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Prefrontalcortex rTMS enhances action naming in progressive non-fluent aphasia

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Background and purpose: Progressive non-fluent aphasia (PNFA) is a neurodegenerative disorder that is characterized by non-fluent speech with naming impairment and grammatical errors. It has been recently demonstrated that repetitive transcranial magnetic stimulation (rTMS) over the dorsolateral pre-frontal cortex (DLPFC) improves action naming in healthy subjects and in subjects with Alzheimer's disease.
Purpose: To investigate whether the modulation of DLPFC circuits by rTMS modifies naming performance in patients with PNFA.
Methods: Ten patients with a diagnosis of PNFA were enrolled. High-frequency rTMS was applied to the left and right DLPFC and the sham (i.e. placebo) condition during object and action naming. A subgroup of patients with semantic dementia was enrolled as a comparison group.
Results: A repeated-measure analysis of variance with stimulus site (sham, left and right rTMS) showed significant effects. Action-naming performances during stimulation of both the left and right DLPFC were better than during placebo stimulation. No facilitating effect of rTMS to the DLPFC on object naming was observed. In patients with a diagnosis of semantic dementia, no effect of stimulation was reported.
Conclusions: Our study demonstrated that rTMS improved action naming in subjects with PNFA, possibly due to the modulation of DLPFC pathways and a facilitation effect on lexical retrieval processes. Future studies on the potential of a rehabilitative protocol using rTMS applied to the DLPFC in this orphan disorder are required.

Introduction

Humans are highly dependent on language in their day-to-day functioning. As a result, language disorders are associated with substantial disability [1].

Progressive non-fluent aphasia (PNFA) is a neurodegenerative condition that presents in the presenium and belongs to the primary progressive aphasia spectrum that includes semantic dementia (SD) and logopenic progressive aphasia [2]. PNFA is characterized by a progressive effortful, non-fluent speech with grammatical errors and omissions [1,3] and naming impairment, with greater difficulty in naming actions than in naming objects [4]. Speech worsens gradually, and patients eventually become mute.

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The anatomical localization of PNFA is represented by focal anterior peri-Sylvian atrophy that involves the inferior, opercular and insular portions of the left frontal lobe and the left dorsolateral pre-frontal cortex (DLPFC) [2,5].

Progressive non-fluent aphasia is considered an orphan disorder because no evidence-based treatments are currently available to improve language performances or delay disease progression.

It has been recently demonstrated that repetitive transcranial magnetic stimulation (rTMS) is effective in modulating the excitability of the DLPFC circuits and in facilitating naming [6–10]. In particular online, high-frequency repetitive transcranial magnetic stimulation (rTMS) administered at appropriate time intervals reduces vocal reaction times (vRTs) for picture naming in healthy individuals [7,11] and improves the number of correct responses in patients with Alzheimer's disease [8,9]. Although the neuropsychological mechanisms responsible for rTMS-induced facilitation are still

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unclear, it has been postulated that rTMS may promote novel activity patterns within the affected functional brain networks [12].

Repetitive transcranial magnetic stimulation is thought to induce long-lasting changes in cortical excitability, depending on a number of variables, such as the frequency of stimulation, stimulus intensity, site of stimulation and number of applications. One of these parameters, the frequency of stimulation, is widely thought to be a critical determinant in the modification of the cortical response. Both high (>5 Hz) and low-frequency (≤ 1 Hz) rTMS have been employed, with the former mainly having an excitatory effect and the latter mainly having an inhibitory effect [13].

Deficits in action naming are the core feature in PNFA, which selectively involves DLPFC networks; therefore, it might be predicted that high-frequency rTMS of the DLPFC may be of help in efforts to improve action naming.

In this study, we used high-frequency rTMS to investigate whether the modulation of activity of the DLPFC could modify the naming performance in PNFA. To test the specificity of the rTMS effect on language impairment in patients with PNFA, a group of patients with SD was used as a comparison group.

Materials and methods

Subjects

Ten patients who fulfilled the current clinical criteria for PNFA [14–16] were recruited from the Centre for Ageing Brain and Neurodegenerative Disorders at the University of Brescia and from IRCCS Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy. Additionally, four patients with a diagnosis of SD were enrolled as a comparison group. Stringent exclusion criteria were applied as follows: (i) cerebrovascular disorders, hydrocephalus and intra-cranial mass, documented by MRI; (ii) a history of traumatic brain injury or another neurological disease; (iii) significant medical problems (e.g. poorly controlled diabetes or hypertension or cancer within the past 5 years); (iv) major depressive disorder, bipolar disorder, schizophrenia, substance use disorder or mental retardation according to the criteria of the DSM-IV; and (v) implanted metal objects or a history of seizures or any contraindication for rTMS [17].

The inclusion criteria were as follows: (i) only patients with mild to moderate language impairment (Aachener Aphasie Test subtests with no severe impairment) entered the study, and (ii) patients had to be observed for at least 1 year after enrolment, and the diagnosis had to be confirmed.

