



A pilot study of repetitive transcranial magnetic stimulation in primary progressive aphasia



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Frontotemporal dementia
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Dear Editors,

Frontotemporal dementias (FTD) are uncommon early-onset degenerative brain disorders with prevalence of 15–22 per 100,000 persons aged 45–64 [1,2]. The clinical syndromes include primary progressive aphasias (PPA), such as semantic dementia, and progressive nonfluent aphasia (including agrammatic and logopenic variants) [3–5]. Due to low prevalence, little has been invested in research for PPA treatments, and there is no treatment approved for reducing its progressive deficits.

Recent studies suggest that repetitive transcranial magnetic stimulation (rTMS) may reduce symptoms in FTD variants [6–8]. We aimed to replicate findings of a prior study [6], showing improved Action vs. Object Naming with rTMS of dorsolateral prefrontal cortex (DLPFC) in nonfluent PPA. We hypothesized that effects would be stronger with stimulation of left than right DLPFC, as left hemisphere is typically dominant for language. We also explored effects of rTMS on other cognitive tasks.

Participants and procedures

We applied high-frequency rTMS to both hemispheres in conjunction with on-line cognitive assessments described in proof of concept studies in Alzheimer's disease (AD) and nonfluent PPA [6–9]. Participants were 6 right-handed men ($n = 4$) and women ($n = 2$) (age = 67 ± 7 years, education = 15 ± 2 years) with very mild to moderate dementia.

rTMS was applied using Neurostar XPLOR® equipped with active and matching sham stimulation coils. The TMS coil was placed on the scalp over DLPFC (5 cm anterior to the optimal position for the hand region of primary motor cortex). Participants were seen for 2 rTMS sessions. Each session, participants received sham followed by active stimulation of either left or right DLPFC (hemisphere stimulated first was randomized across participants). Participants were blinded to stimulation-condition (sham vs. active), but researchers were not. Stimulation consisted of 84 trains of rTMS (1000 milliseconds [ms] of stimulation at a frequency of 20 Hz in each train = 20 pulses per train) at an

intensity of 90% of motor threshold (the minimum power necessary to produce a stimulation response 50% of the time). The inter-train (no stimulation) interval was 6.5–7.5 seconds. Total rTMS dose per session day was 3360 sham pulses and 3360 active pulses.

During rTMS administration, on-line (i.e., acute, within-task) performances on an Action/Object Naming task [6], and a Stroop paradigm were elicited. On-line tasks used 84 intermixed stimuli (Action/Object: 42 action and 42 object items; Stroop: 42 word-reading and 42 ink-naming items presented in incongruent ink) displayed on a flat screen Samsung TV monitor (35 × 20 inches) connected via HDMI cable to an Ultrabook PC laptop (resolution of 1920 × 1080/90p with a viewing distance of 72 inches) running E-Prime 2.0 software. Timing and presentation of stimuli were identical across tasks. Order of stimuli was randomized across participants and conditions.

Global cognition (Montreal Cognitive Assessment [10] MOCA) and a Letter Fluency task (FAS) were assessed at baseline (prior to any stimulation) and ~10-min post-rTMS sessions. Participants and their caregivers were contacted to report perceived benefits or side-effects within 24-h. Within-subject comparison of on-line effects for sham and active rTMS stimulation, as well as pre- and post-session MOCA and Letter Fluency scores, were assessed with one-sample Wilcoxon signed-ranked tests with ties removed in R.

Results (Fig. 1A, B, C)

Action Naming

Left DLPFC. Action Naming accuracy significantly increased from sham to active stimulation (Sham: Mean (M) = 44%; Median (Md) = 38% with interquartile range (IQR) = 25%; Active: M = 58%; Md = 62% with IQR = 27%; $p = 0.036$).

Right DLPFC. Action Naming accuracy was not significantly different across sham or active conditions (Sham: M = 46%; Md = 45% with IQR = 23%; Active: M = 41%; Md = 38% with IQR = 35%; $p = 0.094$).

