
# Improved language performance in Alzheimer disease following brain stimulation

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## ABSTRACT

**Objectives** Repetitive transcranial magnetic stimulation (rTMS) has been proposed as a possible treatment for the cognitive deficits associated with Alzheimer disease (AD). The aim of this study was to assess the long-term effects, on cognitive performance, of rTMS applied to the left dorsolateral prefrontal cortex (DLPFC) in AD patients.

**Methods** Ten AD patients were randomly assigned to one of two study groups. Multiple-baseline design was used.The first group underwent a 4-week real rTMS stimulation protocol, while the second underwent a 2-week placebo treatment, followed by 2 weeks of real rTMS stimulation. Each session consisted of the application of rhythmic high-frequency rTMS over the DLPFC for 25 min. Sessions occurred once daily, 5 days/week. The main analysed outcome was the change in cognitive test performance at 2 and 4 weeks after rTMS treatment initiation, with a follow-up performed 8 weeks after the end of rTMS, in comparison with baseline performance.

**Results** A significant difference was found between groups over sessions in terms of the percentage of correct responses of auditory sentence comprehension. Only real treatment induced an improvement in performance with respect to baseline or placebo. Moreover, both groups showed a lasting effect on the improved performance 8 weeks after the end of treatment.

**Conclusion** The findings provide initial evidence for the persistent beneficial effects of rTMS on sentence comprehension in AD patients. Rhythmic rTMS, in conjunction with other therapeutic interventions, may represent a novel approach to the treatment of language dysfunction in AD patients.

## INTRODUCTION

Alzheimer's disease (AD) is a progressive disorder that impacts memory, language and several other cognitive functions. Given the limited effectiveness of pharmacological treatments, non-pharmacological interventions in AD have gained attention in recent years, and there are currently many different approaches under study, ranging from multistrategy approaches to cognitive training.[1]

Despite the potential therapeutic impact of the non-pharmacological approaches, the neural mechanisms underlying the beneficial effects of behavioural interventions remain largely unknown. Functional neuroimaging studies have shown that rehabilitation in patients with developmental and acquired cerebral damage may lead to functional cortical reorganisation, a process mediated by activity-dependent plasticity mechanisms.[2] These 'plastic' mechanisms may also play a role in the ageing brain and in AD.[3]

In recent years, new techniques for studying the human brain that allow for the non-invasive neurostimulation have emerged. Repetitive transcranial magnetic stimulation (rTMS) is a technique that delivers several magnetic pulses in rapid sequence up to frequencies of 100 Hz. rTMS can modulate neuronal activity, with effects depending on the stimulation frequency (ie, ≤1 Hz stimulation results in inhibition, while ≥5 Hz stimulation mostly leads to excitation). There have been no studies to date that have explored the long-term effects of rhythmic off-line rTMS in AD patients. Therefore, the main purpose of the present study was to investigate whether the application of high-frequency rhythmic rTMS, for 2 or 4 weeks, to the left dorsolateral prefrontal cortex (DLPFC) resulted in cognitive improvements[4] in patients with AD. More specifically, we hypothesised that this type of stimulation may lead to improved language performance, that is, production and/or comprehension. Such prediction comes from a previous work on naming in AD patients.[5 6] A possible effect on sentence comprehension was predicted on the basis of a study in young normal subjects,[7] which provided direct evidence of DLPFC involvement in sentence comprehension.

In addition, an important goal of the present study was to verify whether the cognitive benefits, previously recorded solely during on-line rTMS, might persist after the end of the stimulation. We adopted a multiple-baseline design, comparing the stimulation effects with a placebo condition (sham-stimulation) during the first 2 weeks of treatment. This phase was followed by 2 weeks of rTMS stimulation in all patients, in order to evaluate whether a longer rTMS application (4 vs 2 weeks) would further improve the expected benefits in the patient's performance. Finally, we assessed the persistence of the effects 8 weeks after the end of the treatment (figure 1A).

## SUBJECTS AND METHODS

### Participants

Outpatients (n=10) diagnosed as having probable moderate AD, according to the NINCDS-ADRDA[8] criteria, were enrolled.

