coupling during working memory performance.

Materials and methods

This study was conducted at the Centre for Addiction and Mental Health (CAMH), a teaching hospital at the University of Toronto. CAMH Research Ethics Board approved the study in accordance with the declaration of Helsinki. All participants provided their informed written consent. The trial was registered at Clinicaltrials.gov # NCT01847586.

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Participants and clinical and cognitive assessments

Participants were recruited from CAMH and other collaborating hospitals in Toronto from May 2013 to October 2016. To be eligible, they had to meet the criteria for probable AD following the National Institute of Neurological and Communicative Disorders and Stroke, and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (Dubois *et al.*, 2007); score 17 or above on the Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975); either not be taking an AChEI or be on a stable dose for at least 3 months; and not have any contraindication for TMS. Participants were assessed using the NINCDS-ADRDA criteria and the Structured Clinical Interview for DSM-IV (First, 2002) to verify the diagnosis and rule out exclusionary psychiatric illnesses. They also underwent a thorough clinical assessment by a study psychiatrist. All participants underwent assessment of cognition using MMSE, Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph *et al.*, 1998), and Executive Interview (EXIT) (Royall *et al.*, 1992) at baseline. Mood was assessed at baseline using the Cornell Scale for Depression in Dementia (CSDD) (Alexopoulos *et al.*, 1988).

Sample size calculation

In a previous study, we observed an effect size, Cohen's $d = 1.4$, between active and sham PAS conditions (Rajji *et al.*, 2013). We estimated that a sample of 32 (16 in each arm) will provide us with 80% power to detect a time × condition interaction for acute PAS effects at post-rPAS day 1 for an effect size of Cohen' $d = 1.02$ at alpha = 0.05.

Plasticity, working memory, and theta–gamma coupling assessments

Baseline DLPFC plasticity was assessed using PAS-EEG as previously described (Kumar *et al.*, 2017). EEG recordings were done using the TMS-EEG protocol through a 64-channel Synamps 2 Neuroscan EEG system. Electrodes were placed as per 10–20 International System using an EEG cap, and the impedance at each electrode was set at $\leq 5\,k\Omega$. EEG signals were recorded using DC and a low-pass filter of 100 Hz at a 20 kHz sampling rate as per protocol in our published TMS-EEG experiments (Rajji *et al.*, 2013; Daskalakis *et al.*, 2008). Working memory was assessed using N-back task (Kumar *et al.*, 2017). Only 1- and 2-back tasks were used because AD participants were not able to perform the 3-back or more difficult conditions. All participants were offered both tasks. A prime (A') was used as the outcome measure for N-back task as it takes into account both the hit rate and false alarm rate (Kumar *et al.*, 2017). To assess baseline, theta–gamma coupling EEG was also recorded while participants were performing the N-back task (Goodman *et al.*, 2018). Assessments of DLPFC plasticity using PAS-EEG, of working memory using N-back task, and of theta–gamma coupling using EEG during the N-back task were repeated at days 1, 7, and 14 after the rPAS intervention.

Randomization

Participants were randomized 1:1 in a double-blinded manner using a balanced random assignment to 10 sessions (daily, 5 days per week) of active or control rPAS (further details below). Randomization sequence was generated on the computer by assigned staff who was not involved in any other study procedures. Intervention setup was done by a staff person not involved in the study to keep the interventionists blinded. Participants, interventionists, assessors, and investigators remained blinded to the treatment allocation.

Intervention

Active rPAS consisted of a repetitive pairing of electrical stimulation of the median nerve at the right wrist (180 pulses at 0.1 Hz) with TMS of the contralateral left DLPFC with an interstimulus interval of 25 ms. An identical procedure was followed for control rPAS except that the interstimulus interval was 100 ms, which has been shown not to induce LTP-like activity (Rajji *et al.*, 2013). Site of stimulation at the DLPFC was localized using the MRIcro/reg software and the MINIBIRD system (Ascension Technologies, USA) as previously described (Daskalakis *et al.*, 2008). TMS pulses were delivered at stimulus strength sufficient to induce a peak-to-peak 1 millivolt motor-evoked potential using a 7 cm figure-of-eight coil and a Bistim module (Magstim Company Ltd., UK). Median nerve stimulation was delivered at electrical stimulus strength equivalent to 300% of the participants' sensory threshold. Participants were asked to keep a count of the sensory stimuli and were randomly asked about the count to focus their attention on the stimulus which has been shown to be important for LTP induction using PAS (Rajji *et al.*, 2013).