Object Naming

Object Naming accuracy was not significantly different across sham or active conditions for either the Left DLPFC (Sham: M = 75%; Md = 76% with IQR = 14%; Active: M = 71%; Md = 71% with IQR = 32%; $p = 0.833$), or the Right DLPFC (Sham: M = 76%; Md = 81% with IQR = 36%; Active: M = 72%; Md = 76% with IQR = 15%; $p = 0.192$).

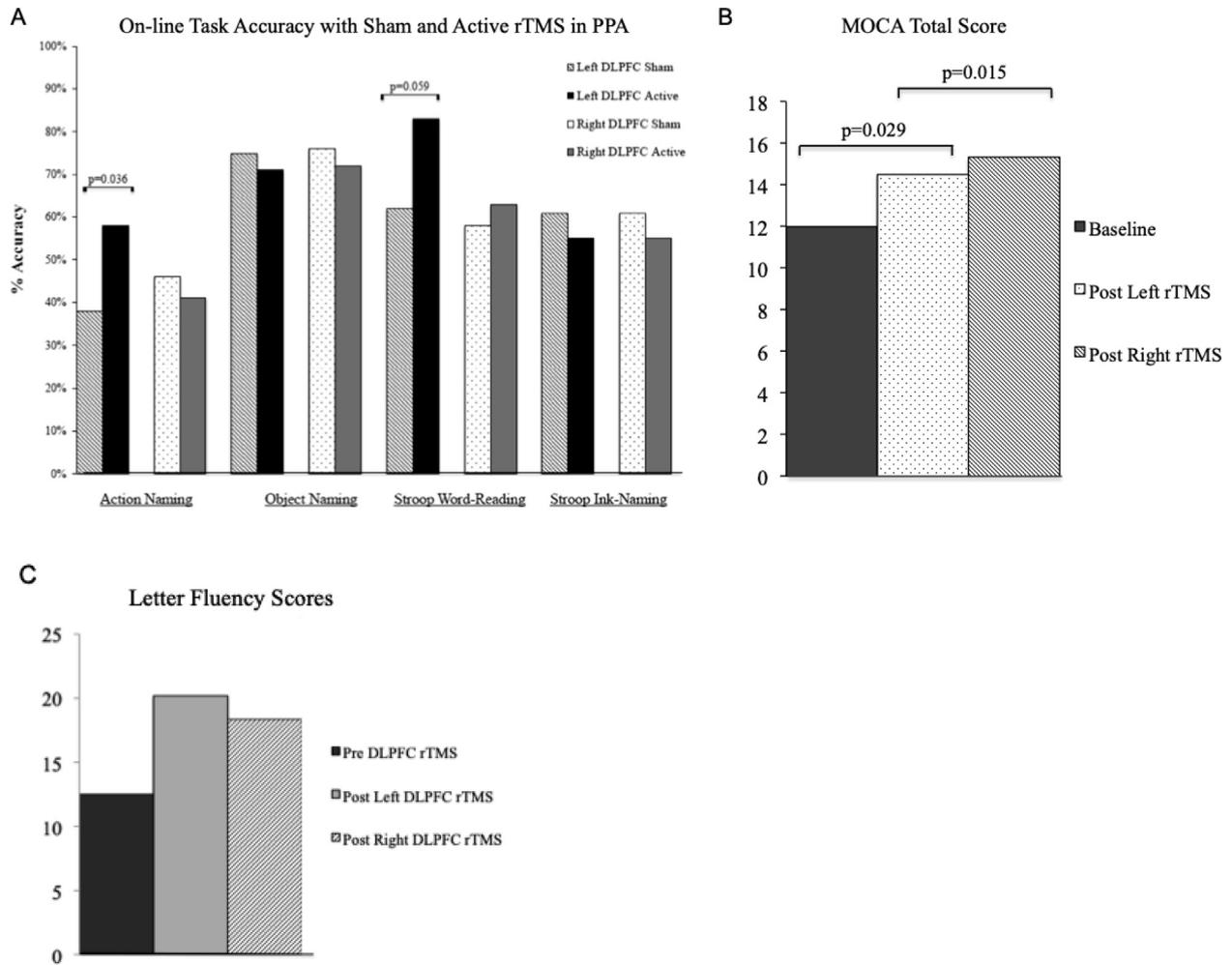


Fig. 1. On-line (sham vs. active) and pre- to post-rTMS session cognitive test scores.

