Effect of Transcranial Magnetic Stimulation on Action Naming in Patients With Alzheimer Disease

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Objective: To assess the effect of repetitive transcranial magnetic stimulation (rTMS) to the dorsolateral prefrontal cortex (DLPFC) on picture naming in patients with Alzheimer disease (AD).

Design: Experimental study. Patients with AD underwent rTMS in real and control conditions during picture-naming tasks.

Setting: San Giovanni di Dio Fatebenefratelli Scientific Institute in Brescia, Italy.

Patients: Fifteen patients with probable AD.

Intervention: High-frequency rTMS was applied to the left and right DLPFC during object and action naming.

Main Outcome Measures: Language ability was assessed by accuracy of verbal response during online rTMS.

Results: Stimulation to the left and right DLPFC improved accuracy in action naming.

Conclusions: These findings indicate that rTMS to the DLPFC, which speeds up action naming in normal controls, improves performance in patients with AD. While the mechanisms of rTMS-induced naming facilitation in these patients are unknown, the procedure may be worth testing as a novel approach to the treatment of language dysfunction.

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WORD-FINDING DIFFICULTY (anomia) is commonly present in the early stages of Alzheimer disease (AD) dementia. Several studies also have shown that action naming may be more difficult than object naming in patients with aphasia and dementia.[1-4] Selective deficits have been described for grammatical classes of words, such as nouns and verbs.[5] Lesion and imaging studies have supported the hypothesis of a central role of the left prefrontal and parietal areas in verb processing.[6]

Perani et al,[7] using a lexical decision task, found that some left hemispheric areas, including the dorsolateral frontal and lateral temporal cortex, were activated only by verbs, while there were no brain areas more active in response to nouns. More recently, using event-related magnetic resonance imaging, Shapiro et al[8] found verb-specific responses in the left prefrontal and parietal areas, while noun-specific activations involved the inferior temporal lobe. Using repetitive transcranial magnetic stimulation (rTMS) in young subjects, Cappa et al[9] reported a selective facilitation during verb naming when the subjects received stimulation to the dorsolateral prefrontal cortex (DLPFC). The aim of this study was to assess whether the same procedure results in an improved performance in subjects with AD. Since lesion and imaging studies have supported the hypothesis of a central role of left prefrontal and parietal areas in verb processing, we predicted a selective improvement of action naming during the stimulation of the DLPFC.

METHODS

PATIENTS

Fifteen patients were consecutively recruited at the San Giovanni di Dio Fatebenefratelli Scientific Institute in Brescia, Italy. They were diagnosed as having probable AD based on criteria from the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Associations.[10]

All patients were native Italian speakers and underwent a detailed clinical and neurological evaluation. All patients were receiving cholinesterase inhibitor (donepezil hydrochloride or rivastigmine tartrate) therapy. None of them took memantine.

For each patient, a structural brain magnetic resonance image excluded major causes of cerebrovascular disease and white matter lesions. Magnetic resonance imaging did not show evidence of focal atrophy, lacunes, or severe subcortical vascular disease. All patients showed atrophy in the medial temporal and cortical temporoparietal regions,

and 4 of 15 presented with mild to moderate periventricular leukoaraiosis.

Patients with potentially confounding neurological and psychiatric disorders, clinically known hearing or vision impairment, or a history of alcohol abuse, psychosis, or major depression were not included in the study. None of the subjects had implanted metal objects or history of seizure. These exclusion criteria were based on keeping the stimulation as safe as possible.[11] Only patients with a mild to moderate form of cognitive decline were included (mean [SD] Mini-Mental State Examination[12] score, 17.8 [3.7]; mean [SD] age, 76.6 [6.0] years; mean [SD] education, 6.0 [2.0] years). The local Human Ethics Committee approved the protocol.

A baseline evaluation of naming abilities was performed. The stimuli used in the action-object picture-naming task were taken from the Center for Research in Language International Picture-Naming Project corpus,[13] which contains 795 black-and-white, 2-dimensional line drawings representing actions and objects. These items have been tested and normed in healthy and patient populations across 7 different international sites and languages. Items are coded for a number of variables known to influence naming difficulty. Among others, these are initial word frequency, age of acquisition, and picture imageability scores, which were tested to assess their influence on the participants' naming performance.

For this particular set of patients, we used a subset of 120 items from the original corpus. These were 60 actions and 60 objects. All the selected stimuli were high-imagery items. The nouns and verbs corresponding to the set of objects and actions were matched for word frequency and word length.[14] In this evaluation, patients with AD showed a worse performance in action (mean [SD], 65.31% [17%]) than in object (mean [SD], 77.86% [17%]) naming.

EXPERIMENTAL EVALUATION

Stimuli

For the rTMS task, we used a subset of 70 items from the original corpus, different from the 120 stimuli used for baseline testing. These were 35 actions and 35 objects. None of the actions included in the picture-naming task was associated with the objects. The nouns and verbs corresponding to the set of objects and actions were matched for target-word frequency and length. Ten of the items were assigned to a practice block (5 action and 5 objects); the remaining items were divided in 3 blocks designed for the 3 stimulation conditions. The frequency, length, and grammatical category (noun or verb) of the target word were counterbalanced in the experimental blocks. Visual complexity and imageability of the pictures were also matched between the 2 sets.

Procedure

Patients sat in front of a 17-inch monitor controlled by a personal computer running Presentation software (version 9.80; Neurobehavioral Systems, Albany, Calif, www.neurobs.com). The patient task was to name as fast as possible a picture presented on the monitor until the response. Verbal responses were recorded and digitized with the program GoldWave (version 5.12; GoldWave Inc, St John's, Newfoundland, www.goldwave.com) at 44.1 kHz. The responses were then analyzed offline for accuracy.