Data processing

EEG data was processed offline using MATLAB (The MathWorks Inc., USA) and the EEGLAB toolbox using published methods (Kumar *et al.*, 2017; Rajji *et al.*, 2017). For TMS-EEG analyses,

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the data were downsampled to 1000 Hz and segmented from −1000 to 2000 ms relative to the onset of TMS pulse, baseline corrected, re-segmented, and then digitally filtered using the second order, Butterworth, zero-phase shift 1–55 Hz band-pass filter. EEG signals from pre-PAS, and 0, 17, and 34 min post-PAS were concatenated, and then cleaned using a combination of manual and automated techniques (Kumar *et al.*, 2017). EEG data was then re-referenced to the average electrode for further analysis. DLPFC plasticity was calculated as potentiation of cortical-evoked activity (hereafter referred to as PAS-LTP), defined as the maximum ratio of post/pre-PAS cortical-evoked activity between 50 and 275 ms post-TMS pulse (Kumar *et al.*, 2017).

For N-back EEG analyses, data were filtered and segmented from −1400 to +3100 ms relative to the stimulus onset, and then cleaned using a combination of automated and manual methods as described above (Rajji *et al.*, 2017; Goodman *et al.*, 2018). Then, we filtered the raw EEG data for theta (4–7 Hz) and gamma (30–50 Hz) frequencies with second-order zero-phase shift filter and created the time series for gamma amplitude and theta phase using the Hilbert transform. Subsequently, we created a concatenated signal of 5000 ± 150 ms separately for different N-back trial types (target correct, target not correct, nontarget correct, and nontarget not correct) and conditions (1- and 2-back) at each electrode. All included epochs had to include the time interval from the stimulus onset to the time of response. We used modulation index (MI) as the measure of theta–gamma coupling (Rajji *et al.*, 2017; Goodman *et al.*, 2018; Tort *et al.*, 2010). To calculate MI, each phase of theta was binned into 18 intervals of 20 ° each. The average amplitude of gamma at each theta bin was calculated and normalized, resulting in phase–amplitude distribution function. We then calculated the MI for each electrode by measuring the divergence of the observed amplitude distribution from a uniform distribution (Rajji *et al.*, 2017; Goodman *et al.*, 2018; Tort *et al.*, 2010). Finally, MI during target trials was calculated as a weighted average based on the number of correct and incorrect responses for all target trials.

Statistical analyses

All data were analyzed using the Statistical Program for Social Sciences (SPSS) version 24.0 (SPSS Inc., Chicago, IL, USA). Data distribution was examined using box plots. Data were transformed to Ln distribution to achieve normality as needed. χ^2 and independent samples *t*-tests were employed to evaluate differences between the active and control rPAS groups on demographic variables. Further analyses were conducted using repeated-measures analysis of variance (ANOVA) to compare DLPFC plasticity, working memory, and theta–gamma coupling across post-days 1, 7, and 14 after the intervention. For DLPFC plasticity, repeated-measure ANOVA was conducted with PAS-LTP as dependent variable, intervention group (active and control rPAS) as between-subject variable and time points (baseline, post-intervention days 1, 7, and 14) as within-subject independent variables. For working memory, separate repeated-measures ANOVAs were conducted for 1- and 2-back conditions with A' as dependent variable, intervention group (active and control rPAS) as between-subject variable and time points (baseline, post-intervention days 1, 7, and 14) as within-subject independent variables. Following the same procedure, separate repeated-measures ANOVAs were carried out with MI during 1- and 2-back tasks as dependent variables to compare theta–gamma coupling between the groups across time. Additionally, to generate hypotheses for future research, we calculated simple main effects of time in both groups and conducted *post hoc* within-group analyses using independent sample and paired sample *t*-tests to compare DLPFC plasticity (PAS-LTP), working memory (A'), and theta–gamma coupling (MI) between baseline and post-intervention days 1, 7, and 14 across and within the groups. Effect sizes were calculated using Cohen's d using G * Power and confidence intervals were calculated using established methods (Faul *et al.*, 2007; Smithson, 2003). Pooled pre–post-standard deviation and paired group correlations were used to calculate effect sizes for paired *t*-tests. Further, we conducted exploratory subgroup analyses after selecting participants based on the degree of cognitive impairment (MMSE ≤ 24), executive function impairment (EXIT interview score ≥ 15), and use of AChEIs, and compared the plasticity, working memory performance (2-back), and theta–gamma coupling during working memory performance between the active and control groups at baseline and post-day 1 using independent sample *t*-tests. Finally, we examined the relationship between DLPFC plasticity, working memory, and theta–gamma coupling using Pearson's correlation. For all analyses, the level of statistical significance was set at $\alpha = 0.05$.