Patients with potentially confounding neurological and psychiatric disorders, epilepsy, clinically recorded hearing or vision impairment, or with a history of alcohol abuse, psychosis or major depression were not included in the study. All patients had been on a stable dose of cholinesterase

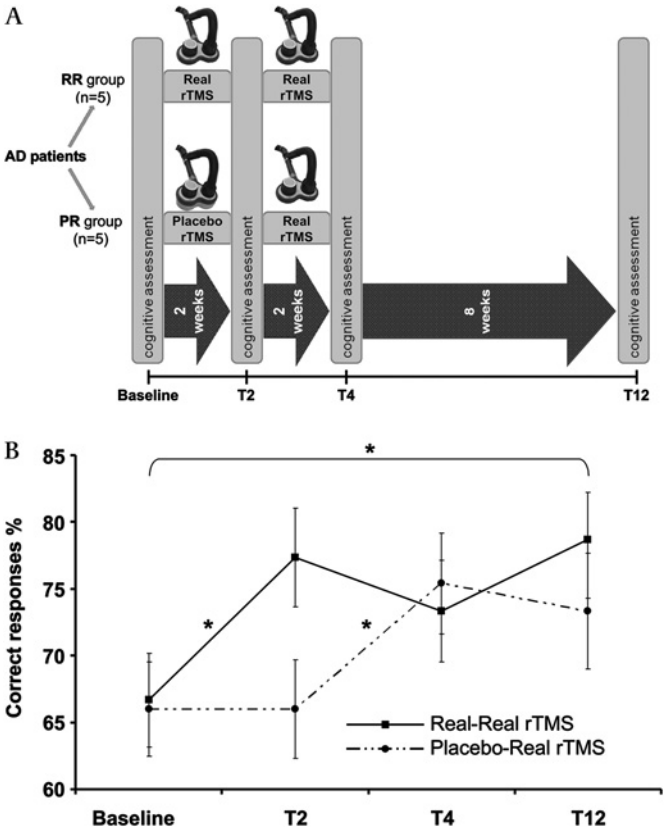


**Figure 1** (A) Experimental paradigm. AD, Alzheimer disease; PR, placebo—real treatment; RR, real—real treatment; T2, assessment at 2 weeks from the baseline; T4, assessment at 4 weeks from the baseline; T12, assessment at 12 weeks from the baseline (ie, 8 weeks after repetitive transcranial magnetic stimulation (rTMS) treatment). (B) Comparison of percentage of correct responses on the auditory sentence comprehension subtest from the Battery for Analysis of Aphasic Deficits at T2, T4 and T12 between groups (real—real rTMS vs placebo—real rTMS). T2, assessment at 2 weeks from the baseline; T4, assessment at 4 weeks from the baseline; T12, assessment at 12 weeks from the baseline (ie, 8 weeks after rTMS treatment). The mean and SEs are displayed. *p<0.05.

inhibitor (donepezil or rivastigmine) for at least 6 months prior to the onset of the study. The use of drugs with anticolinergic properties was used as an exclusion criterion.

## rTMS

Patients were randomly assigned to one of the two groups: (1) real—real group (RR), in which the patients received 4 weeks of rTMS stimulation of the DLPFC; (2) placebo—real group (PR), in which patients received DLPFC placebo stimulation during the first 2 weeks followed by 2 weeks of real stimulation (figure 1A). Each week of rTMS treatment consisted of five sessions (25 min each, one per day). rTMS was delivered by a Magstim unit featuring a double 70 mm cooled coil. Before starting the rTMS treatment, the motor excitability stimulation threshold was established for each subject (mean 51.56±5.9%). The stimulation intensity used during the experiment was set to 100% of each subject's motor threshold. Trains of rhythmic high-frequency (20 Hz) rTMS were delivered in short periods (2 s duration) separated by longer periods (28 s) of no stimulation, for each daily session. The total number of pulses for each session was 2000 (40 stimuli/train, 50 trains). These parameters are consistent with safety recommendations for rTMS.[9] Furthermore, all participants tolerated rTMS well and did not report any adverse effects. In the placebo condition, a sham coil was used.[10]

We localised the target areas using the SofTaxic neuronavigator system (http://www.emsmedical.net) on an MRI template. Based on these estimated MRIs, the average location of the stimulating points was centred on Talairach coordinates x=−35, y=24, z=48, corresponding to the DLPFC (Brodmann Area 8/9). We chose to stimulate this area based on the results of previous experiments.[5–7 11] To stimulate the DLPFC, the coil was placed with the junction of the two coil wings above the target point. During the experiment, the coil was fixed by means of a mechanical support.

