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Phonemic fluency improved after inhibitory transcranial magnetic stimulation in a case of chronic aphasia

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Twenty-six months after a left hemispheric ischemic stroke an aphasic patient showed a significant improvement in verbal fluency following ten daily sessions of inhibitory 1 Hz repetitive transcranial magnetic stimulation over the right cortex homologous to the Broca's area.

No improvement was observed for other linguistic functions or for executive ones. Results confirm the segregation of neural circuitries subtending phonemic and semantic fluency and suggest a selective usefulness of the repetitive transcranial magnetic stimulation treatment. *International Journal of Rehabilitation Research* 00:000–000 Copyright © 2018 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Aphasia is characterized by the partial or total loss of verbal communication because of brain hemispheric lesions. It may cause deficits in word production and/or comprehension. Almost invariably the left hemisphere is affected. Anomic aphasia is one of the milder forms of this syndrome and, although it may appear as isolated, it typically represents the highest attainable level of recovery in more severe forms of aphasia. Usually patients show difficulties recalling words and frequently use circumlocutions. They adopt protracted pauses in oral speaking. This behavior eventually leads to a poor content of verbal output. In recent years, a growing interest has developed in noninvasive brain stimulation techniques, such as repetitive transcranial magnetic stimulation (rTMS). These were applied to the treatment of a variety of psychiatric and neurological conditions, including aphasia. In unilateral brain lesions, both the affected and the unaffected hemispheres have been targeted. Studies with functional MRI suggest that hyperactivity in the right (contralesional) perisylvian regions, leading to interhemispheric inhibition, is associated with persistent deficits in nonfluent aphasia (Naeser *et al.*, 2004). Consistent with this perspective, downregulating the right inferior frontal gyrus by inhibitory 1-Hz rTMS was found to be associated with amelioration of various aphasic symptoms (Lefaucheur, 2006; Martin *et al.*, 2009) both in subacute and in chronic patients. In this study, a chronic anomic patient was treated with low-frequency rTMS over the Broca's homologous area in an attempt to boost verbal fluency.

Patients and methods

Patient

The patient was a 64-year-old woman, university-educated, right-handed, whose mother tongue is Italian. She had a history of dyslipidemia. Twenty-three months before recruitment, she suffered from an ischemic stroke because of the occlusion of the left internal cerebral artery. She developed a sudden speech impairment and right-sided hemiplegia, and received urgent arterial fibrinolytic treatment leading to partial motor recovery. However, aphasia persisted. Brain computed tomography scan and MRI evidenced an ischemic lesion of the left basal ganglia, the periventricular white matter, and the temporal lobe.

Repetitive transcranial magnetic stimulation procedure

Nine months after the stroke a structural brain MRI exam was performed using a 1.5-T scanner (Siemens Magnetom Avanto, Erlangen, Germany) (Fig. 1).

The patient's brain MRI was fed into a SofTaxic Neuronavigation System, version 3.0 (*http://www.softaxic.com*; E.M.S., Bologna, Italy). On the right hemisphere, the area homologous to the Broca's area was identified as the target for inhibitory rTMS, as localized through a neuronavigation system with an optical tracking system (NDI Polaris Vicra; NDI International, Waterloo, Ontario, Canada).

rTMS was applied through a cooled angulated figure-of-eight coil (AFEC-02-100-C) connected to a Neuro-MS/D Therapeutic Variant magnetic stimulator (Neurosoft,