Results

Demographic and baseline characteristics

Thirty-two AD participants were included out of which 16 (females = 9, mean (SD) age = 76.5 (6.8)) were randomized to active rPAS and 16

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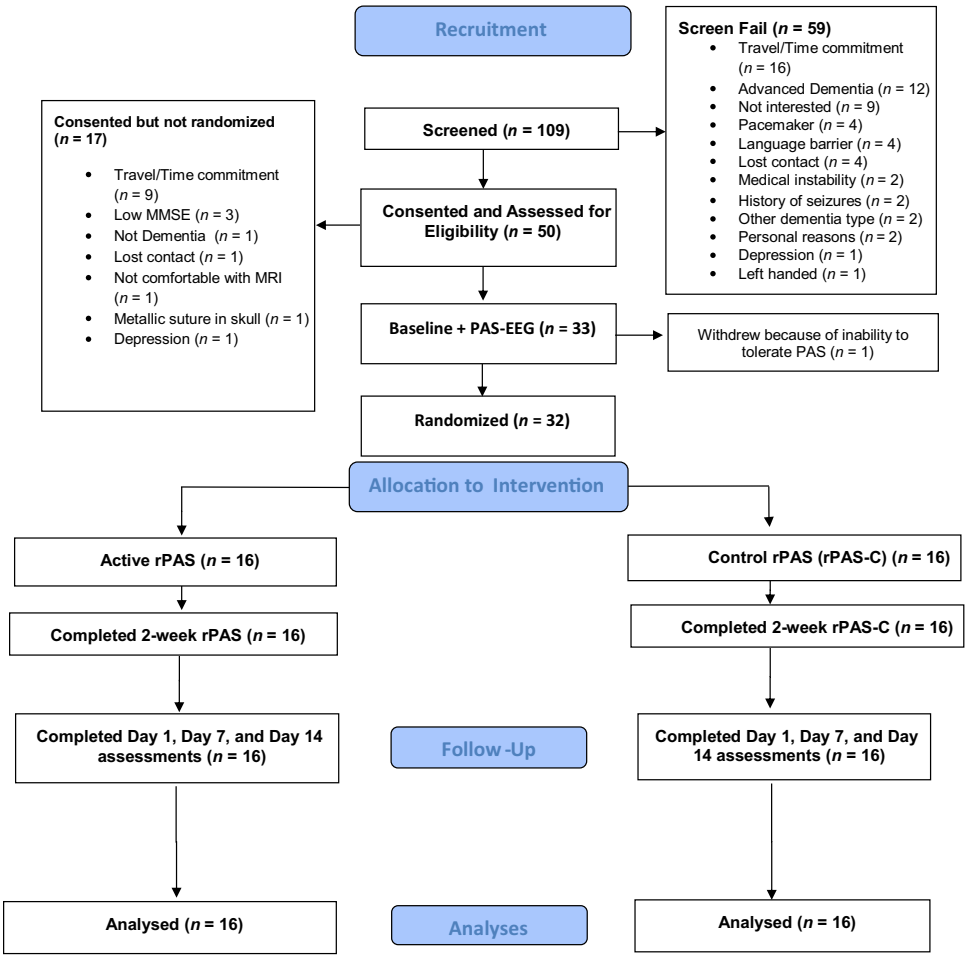

Figure 1. Consort chart showing recruitment and flow of participants in the study.

(females = 7, mean (SD) age = 76.4 (6.0)) to control rPAS (Figure 1). There were no significant differences between the two groups at baseline in age, gender, education, or cognition as assessed by MMSE, RBANS, and EXIT, or mood symptoms as assessed by CSDD. The two groups did not differ in baseline resting motor threshold, baseline pre-PAS cortical-evoked activity, DLPFC plasticity, attention during PAS (assessed by the difference between participant's count of sensory stimuli during PAS and the actual number of sensory stimuli), 1- and 2-back tasks, or theta–gamma coupling during N-back. Only the sensory threshold at the wrist was lower in the active rPAS group than in the control rPAS group at baseline (Table 1). All 16 participants in each group performed 1-back task at baseline and follow-up points. In the active group, 15 participants performed the 2-back task at baseline, 14 at post-day 1, 15 at post-day 7, and 15 at post-day 14. In the control group, 13 participants performed the 2-back task at baseline, 14 at post-day 1, 13 at post-day 7, and 13 at post-day 14.

DLPFC plasticity

On the primary analysis, there was no significant group × time interaction for DLPFC plasticity (PAS-LTP) ($F_{3,90} = 1.9$, $p = 0.14$). There was a significant simple main effect of time on DLPFC plasticity only for the active rPAS group ($F_{3,45} = 3.65$, $p = .019$, partial $\eta^2 = 0.20$). However, on post-rPAS day 1, there was no significant difference in PAS-LTP between the active (mean (SD) = 1.65 (0.81)) and control group (mean (SD) = 1.22 (0.58), $t = 1.7$, $df = 30$, $p = 0.1$, Cohen's $d = 0.6$, 95% CI [–0.11, 1.30]). Further, *post hoc* within-group comparisons showed that only the active rPAS group experienced a significant increase in DLPFC plasticity from baseline to post-rPAS day 1 ($t = 2.27$, $df = 15$, $p = 0.038$, Cohen's $d = 0.7$), while there was no such change in DLPFC plasticity in the control rPAS group ($t = 0.06$, $df = 15$, $p = 0.954$, Cohen's $d = 0.02$). There were no within-group differences between DLPFC plasticity at baseline versus any other time points (post-intervention days 7 and 14) in either group (Figure 2A).