## Cognitive assessment

Standard cognitive assessment was divided into two sessions. Neuropsychological testing was administered by an experienced examiner who was blind to patient treatment allocations. The cognitive assessment included tests to screen for dementia, together with neuropsychological tests for memory, executive functions and language. The results of the cognitive assessments at baseline, before rTMS treatment, at 2, (T2) 4 (T4) and 12 (T12) weeks after the onset of the rTMS treatment are reported in table 1 for both experimental groups (note that T12 corresponds to 8 weeks after the end of the treatment). All the tests were administered and scored according to standard procedures.[12 13]

## Statistical analysis

Demographic variables (age and education) of the two groups were compared at baseline, using parametric analyses (paired t test). A p value <0.05 was considered significant.

The behavioural effects induced by the rTMS protocol after 2 weeks of daily stimulation were assessed using a mixed-model ANOVA, considering group (real—real vs placebo—real) as a between-subjects factor, and time (baseline vs 2 weeks) as a within-subject factor. Further analysis was performed to assess the long-term efficacy of rTMS treatment using four time instants (baseline vs 2 weeks, 4 weeks and 12 weeks) as a within-subject factor.

# RESULTS

We identified no significant differences in the demographic variables between groups (table 1, p>0.05).

To verify the presence of short-term behavioural effects induced by rTMS, we compared the performance of both groups at baseline and at the 2-week evaluation. A significant difference between groups was found in terms of the percentage of correct responses only in auditory sentence comprehension subtest from the Battery for Analysis of Aphasic Deficits (SC-BADA) over time (group×time interaction: $F(1, 8)=6.07$, $p=0.04$; $\eta_p^2=0.43$). The real—real group improved its performance ($p=0.008$) at 2 weeks (77.3±6.5) with respect to baseline (66.6±8.6), whereas the placebo—real group showed no significant differences ($p=0.99$) between baseline (66.0±7.1) and 2 weeks of placebo rTMS (65.9, ±9.6).

We further analysed SC-BADA scores at baseline, 2, 4 and 12 weeks to assess the long-term efficacy of rTMS in both groups. A significant main effect of time ($F(3, 24)=3.87$, $p=0.02$) was found. Post-hoc analysis, Bonferroni, showed that the percentage of correct responses in SC-BADA at 12 weeks (77.2±2.7) was still significantly different ($p=0.02$) from baseline (66.3±7.45) (figure 1B). No significant differences were found for other language abilities, or for other cognitive