Of the ten patients with PNFA who were included in the study, eight were women and two were men. The mean ($\pm$standard deviation) age of the patients with PNFA was 69.1 ($\pm$9.3) years, and the mean age at onset was 66.8 ($\pm$9.1) years. A positive family history for dementia was recorded in 40% of cases. On average, patients had received 8.1 years ($\pm$4.1) of formal education. Two patients of 10 carried the *PGRN Thr272fs* mutation.

Four patients with SD (one woman and three men) were considered as the comparison group to test the specificity of rTMS on language disturbances in patients with primary progressive aphasia. For patients with SD, the mean age was 68.2 ($\pm$10.1) years, and the mean age at onset was 66.2 years ($\pm$12.7).

These two groups did not differ significantly with regard to age [$t(12) = 0.19$, $P > 0.05$] or education [$t(12) = 0.06, P > 0.05$]. PNFA was diagnosed when the first symptom was an isolated disorder of expressive language, whilst other aspects of cognition and daily living functions were relatively well preserved. PNFA was characterized by a reduction in the rate of speech with apraxia of speech, speech sound errors and agrammatism and relatively well-preserved single-word comprehension.

Semantic dementia was defined by a prominent single-word comprehension disorder (e.g. an impaired understanding of word meaning and/or object identity) and difficulty with confrontation naming.

The diagnostic assessment involved a review of the full medical history, a semi-structured neurological examination, a neuropsychological evaluation and a brain MRI study. All subjects underwent a brain MRI scan performed at 1.5 T Siemens (Symphony, Siemens, Erlangen, Germany) along with a 99 mTc-ECD SPEscan. Patients were administered an intravenous injection of 1110 MBq ^{99m}Tc-ECD (ethylcysteinate dimer, Neurolite, Bristol-Myers Squibb Pharma) whilst resting and were imaged using a dual-head rotating gamma camera (VG Millenium GE) fitted with a low-energy, high-resolution collimator, 30 min after the intravenous injection of ^{99m}Tc-ECD, as previously described (GE General Eletric Company, Easton Turnpike Fairfield, CT, USA).

Statistical Parametric Mapping (SPM2; Welcome Department of Cognitive Neurology, University College, London) and Matlab 6.1 (Mathworks Inc., Sherborn, MA, USA) were used for image pre-processing. Images were spatially normalized to a reference stereotactic template [Montreal Neurological Institute (MNI)] and smoothed by a Gaussian kernel of $8 \times 8 \times 8$ mm FWHM.

Single-photon emission computed tomography (SPECT) data analysis was performed by researchers who were blinded to the clinical data.

Genetic sequencing of *Microtubule-Associated Protein Tau* and *Progranulin* was also performed. The work was conducted in accordance with local clinical research regulations and conformed to the Helsinki Declaration. The study was approved by the local ethics committee, and informed consent was obtained from all participants prior to the beginning of the experiment. All of the included subjects were right-handed.

Baseline cognitive assessment included screening tests for dementia (MMSE; Frontotemporal Lobar Degeneration modified Clinical Dementia Rating Scale, FTLD-modified CDR [18–20]) and neuropsychological tests for non-verbal reasoning (Raven Coloured Progressive Matrices), verbal fluency (phonemic and semantic), long-term memory (Story recall; Rey-Osterrieth Complex Figure, Recall), constructional and visuospatial abilities (Rey-Osterrieth Complex Figure, Copy) and attention and executive functions (Trial-Making Tests A and B). All the tests were administered and scored according to standard procedures [21]. The results of the baseline cognitive assessment are reported in Table 1. In addition, language functions were formally assessed with the full Italian version of the Aachener Aphasie Test (AAT).

Table 1 Neuropsychological assessment in patients with progressive non-fluent aphasia (PNFA) and semantic dementia (SD)

	PNFA (n = 10)	SD (n = 4)	Cut-offs
Screening for dementia			
MMSE	**18.0 (3.7)**	**22.9 (5.3)**	> 24
FTLD-modified CDR	4.0 (2.3)	3.0 (0.6)	
Non-verbal reasoning			
Raven Coloured Progressive Matrices	17.8 (8.8)	26.3 (7.1)	> 17.5
Memory			
Short Story, recall	**7.2 (2.8)**	**6.8 (3.0)**	> 7.5
Rey-Osterrieth Complex Figure, Recall	**8.9 (3.9)**	**8.0 (7.6)**	> 9.46
Digit Span	4.0 (0.3)	4.2 (0.3)	> 3.75
Language			
Fluency, phonemic	**12.6 (6.4)**	16.2 (11.4)	> 16
Fluency, semantic	**21.2 (6.4)**	**14.2 (9.9)**	> 24
Constructional and visuospatial abilities			
Rey-Osterrieth Complex Figure, Copy	**13.2 (8.9)**	31.3 (1.8)	> 28.87
Executive functions			
Trail-Making Test A	**257.5 (194.2)**	**95.0 (93.8)**	< 93.0
Trail-Making Test B	**418.8 (28.0)**	274.0 (99.1)	< 282.0

Results corrected for age and schooling. Cut-off scores referred to Italian normative data. MMSE, Mini-Mental State Examination. Standard deviation between brackets. Bold data refer to pathological scores.

The neuropsychological data indicated that patients with PNFA showed impairment performance in all the assessed functions and preserved verbal short-term memory.