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Table 1. Baseline participant characteristics including demographics, cognitive status, and neurophysiological characteristics

	PAS ($n = 16$) MEAN (SD)	C-PAS ($n = 16$) MEAN (SD)	T OR X^2	DF	P
Age (years)	76.5 (6.8)	76.4 (6.0)	0.055	30	0.956
Sex (M:F)	7:9	9:7	0.500	1	0.480
Years of education	12.8 (3.5)	14.4 (3.9)	1.299	30	0.204
MMSE	22.2(3.6)	22.8(2.7)	0.560	30	0.580
CSDD	2.1 (2.2)	2.6 (2.1)	0.735	30	0.468
EXIT	13.8 (5.8)	16.3 (5.1)	1.332	30	0.193
RBANS total index score	60.1 (9.1)	57.3 (9.9)	0.819	30	0.419
WM, 1-back (A')	0.76 (0.2)	0.80(0.2)	0.765	29	0.450
WM 2-back (′)	0.53 (0.2)	0.54 (0.3)	0.584	29	0.564
Ln modulation index* (1-back)	− 6.5 (1.1)	− 6.0 (1.2)	1.275	29	0.212
Ln modulation index* (2-back)	− .3 (0.9)	− 7.0 (1.0)	0.754	23	0.458
Resting motor threshold (RMT)**	54.1 (12.1)	48.7 (13.4)	1.188	30	0.244
Stimulus intensity sufficient to induce 1 millivolt peak-to-peak MEP (RMT_{1mv})	69.4 (18.9)	60.4 (18.0)	1.377	30	0.179
Sensory threshold for median nerve at the wrist	8.0 (3.3)	10.9 (4.1)	2.158	30	0.039***
Pre-PAS cortical-evoked activity	1060.3 (936.3)	1192. 2 (825.3)	0.423	30	0.675
Attention during PAS (count difference)	24.6 (34.4)	28.6 (35.4)	0.324	30	0.748
Potentiation at site of stimulation (PAS-LTP)	1.1 (0.2)	1.2 (0.3)	0.788	30	0.430
Cognitive enhancer medications (number of participants taking the medication)					
Any medication	9	8	0.027	1	0.870
Donepezil	9	5			
Galantamine	0	2			
Rivastigmine	0	1			
Memantine	1	1			

Abbreviations: PAS, Paired Associative Stimulation with interstimulus interval = 25 ms (active condition); C-PAS, Control rPAS condition with interstimulus interval = 100 ms; M, Male; F, Female; MMSE, Mini-Mental State Examination (score out of 30, a higher score indicates better performance); CSDD: Cornell Scale for Depression in Dementia (score ranges from 0 to 38, a higher score indicates worse depression); EXIT, Executive Interview (score ranges from 0 to 50, a higher score indicates worse performance); RBANS, Repeatable Battery for the Assessment of Neuropsychological Status (score ranges from 40 to 160, a higher score means better performance); PAS-LTP, Ratio of post-PAS to pre-PAS cortical-evoked activity, a measure of long-term potentiation-like activity.

*Natural log of modulation index, the measure of theta–gamma coupling.
**Motor threshold is expressed in terms of the percentage of maximum TMS machine output.
***Statistically significant, for all statistical tests, the level of significance was set for $\alpha = 0.05$.

Working memory

There was no significant group × time interaction for working memory performance on 2-back ($F_{3,54} = 0.9$, $p = 0.444$) or 1-back ($F_{3,66} = 0.3$, $p = 0.824$) tasks with A' as dependent variable and the intervention groups and follow-up time points as independent variables. There was a significant simple main effect of time on 2-back performance only for the active rPAS group ($F_{3,27} = 3.74$, $p = .023$, partial $\eta^2 = 0.29$). Again, on post-rPAS day 1, there was no significant difference between working memory (2-back task) performance between the active rPAS (mean (SD) $A' = 0.75$ (0.16)) and control rPAS group (mean (SD) $A' = 0.63$ (0.20), $t = 1.7$, $df = 21$, $p = 0.102$, Cohen's $d = 0.7$, 95% CI [-0.14, 1.55]). However, on *post hoc* within-group analyses for performance on the 2-back task, only the active rPAS group showed improvement at post-rPAS day1 as compared to baseline ($t = 2.3$, $df = 10$, $p = 0.043$, Cohen's $d = 0.7$), while there was no such change in the control rPAS group ($t = 0.5$, $df = 10$, $p = 0.7$, Cohen's $d = 0.2$). The control rPAS group showed improvement in 2-back performance only at post-day 14 as compared to baseline ($t = 2.4$, $df = 11$, $p = 0.033$) (Figure 2B). There was no change in 1-back performance across time in either group.