**Table 1** Demographic and neuropsychological data

| | Real–real (n=5) | | Placebo–real (n=5) | | p Value Group | Time | Time×group | Real–real (n=5) | | Placebo–real (n=5) | | p Value Group | Time | Time×group |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age (years) | 71.2±6.1 | | 74.4±3.8 | | 0.40 | | | | | | | | | |
| Education (years) | 6.4±1.3 | | 4.8±0.4 | | 0.06 | | | | | | | | | |
| | Baseline | 2 weeks | Baseline | 2 weeks | | | | 4 weeks | 12 weeks | 4 weeks | 12 weeks | | | |
| Mini-Mental State Examination | 16.2±2.7 | 16.0±3.3 | 16.0±2.0 | 16±2.1 | 0.95 | 0.90 | 0.90 | 15.4±3.4 | 16.4±2.8 | 16.2±2.4 | 14.5±3.7 | 0.76 | 0.75 | 0.59 |
| Basic Activities of Daily Living | 1.2±1.2 | 1.2±1.2 | 2.0±1.2 | 2.0±1.2 | 0.09 | – | – | 1.2±1.2 | 1.2±1.2 | 2.0±1.2 | 2.0±1.2 | 0.09 | – | – |
| Instrumental Activities of Daily Living | 6.0±1.8 | 6.0±1.8 | 6.6±1.7 | 6.6±1.7 | 0.43 | 0.34 | 0.34 | 6.0±1.8 | 6.0±1.8 | 6.6±1.7 | 6.6±1.7 | 0.43 | 0.34 | 0.34 |
| Picture-naming task | | | | | | | | | | | | | | |
| Objects | 61.9±8.5 | 60.6±11.5 | 54.7±7.4 | 55.0±8.7 | 0.37 | 0.95 | 0.75 | 63.0±18.7 | 65.7±19.6 | 51.0±14.8 | 48.3±12.7 | 0.18 | 0.82 | 0.22 |
| Actions | 42.2±9.7 | 48.3±5.2 | 38.2±7.5 | 40.7±10.2 | 0.23 | 0.31 | 0.70 | 47.0±7.4 | 47.9±8.7 | 41.7±15.0 | 45.0±16.0 | 0.41 | 0.29 | 0.82 |
| Battery for Analysis of Aphasic Deficits (correct responses, %) | | | | | | | | | | | | | | |
| Oral object naming | 60.0±9.5 | | 47.4±10.1 | | 0.11 | | | | | | | | | |
| Oral action naming | 40.3±10.5 | | 35.6±8.4 | | 0.51 | | | | | | | | | |
| Sentence comprehension* | 66.7±7.7 | 77.3±5.8 | 66.0±6.4 | 66.0±8.6 | 0.22 | **0.04*** | **0.04*** | 73.3±6.6 | 78.7±7.9 | 75.4±9.9 | 75.7±9.2 | 0.36 | **0.02*** | 0.23 |
| Aachener Aphasie Test | | | | | | | | | | | | | | |
| Token test (errors) | 21.2±5.1 | 22.6±7.7 | 19.2±6.2 | 17.6±8.1 | 0.47 | 0.94 | 0.33 | 25.2±6.7 | 21.2±10.5 | 17.6±10.0 | 19.5±10.1 | 0.64 | 0.77 | 0.50 |
| Repetition | 137.2±13.1 | 133.6±18.0 | 131±13.0 | 131.6±11.4 | 0.68 | 0.43 | 0.28 | 139.8±7.8 | 136.6±13.8 | 132.2±10.8 | 129.5±12.6 | 0.45 | 0.61 | 0.50 |
| Writing | 71.6±15.8 | 77.2±11.5 | 73.8±11.0 | 76.8±14.2 | 0.92 | 0.23 | 0.70 | 78.2±5.9 | 78.0±8.3 | 78.0±10.7 | 77.5±15.8 | 0.94 | 0.42 | 0.98 |
| Naming | 90.8±6.5 | 91.2±7.4 | 88±4.6 | 90.2±9.7 | 0.68 | 0.63 | 0.74 | 94.2±5.8 | 99.0±6.0 | 91.6±11.6 | 92.8±10.3 | 0.41 | 0.15 | 0.92 |
| Comprehension | 85.6±3.9 | 92.6±9.1 | 86.4±3.6 | 90.8±8.4 | 0.90 | 0.07 | 0.64 | 91.6±9.6 | 94.8±5.6 | 90.2±12.2 | 86.0±14.0 | 0.47 | 0.23 | 0.49 |
| Serial curve position | | | | | | | | | | | | | | |
| Primacy | 3.8±3.2 | 5.0±4.5 | 5.0±2.6 | 7.0±4.3 | 0.55 | 0.06 | 0.57 | 3.8±3.6 | 3.4±4.2 | 6.6±4.8 | 7.0±2.8 | 0.29 | 0.23 | 0.63 |
| Recency | 4.6±2.6 | 5.8±2.9 | 5.8±1.6 | 3.8±1.1 | 0.74 | 0.61 | 0.07 | 7.8±5.4 | 8.2±7.2 | 4.0±3.1 | 6.6±2.1 | 0.22 | 0.08 | 0.08 |
| First item | 1.8±1.9 | 1.8±1.9 | 2.6±2.1 | 3.2±2.3 | 0.44 | 0.54 | 0.54 | 1.6±2.1 | 0.5±1.0 | 3.6±2.5 | 1.3±1.5 | 0.33 | 0.07 | 0.62 |
| Cognitive estimation test | | | | | | | | | | | | | | |
| Errors | 21.8±4.6 | 24.0±3.5 | 22.8±1.0 | 23.2±5.0 | 0.96 | 0.48 | 0.62 | 24.0±2.2 | 23.8±3.8 | 22.6±3.0 | 21.8±2.1 | 0.95 | 0.61 | 0.69 |
| Bizarreness | 9.4±3.1 | 8.6±2.9 | 9.8±1.9 | 7.6±3.8 | 0.88 | 0.10 | 0.41 | 9.4±2.7 | 10.6±2.9 | 7.6±2.5 | 7.5±3.7 | 0.60 | 0.64 | 0.31 |