The experiment included 3 blocks corresponding to 3 stimulation sites: left DLPFC and right DLPFC and sham stimulation. Each block contained an equal number of objects and actions, presented in a random order, and the stimulation site (left, sham, or right rTMS) was counterbalanced. The stimulation site for the sham condition was on vertex (Cz in 10/20 electroencephalography system), but the coil was positioned perpendicular to the scalp, thus ensuring that no magnetic stimulation reached the brain during the sham condition. We localized the left and right DLPFCs on the basis of a reconstruction of cerebral cortex in the Talairach coordinate system using the SofTaxic Evolution navigator system (version 1.0; EMS srl, Bologna, Italy, www.emsmedical.net). The subjects wore a close-fitting skullcap, and using this system, we marked a stimulation site above Brodmann area 8 (Talairach coordinates, x=±35, y=24, and z=48, middle frontal gyrus, at about halfway between F3/4 and F7/8, respectively) on the skullcap. To stimulate the DLPFC, we used a figure-of-8 coil and placed the anterior end of the junction of the 2 coil wings above the marked point. We delivered rTMS for 600 milliseconds from the onset of the visual stimulus, using a train of 10 pulses with a frequency of 20 Hz. We decided to stimulate for the first 600 milliseconds with a frequency of 20 Hz because we were looking for a facilitation effect, as reported in the previous study.[9] The stimulation intensity used during the experiment was set at 90% of each subject's motor threshold. These parameters are in line with safety recommendations for rTMS,[11] and none of the patients showed adverse effects of stimulation.

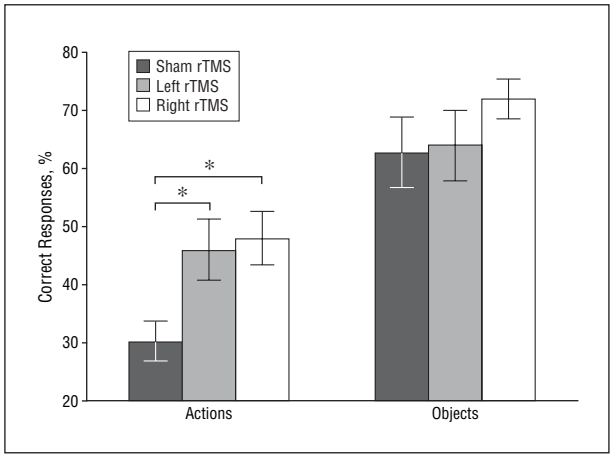

Figure. The graphs show the percentage of correct naming, divided by stimulus category (action vs object), in patients with Alzheimer disease for different sites of repetitive transcranial magnetic stimulation (rTMS).*$P<.05$.

RESULTS

The **Figure** shows the mean naming scores in each of the stimulation conditions, plotted separately for objects and actions. Naming ability, measured as the performance in action and object naming in the sham condition, was not correlated with the raw Mini-Mental State Examination score ($P>.05$) or education ($P>.05$). The results were analyzed with repeated-measures analysis of variance with stimulus category (action and object) and site (sham and left and right rTMS) as factors. This indicated significant effects of both stimulus category ($F_{1,14}=50.24$; $P<.001$) and site ($F_{2,28}=8.16$; $P=.001$), as well as a stimulus category × site interaction ($F_{2,28}=4.0$; $P=.02$).

Post hoc analysis (with Bonferroni correction) revealed that for actions, naming performance was better during stimulation of both the left ($P<.001$) and right DLPFC ($P<.001$) compared with sham stimulation. However, this was not true for objects, where performance did not differ significantly between conditions. The improvement in action naming following rTMS to both the left and right DLPFC was present in each of the 15 subjects.

COMMENT

The present findings provide direct evidence for a causal role of the DLPFC in action naming. The same procedure, which in young control subjects shortened naming latency, resulted in an increased number of correct responses in patients with anomic AD. This suggests that the failure to observe an effect on performance accuracy in normal controls was due to a ceiling effect.[9] While the rTMS effect in normal controls was limited to the left-sided stimulation, the facilitation was bilateral in patients with AD. The presence of a bilateral facilitation effect in patients with AD could be attributed to the presence of a compensatory mechanism based on the recruitment of right hemispheric resources to support residual naming performance. It has been shown that early in the course of the dementia, the brains of patients with AD retain a significant degree of functional plasticity.[15,16] A shift from unilateral to bihemispheric engagement has been repeatedly observed in healthy aging as well as in dementia in the case of memory tasks and has been suggested to play a compensatory role.[17,18] In the case of language, the right hemisphere has been traditionally assigned a crucial role in supporting performance after left hemispheric damage.[19]

Transcranial magnetic stimulation can transiently increase or decrease cortical excitability,[20] depending on the stimulation frequency (inhibition ≤ 1 Hz vs facilitation ≥ 5 Hz). This possibility has generated interest in experiments aiming to improve deficits in the cognitive domain,[21] as well as in clinical applications in the field of neuropsychiatry (eg, treatment of depression). While the neurophysiological mechanisms responsible for rTMS-induced facilitation remain essentially unknown, it has been shown that transcranial magnetic stimulation can influence the activity of brain centers distant from the stimulated site, presumably via cortico-cortical connections.[22] The present findings may reflect a transcranial magnetic stimulation–induced modulation, or even a rearrangement of synaptic efficiency within the language network. Repetitive transcranial magnetic stimulation may be worth testing as a novel treatment approach for language deficits, based on the modulation of a distributed, bihemispheric language network.

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