Theta–Gamma coupling

There were no group × time interactions for theta–gamma coupling (MI) during either 2-back ($F_{3,48} = 1.6$, $p = 0.21$) or 1-back, $F_{3,78} = 1.4$, $p = 0.3$) tasks. Similar to what we observed for DLPFC plasticity and working memory

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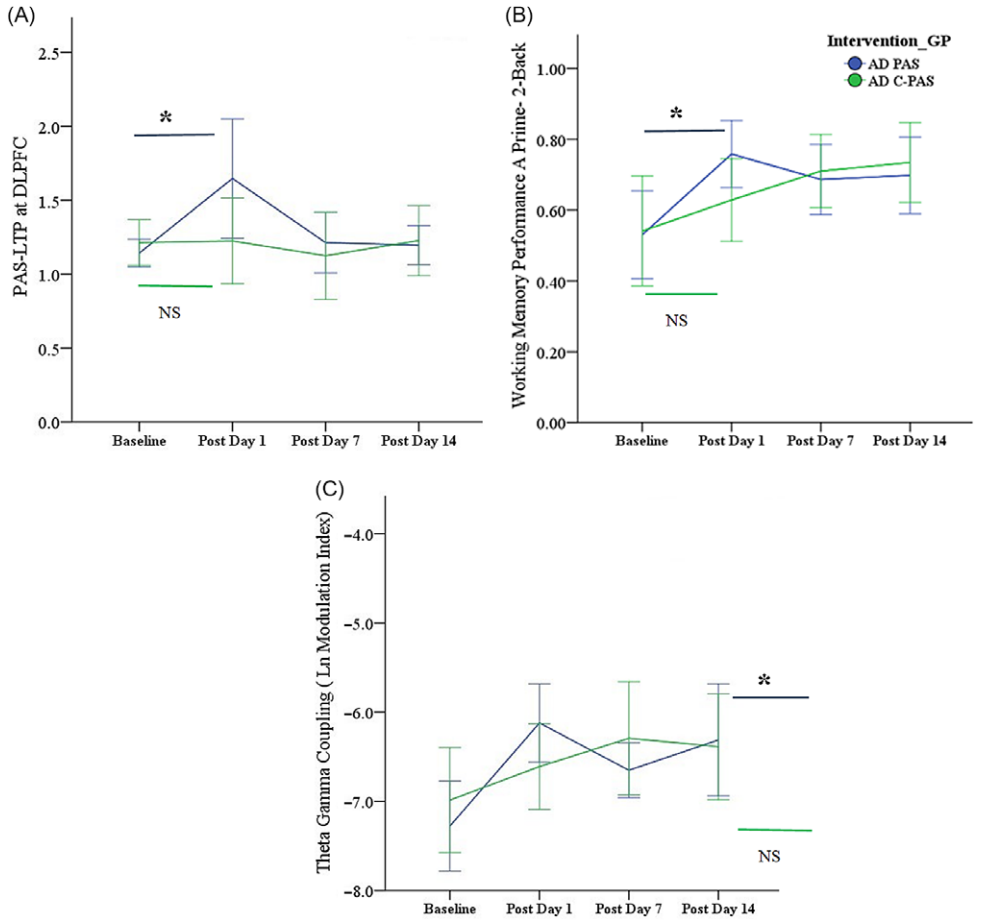

Figure 2. Changes in DLPFC plasticity, working memory, and theta–gamma coupling in active and control rPAS groups. A. Line diagram showing DLPFC plasticity as assessed at the site of stimulation (DLPFC) using PAS, across baseline and post-intervention days 1, 7, and 14. PAS-LTP is defined as the ratio of post-PAS to pre-PAS cortical-evoked activity. Active rPAS group received a 2-week course of rPAS with ISI = 25 ms, control rPAS group received a 2-week course of rPAS with ISI = 100 ms. B. Line diagram showing working memory performance (2-back task) in active and control rPAS groups at baseline and at post-intervention days 1, 7, and 14. *Y*-axis represents A prime (*A′*) which takes into account the hit rate and false alarm rate and is corrected for extreme values. C. Line diagram showing theta–gamma coupling assessed from electroencephalography (EEG) recorded during the working memory task (2-back task) and represented as natural log of modulation index in active and control rPAS groups at baseline and at post-intervention days 1, 7, and 14. *Y*-axis represents modulation index. Abbreviations: DLPFC, Dorsolateral Prefrontal cortex; PAS, Paired Associative Stimulation; LTP, Long-Term Potentiation; ISI, Interstimulus Interval (between median nerve stimulation and DLPFC stimulation); NS – not statistically significant. Error bars represent +/− 2 standard error. * – Statistically significant ($p < 0.05$).