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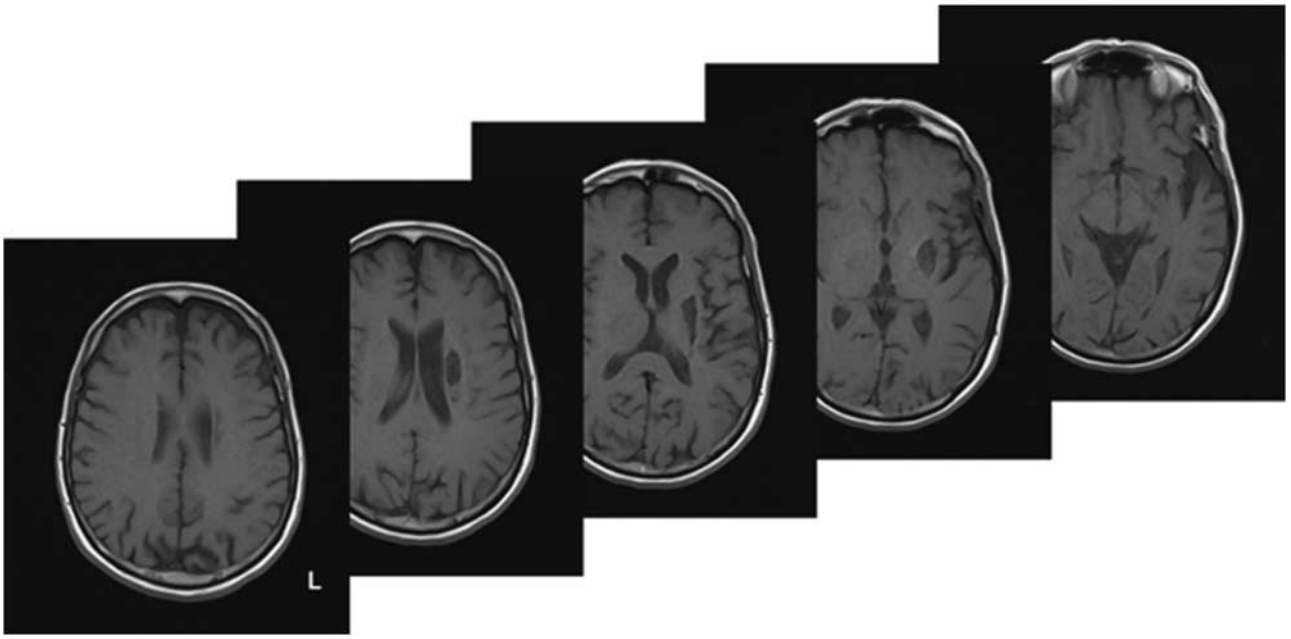
Fig. 1



Aphasic patient, woman, 64 years old. T1-weighted RM sequences 9 months after stroke. The ischemic lesion affected the left (L) basal ganglia and the temporal lobe.

Ivanovo, Russia), which provides repetitive biphasic pulses. The coil was held manually in contact with the patient's scalp and guided through the optical navigation system over the right hemisphere. Supraliminal stimuli (about 80% of the maximum stimulator output) were delivered to the primary motor cortex (M1 area) until the 'hot spot' inducing the highest surface electromyography potential from the first dorsal interosseous on the left hand could be localized. Then, the resting motor threshold, measured in terms of percent of maximum stimulator output, was looked for by gradually lowering the intensity of the stimulus in steps of 1–3% until evoking five motor-evoked potentials of at least 50 μV peak-to-peak amplitude out of 10 given stimuli. Then, a stimulus intensity of 90% resting motor threshold was used for repetitive stimulation. A train of 1-Hz rTMS pulses was delivered to the right Broca's homologue area. A total of 1200 pulses were applied in each session. The treatment spanned over 10 working days for two consecutive weeks. This rTMS protocol has been previously defined and adopted by Tsai *et al.* (2014), and it was carried out in accordance with the guidelines for safe use of rTMS (Rossi *et al.*, 2009).

Neuropsychological assessment

The patient underwent a cognitive evaluation 11 months after stroke (T1, baseline). Twenty-3 months after the stroke onset, before enrollment in this study, the patient underwent a brief neuropsychological re-evaluation by a trained neuropsychologist (April 2017, T2). Her language was fluent, but affected by frequent anomies and by an increased within-words latency. Language skills were then re-assessed immediately (T3) and 2 months (T4) after rTMS treatment. The battery included the Boston Naming Test (Kaplan *et al.*, 1983) and the Italian version of semantic and phonemic fluency tests (Novelli *et al.*, 1986).

To exclude a nonspecific effect of the stimulation, the executive functions were also tested through the Stroop test (Italian brief version of the Stroop test, Caffarra *et al.*, 2002). In this well-known test, the patient is requested to name the ink color of written words. Difficulties arise in suppressing the interference of the word when it is the name of a color different from the ink color. Tests scores (the higher the scores, the better the condition) of the cognitive evaluation given at T1 are shown in Table 1. The results of fluency, denomination, and Stroop tests, both at baseline and in subsequent assessments, are reported in Table 2.

Statistics: measuring change

The goal of the present study was to measure changes in performances after rTMS stimulation. The minimal real difference (MRD) was adopted as a threshold to define a significant change. This value represents the minimum individual change exceeding the one expected by chance alone at a given confidence level. The MRD is an index of reliability of the measurement itself determined in a previous 'generalizability' study and thus irrespective of the sample at hand (Roebroeck *et al.*, 1993).