Stroop word-reading

Left DLPFC. Word-Reading accuracy showed a trend towards improvement with active stimulation (Sham: $M = 62\%$; $Md = 55\%$ with $IQR = 61\%$; Active: $M = 83\%$; $Md = 90\%$ with $IQR = 33\%$; $p = 0.059$).

Right DLPFC. Word-Reading accuracy was not significantly different across sham or active conditions (Sham: $M = 58\%$; $Md = 60\%$ with $IQR = 71\%$; Active: $M = 63\%$; $Md = 52\%$ with $IQR = 56\%$; $p = 0.834$).

Stroop ink-naming

Ink-Naming accuracy was not significantly different across sham or active conditions for either the Left DLPFC (Sham: $M = 61\%$; $Md = 64\%$ with $IQR = 64\%$; Active: $M = 55\%$; $Md = 67\%$ with $IQR = 70\%$; $p = 0.584$), or the Right DLPFC (Sham: $M = 61\%$; $Md = 64\%$ with $IQR = 50\%$; Active: $M = 55\%$; $Md = 55\%$ with $IQR = 40\%$; $p = 0.343$).

MOCA

Relative to MOCA total scores at the pre-rTMS (baseline) session ($M = 12$; $Md = 11.5$ with $IQR = 9.8$), all participants demonstrated improvements following left and right rTMS sessions (Left: $M = 14.5$; $Md = 14$ with $IQR = 8.8$; Right: $M = 15.33$; $Md = 16$

with $IQR = 12.5$). These improvements were significant (Left: $p = 0.029$; Right: $p = 0.015$).

Letter Fluency

Although there was relative improvement in overall Letter Fluency from the pre-rTMS (baseline) session ($M = 12.5$; $Md = 14.5$ with $IQR = 11.5$) to left (Left: $M = 20.17$; $Md = 22$ with $IQR = 24.8$) and right-sided ($M = 18.33$; $Md = 19.5$ with $IQR = 22.8$) rTMS sessions, these differences were not significant (Left: $p = 0.122$; Right: $p = 0.207$).

Post-rTMS subjective reports

Participants and their caregivers remarked on the following benefits: improved participant focus, clearer speech, and/or increased memory. One participant did not perceive any benefits. Reported side-effects included: mild and transient headache, fatigue, mild and temporary decrease in hearing, fleeting anxiety, trouble sleeping, and/or temporarily decreased mental clarity.

Discussion

As hypothesized, results suggest that left-sided DLPFC rTMS may be more beneficial for treatment of nonfluent PPA than right-sided DLPFC rTMS. Specifically, left DLPFC rTMS led to

significant on-line improvements in Action Naming along with post-session gains in global cognition, as well as near-significant gains in on-line Word Reading and encouraging but non-significant gains in Letter Fluency. Right DLPFC rTMS also enhanced post-session global cognition but had no other significant effects. These findings reinforce and extend those reported by Cotelli et al. [6], who also found that Action but not Object Naming improved with left-sided rTMS.

Importantly, participants and their caregivers reported that rTMS was well-tolerated and had perceived benefits with few, relatively mild/transient, side-effects. Thus, rTMS may be a feasible and safe means of treating nonfluent PPA. This study is limited by its single-blind design, small sample, and reliance on non-parametric statistics. Also, order effects may partially explain pre- to post-session assessment gains. Therefore, larger randomized controlled trials are needed to establish efficacy.

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Declarations of interest

None.

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