performance, there was a significant simple main effect of time on theta–gamma coupling during 2-back performance only for the active rPAS group ($F_{3,27} = 4.88$, $p = 0.008$, partial $\eta^2 = 0.35$). There was no significant difference between theta–gamma coupling (2-back task) between the active rPAS (mean (SD) Ln MI = − 6.1(0.8)) and control rPAS group (mean (SD) Ln MI = − 6.6 (0.8), $t = 1.5$, $df = 23$, $p = 0.2$, Cohen's $d = 0.6$, 95% CI [–0.21, 1.40]) (Figure 2C). Again, on *post hoc* tests, there was an enhancement of theta–gamma coupling during the 2-back task in the active rPAS group at post-day 1 as compared to baseline ($t = 2.9$, $df = 11$, $p = 0.02$, Cohen's $d = 0.9$), and not in the control group ($t = 0.9$, $df = 8$, $p = 0.4$, Cohen's $d = 0.3$). Theta–gamma coupling enhancement during the 2-back task was also noted at post-day 14 in both active ($t = 2.3$, $df = 10$, $p = 0.043$) and control groups ($t = 3.2$, $df = 8$, $p = 0.013$).

There was no change in theta–gamma coupling across time during the 1-back task in either of the groups, which is similar to the fact that the two groups did not also experience any change in performance on the 1-back task.

Exploratory subgroup analyses

Twenty-five participants had MMSE ≤ 24, out of which 12 were randomized to active rPAS. There

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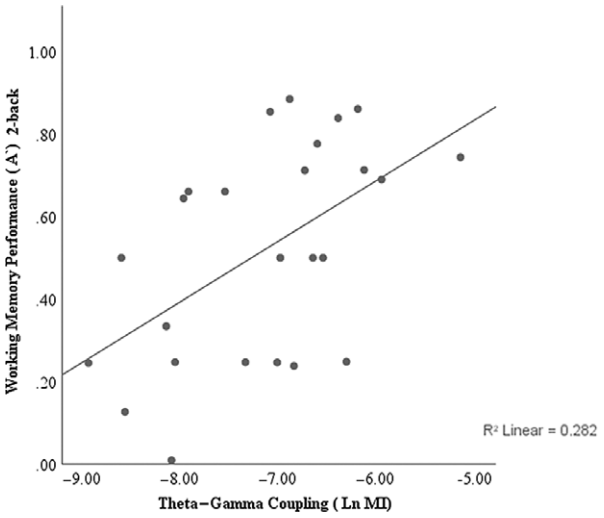

Figure 3. Scatterplot showing the correlation between working memory performance (*Y*-axis – as assessed by N-back tasks 2-back condition, and represented as *A*′) and theta–gamma coupling (*X*–axis – assessed from EEG recorded during the working memory task, and represented as natural log of modulation index – Ln MI). Pearson's correlation, $r = 0.5$, $n = 25$, $p = 0.003$.

were no differences between the active and control groups at baseline, but on post-day 1, active rPAS group had better 2-back performance (mean (SD) $A' = 0.82$ (0.12)) as compared to the control group (mean (SD) $A' = 0.59$ (0.19), $t = 3.05$, $df = 16$, $p = 0.008$). There were no differences between the groups on DLPFC plasticity or theta–gamma coupling. Further, among participants with MMSE > 24 or those selected based on EXIT interview scores, there were no differences between the active and control groups on plasticity, working memory or theta–gamma coupling. Seventeen participants were taking AChEIs, out of which nine were randomized to active rPAS. There were no differences between the groups on DLPFC plasticity or working memory performance. For theta–gamma coupling, there were no differences between the active and control groups at baseline, however, on post-day 1, the active rPAS group had higher theta–gamma coupling (mean (SD) Ln MI = −5.9 (0.48)) as compared to the control group (mean (SD) Ln MI = −6.7 (0.65), $t = 2.43$, $df = 10$, $p = 0.04$). Among participants not taking AChEIs, there were no differences between the active and control groups on plasticity, working memory, or theta–gamma coupling.

Relationships among DLPFC plasticity, working memory, and theta–gamma coupling

There was a significant positive correlation between working memory performance (*A*′) and theta–gamma coupling (MI) during the working memory task, with both groups analyzed together. Pearson's correlation analyses showed a significant positive correlation between 1-back *A*′ and Ln MI during 1-back at baseline ($r = 0.6$, $n = 31$, $p < 0.001$), post-day 1 ($r = 0.5$, $n = 28$, $p = 0.006$), post-day 7 ($r = 0.8$, $n = 29$, $p < 0.001$), and post-day 14 ($r = 0.7$, $n = 26$, $p < 0.001$).

Similarly, there was a positive correlation between 2-back *A*′ and Ln MI during 2-back at baseline ($r = 0.5$, $n = 25$, $p = 0.003$), post-day 7 ($r = 0.4$, $n = 23$, $p = 0.03$), and post-day 14 ($r = 0.5$, $n = 21$, $p = 0.009$) (Figure 3). There was no significant correlation between 2-back A′ and Ln MI at post-day 1 ($r = 0.3$, $n = 22$, $p = 0.09$).