*$p<0.05$.

functions (such as cognitive estimation and memory). See table 1 for more details.

## DISCUSSION

The main purpose of this study was to investigate whether the application of high-frequency rTMS to the left DLPFC for 25 min a day, 5 days a week, for 2 weeks may lead to significant cognitive improvements in patients with AD. Specifically, we hypothesised that this protocol would result in changes in language performance, that is, facilitation of language production and/or comprehension. In addition, we compared the effects of 2 or 4 weeks of stimulation to evaluate whether a longer rTMS application would result in a greater and/or longer-lasting effect. Finally, another important aim of the present study was to verify whether the cognitive benefits recorded immediately after rTMS treatment would persist 8 weeks after the end of the treatment protocol (T12).

Overall, the results of our study show a significant effect of rTMS treatment on auditory sentence comprehension.

In contrast with our previous studies,[5 6] in the present study we failed to observe a significant effect on naming performance in AD. These results may be attributed to the rTMS paradigm used (off-line vs on-line) with a short term facilitation, in our previous study, strictly related to the timing of stimulation (that is, a few milliseconds before the naming). In the present study, we applied an off-line rTMS approach in which patients received daily rTMS treatment, while in the previous studies rTMS was applied to DLPFC during the execution of the naming task.

We also found that the administration of rTMS for 4 weeks did not result in additional improvements in performance compared with the application of rTMS for 2 weeks. A meta-analysis by the Cochrane Collaboration[14] concluded that rTMS significantly improves depression only after a minimum of 2 weeks of treatment. Our results suggest that 2 weeks of rTMS is also sufficient to evidence behavioural improvements in AD patients.

As regards the long-term effects, we identified an improvement in sentence comprehension 8 weeks (T12) after the end of the rTMS intervention. To date, this is the first study that shows a long-lasting cognitive effect of rTMS treatments in AD patients.

Another important result of our study was the absence of any rTMS effects on memory and executive functions suggesting that learning effects cannot explain data. Therefore, the facilitation effect of DLPFC rTMS in AD appears to be specific to the language domain rather than reflecting a general, non-specific effect on cognitive processing.

Why did rTMS induce this improvement in patient language performance? The neurophysiological mechanisms responsible for rTMS-induced facilitation remain unknown. A number of investigations suggest that rhythmic transcranial stimulation can exert positive effects on cognitive performance.[4] A possibility is that the modification of cortical activity through the use of rhythmic stimulation may readjust pathological patterns of brain activity, thus providing an opportunity to induce new, healthier activity patterns within the affected functional networks.[15]

The present findings may reflect an rTMS-induced modulation of short- and/or long-range cortical synaptic efficacy and connectivity that potentiates the system within the language network, leading to more effective processing.

The present preliminary results highlight the therapeutic potential of the induction of long-term neuromodulatory effects using brain stimulation. They hold considerable promise, not only for advancing our understanding of brain plasticity mechanisms, but also for designing new rehabilitation strategies in patients with neurodegenerative disease.

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**Competing interests** None.

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