Table 1 Patient's cognitive evaluation at T1

	Range	Raw score	Adjusted score	Normative cutoff
Mini mental state examination	0–30	25	–	26
Esame neuropsicologico per l'afasia				
Word comprehension	0–20	19	18.4	18.4
Sentence comprehension	0–14	14	14	11.6
Token test	0–36	31	29.5	26.5
Sentence generation	18	10	8.25	6.25
Digit span	0–9	4	3.75	3.75
Progressive coloured matrix	0–36	20	19.5	18

Table 2 Tasks scores on subsequent assessments

	Months and time points after stroke			
Tests	11 T1	23 T2	24 T3	26 T4
Phonemic fluency	6	6	9	16
Semantic fluency	–	24	25	26
Boston Naming Test	41	41	43	42
Stroop – time[a]	34	41	59	51.5
Stroop – errors[a]	7.5	6	8	3.5

[a]Lower scores = better condition.

The following formula was applied (see Tesio, 2012 for details):

$$\mathrm{MRD} = \text{ƶ} \times \mathrm{SEP},$$

where ƶ = normal SD, here 1.96 for the common 95% confidence limits and SEP = SE of prediction = joint $\mathrm{SD} \times (1 - r^2)^{0.5}$.

Here, r stands for a test–retest reliability index. Both the SD and r were taken from the literature on test–retest studies, whenever possible. Spearman's correlation was applied for both fluency tasks (Novelli *et al.*, 1986) and Boston Naming Test (Flanagan and Jackson, 1997). The MRD for the Stroop test could not be estimated, given that no test–retest indexes were found in the literature.

Ethics

The study addressed the principles of the Helsinki declaration for medical research involving human participants (World Medical Association, 2013). Oral informed consent was obtained, formally documented, and witnessed. Safety guidelines were followed (Rossi *et al.*, 2009). No Ethic Committee was involved for two reasons. First, rTMS is adopted as a routine treatment for cognitive deficits in selected cases at the research hospital where the study was carried out. Second, again as per the Helsinki declaration's principles, in this individual case, an unproven intervention was deemed to 'offer hope of re-establishing health or alleviating suffering'.

Results

No adverse events were recorded. As can be found in Table 2, the phonemic fluency score is stable between T1 and T2 (six words), but increases slightly immediately after rTMS (T3, nine words). Two months after treatment, the score improved significantly with respect to the pretreatment values (T4, 10 more words, well beyond the MRD value of 8.20, Table 3). By contrast, denomination and semantic fluency did not show any significant change. Although no MRD is available, it appears that the performance on the Stroop test did not show any trend toward improvement.

Table 3 Minimal real difference and score differences across time points

		Score difference		
Tests	MRD	T4 – T1	T4 – T2	T4 – T3
Phonemic fluency	8.20	10[a]	10[a]	7
Semantic fluency	7.45	–	2	1
Boston Naming Test	2.91	1	1	–1

MRD, minimal real difference.
[a]MRD trespassed.

Discussion

Phonemic and semantic fluency are ascribed to distinct brain areas (Szatkowska *et al.*, 2000). Observations have been reported (Baldo *et al.*, 2006) of two aphasic patients who showed a dissociation between phonemic and semantic fluency, related to different lesion sites (namely, the left frontal cortex for phonemic fluency and the left temporal cortex for semantic fluency). Moreover, a functional MRI study carried out on healthy individuals suggested that different portions of the left Broca's area are activated in either kind of verbal fluency tasks (Paulesu *et al.*, 1997). Along this line of research the present study seems to be the first suggesting that rTMS may selectively boost phonemic fluency in a chronic aphasic patient, thus representing a promising rehabilitation treatment. Albeit observed in a single case, the results discussed here can be considered statistically significant as long as the score changes exceeded the MRD threshold.

These results are in line with a controlled study on 44 healthy individuals (Smirni *et al.*, 2017), showing that rTMS over the right lateral cortex improved phonemic fluency more than sham stimulation. No other functions were tested. Interestingly, in the present study the rTMS treatment seemed to have no effect on the patient's performance on the Stroop test. Rather, some worsening could be observed immediately after the stimulation, suggesting a lower inhibitory control. Traditionally, both phonemic fluency and the Stroop test are considered valid indexes of the executive functions. However, a PET study showed that the Stroop test activates the caudal part of the anterior cingulate cortex in the left frontal lobe, whereas phonemic fluency tasks activate the left inferior frontal cortex and large parts of the left dorsolateral prefrontal cortex (Ravnkilde *et al.*, 2002). Thus, the difference in anatomic substrates may

explain why rTMS might lead to a selective improvement in fluency with no impact on the Stroop test.

In the patient studied here, fluency progressed 2 months after stimulation, in accordance with previous findings, suggesting that amelioration can appear and then increase even months after the stimulation is discontinued (Naeser *et al.*, 2005; Dammekens *et al.*, 2014). All considered, the present results seem to justify further research of rTMS as a rehabilitation treatment of fluency in aphasia.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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