There were no significant correlations between working memory performances and DLPFC plasticity or between theta–gamma coupling and DLPFC plasticity.

Table 2. Details of adverse events experience by participants in active and control rPAS groups

	RPAS ($n = 16$)	C-RPAS ($n = 16$)
Any adverse event, *n*	11	7
Early withdrawals, *n*	0	0
Serious adverse events, *n*	0	0
Specific adverse events		
Headache, *n*	2	1
Nausea, *n*	0	0
Dizziness, *n*	0	0
Pain/discomfort, *n*	3	4
Fatigue, *n*	1	1
Disrupted sleep, *n*	2	0
Frustration, *n*	1	1
Other neurological symptoms (such as blurry vision and weakness)	2	0

Adverse effects

There were no serious adverse events in either arm and there were no early dropouts in either of the two groups. There were 11 adverse events in the active rPAS group and 7 in the control rPAS group. Two participants experienced sleep problems in the active rPAS group and none in the control group. There was one instance of transient blurry vision and one instance of transient muscle weakness in the active group with no such events reported in the control group. These events did not happen during or immediately following the rPAS sessions and were determined to be not related to PAS. Please see Table 2 for details of adverse events in both groups.

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Discussion

This was a pilot randomized double-blind-controlled study to investigate the effects of rPAS delivered to the DLPFC on DLPFC plasticity and working memory in patients with AD. The successful completion of rPAS course by all randomized participants and lack of any serious adverse events shows that the intervention was well tolerated. The study was negative on primary outcome measures in terms of detecting differences between active and control rPAS groups. However, within-group analyses show promising results, mainly that right after the intervention (i.e. post-day 1), active rPAS and not control rPAS, results in enhanced DLPFC plasticity, working memory performance on 2-back, and theta–gamma coupling during 2-back performance. After post-day 1, and without any booster rPAS sessions, the improvement in DLPFC plasticity does not persist while the improvement in working memory and theta–gamma coupling becomes more variable. Our *post hoc* analyses also showed that changes in working memory performances parallel changes in theta–gamma coupling at all time points for both groups (except for one time point for the active group) and that these two measures are strongly correlated, providing further support to the role of theta–gamma coupling in working memory.

To our knowledge, this is the first study to investigate the effects of DLPFC rPAS on DLPFC plasticity and working memory in patients with AD. One small study in nine healthy volunteers showed that a modified rPAS protocol targeted at the motor cortex can result in motor cortex reorganization (McKay *et al.*, 2002). Several small studies have reported beneficial effects of repetitive TMS (rTMS) applied to DLPFC and other brain regions on cognitive function in AD; however, these studies did not assess DLPFC plasticity (Lee *et al.*, 2016; Sabbagh *et al.*, 2019; Bentwich *et al.*, 2011; Rabey *et al.*, 2013; Liao *et al.*, 2015; Dong *et al.*, 2018). Notwithstanding the possibility that rPAS is not effective in enhancing plasticity or working memory, several factors could have contributed to not finding a significant effect. First, this was designed as a small pilot study with no prior pilot data in AD to adequately estimate the sample size needed to detect the effect. The study was powered to detect a large effect size (Cohen's $d = 1.02$), whereas the observed between-group effect sizes were moderate and non-significant (for plasticity, Cohen's $d = 0.6$, 95% CI [–0.11, 1.30] and for working memory, Cohen's $d = 0.7$, 95% CI [–0.14, 1.55]). Second, the primary outcome of this pilot study was to determine whether rPAS could enhance DLPFC plasticity. Thus, rPAS was delivered unilaterally to the left DLPFC. One could argue that to enhance working memory, and possibly plasticity, bilateral rPAS should have been delivered. Third, the variable results after post-day 1 could be due to the lack of ongoing or at least booster rPAS sessions. The goal of having these assessments was in fact to assess the durability of any effect without any booster sessions.

Implications of the preliminary analyses for future research

Our preliminary finding of within-group improvement in DLPFC plasticity and working memory with active rPAS may have important implications for future research. It has been shown that environmental enrichment can promote neurogenesis and LTP in the hippocampus of AD mice (Hu *et al.*, 2010). Further, it has been proposed that exercise can have positive effects on brain plasticity based on the measurement of indirect markers of plasticity such as BDNF and neurotrophic gene expression (Rolland *et al.*, 2008). It has also been shown postmortem that the brains of AD patients may be capable of mounting an adaptive plastic response (Geddes *et al.*, 1985). Some recent studies have shown the importance of frontal brain regions for apathy and other behavioral symptoms in AD (Padala *et al.*, 2020; Nowrangi *et al.*, 2020). Our findings of within-group plasticity and working memory enhancement in the active rPAS group support future use of brain stimulation interventions aimed at frontal brain regions to enhance plasticity, cognition, and behavior in patients with AD. Our results also support the investigation of rPAS with alternative sites (such as bilateral stimulation) or parameters (potentially longer duration) or additional booster sessions and testing these paradigms in larger samples stratified by their cognitive status and other clinical variables such as behavioral symptoms and use of AChEIs.

Our exploratory findings of enhanced theta–gamma coupling in the active rPAS group along with enhanced working memory and of robust correlations between theta–gamma coupling and working memory performance may have important implications for a mechanistic understanding of working memory and cognition in AD. Diagnosis and treatment of dementia remains challenging and may lead to fewer people seeking help for dementia (Poole *et al.*, 2020; Parker *et al.*, 2020). A better understanding of biomarkers underlying cognition is the key to enhance diagnostic accuracy and develop novel treatment interventions. Hippocampal theta–gamma coupling has been associated with memory performance in animal models and humans with surgically implanted electrodes (Tort *et al.*, 2013; Lega *et al.*, 2016). Impaired theta–gamma coupling and its association with cognition has

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been shown in a mouse model of AD linking it with AD pathology (Stoiljkovic *et al.*, 2018). A recent study in older healthy adults showed that enhancing theta–gamma coupling using transcranial Alternating Current Stimulation resulted in enhanced working memory and there was an association between changes in theta–gamma coupling and changes in working memory (Reinhart and Nguyen, 2019). Thus, our findings suggest that theta–gamma coupling may be used as an intermediate biomarker of working memory performance and as a potential target for cognitive-enhancing interventions in AD.

Limitations

The following are additional limitations of this study. First, we screened 109 patients to successfully recruit 32 participants (Figure 1). The top reason for failing screen was the travel and time commitment to the study, which raises the importance of adapting noninvasive brain stimulation to less mobile populations such as AD. In contrast, the retention rate was excellent in our study, demonstrating the high tolerability of noninvasive brain stimulation in AD. Second, 17/32 participants in our study were taking cognitive enhancer medications (Table 1). While this could have contributed to variability overall, it is unlikely to have confounded the working memory or DLPFC plasticity results between groups as the distribution was similar between two groups. Third, we relied on the clinical diagnosis of AD and did not include pathologic markers of AD. Fourth, we did not correct for coil-to-cortex distance to factor in cortical atrophy to determine the intensity of DLPFC stimulation using TMS. However, the intensity of stimulation was individualized by assessing the TMS intensity required to produce a 1 millivolt motor-evoked potential. Finally, this study did not include participants with mild cognitive impairment who could be more amenable to the enhancement of DLPFC plasticity and working memory owing to the earlier stages of illness.

Further directions and potential for translation to a treatment approach

Preliminary findings of our study highlight the need for further research into the effects of rPAS in AD before its translation into clinical care. Still, our findings suggest that using rPAS to enhance cognition in a group of patients with an objectively defined cognitive impairment could result in enhanced cognition. Future well-powered studies targeting such a population are needed, and if successful, additional studies should assess the effects of rPAS on other biological markers and behavioral symptoms of AD and as well as focus on overcoming barriers to implementation of rPAS for clinical use. Future studies should also examine potential relationships between working memory, DLPFC plasticity, and theta–gamma coupling.

Conclusions

This study was negative on the primary outcome and did not show significant differences between active and control rPAS groups with respect to DLPFC plasticity or working memory performance at post-intervention days 1, 7, or 14. Exploratory within-group analyses across time, conducted to generate hypotheses for future research, detected a moderate-to-large effect size for improved DLPFC plasticity, working memory performance, and theta–gamma coupling acutely post-intervention only in the active rPAS group. There was also a robust positive correlation between working memory performance and theta–gamma coupling. Finally, the rPAS intervention was well tolerated without any serious adverse effects. These results indicate the need for future studies to investigate the effect of rPAS in AD with more intensive protocols in larger samples and to also include populations at earlier stages of the illness before the onset of dementia.

Conflict of interest

The authors have no conflicts of interest to report related to this work.

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Reza Zomorrodi – Data curation, Investigation, Methodology, Formal analysis, Writing – review and editing.

Zaid Ghazala – Data curation, Investigation, Methodology, Project administration, Writing – review and editing.

Michelle S. Goodman – Data curation, Investigation, Methodology, Formal analysis, Writing – review and editing.

Daniel M. Blumberger – Conceptualization, Project administration, Supervision, Writing – review and editing.

Zafiris J. Daskalakis – Conceptualization, Project administration, Supervision, Writing – review and editing.

Corinne E. Fischer – Supervision, Resources, Writing – review and editing.

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Bruce G. Pollock – Conceptualization, Project administration, Supervision, Writing – review and editing

Tarek K. Rajji – Conceptualization, Funding acquisition, Resources, Data curation, Formal analysis, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review and editing.

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