Patients with SD obtained low scores on the semantic fluency test, long-term memory test and attention task.

Language information about the patients with PNFA and SD is summarized in Table 2, along with the patients' scores on the four tasks (repetition, naming, writing and comprehension) of the AAT [22]. Formal speech evaluation revealed marked deficits in repetition, writing, naming and comprehension in patients with PNFA, whereas the SD revealed difficulties with repetition, naming and comprehension and a preservation of the ability to create a written record of dictation.

Stimuli

The stimuli used in the action and object naming tasks were taken from the Center for Research in Language-International Picture Naming Project corpus CRL-IPNP [23]. These items have been tested and normalized in healthy and patient populations across seven different international sites and languages.

We used 84 items (42 actions and 42 objects) selected from a previous experiment in healthy ageing subjects [11]. None of the action stimuli included in the task were associated with the objects selected. The nouns and verbs corresponding to the set of objects and actions used were matched for target-word frequency and length. The frequency, length of the target word, visual complexity and imageability of the pictures were matched and counterbalanced between the experimental blocks. The items were divided into three blocks that were designed to represent the three stimulation conditions (left DLPFC, right DLPFC and placebo stimulation). The frequencies and lengths of the target words were counterbalanced in the experimental blocks.

Table 2 Aachener Aphasie Test (AAT) subtests in patients with progressive non-fluent aphasia (PNFA) and semantic dementia (SD)

AAT subtests	Mean scores ± standard deviation		Cut-offs
Token test (errors)	PNFA	**21.0/50 ± 12.0**	< 7
	SD	**18.6/50 ± 9.0**	
Repetition	PNFA	**124.9/150 ± 10.9**	> 142
	SD	**133.0/150 ± 6.5**	
Writing	PNFA	**57.0/90 ± 18.1**	> 81
	SD	83.6/90 ± 5.8	
Naming	PNFA	**86.5/120 ± 19.0**	> 104
	SD	**73.3/120 ± 8.0**	
Comprehension	PNFA	**93.4/120 ± 6.9**	> 108
	SD	**91.0/120 ± 14.7**	

Bold data refer to pathological scores.

The visual complexity and imageability of the pictures were also matched between blocks. Ten additional objects and actions were used for a practice block (five actions and five objects).

Procedure

Subjects sat in front of a 17-inch monitor that was controlled by a personal computer running Presentation software (http://www.neurobs.com). The trial structure is illustrated in Fig. 1. After a frame that indicated the category of the stimulus to the subject ('ACTION' or 'OBJECT'), a warning sound 50 ms in duration was presented at the onset of a centrally located fixation cross that was present for 1000 ms. After disappearance of the fixation cross, the stimulus was presented and remained on the screen for 1000 ms. A blank screen then followed for a time period varying from 4000 to 5000 ms. The subject's task was to name, as rapidly as possible, the stimuli that appeared on the computer screen. Vocal responses were recorded and digitized at 44.1 kHz, using the program GoldWave (V. 5.12; http://www.goldwave.com). The responses were then analysed offline for accuracy and vRTs. The vRT analysis was performed only on correct responses that were <2 standard deviations from the mean RT (3.3% of the responses were eliminated). In the case of uncertain initial vocalization, the start of the response was considered at the beginning of the correct complete response. For each stimulus, we calculated the mean response accuracy percentage and the mean vRTs.

The three stimulation sites (the left and right DLPFC and placebo stimulation) and the block orders were counterbalanced across subjects. For the placebo control condition, a 3-cm-thick piece of plywood was applied to the coil [24] so that no magnetic fields reached the cortex. For the placebo condition, the junction of the two-coil wings was placed over the vertex (CZ in the EEG 10/20 international system) using the same procedure as is used for the real rTMS. For left and right DLPFC, the Talairach coordinates of the cortical sites underlying the coil were estimated for each subject using the SofTaxic Evolution Navigator system (V. 2.0; http://www.emsmedical.net). This system was used to identify the stimulation site on the scalp above the DLPFC (Talairach coordinates $X = \pm 35$, $Y = 24$, $Z = 48$, middle frontal), as in previous studies [8,9,11]. To stimulate the DLPFC, we used a 70-mm figure-eight cooled coil and placed the junction of the two-coil wings above the target point. rTMS was delivered for 500 ms from the onset of the visual stimulus using a frequency of 20 Hz. The stimulation intensity used during the experiment was set at 90% of each subject's resting motor threshold. These parameters are consistent with the safety recommendations for rTMS [17], and none of the subjects showed or reported any side effects of stimulation.

The coil position and the specific brain areas of hypoperfusion for representative patients with PNFA and SD are reported in Fig. 2.

The applied procedure was exactly the same as was used in a recent study on healthy older adults [11] that showed that the naming latency for actions was shortened after stimulation of the left and right DLPFC compared with application of the sham stimulation (actions: left 963 ± 20, right 976 ± 40, sham 1078 ± 36). Stimulation was not observed to have any effect on the accuracy of naming in this healthy group. Interestingly, the older adults included in this previously published report and the patients with PNFA tested in the present work did not differ significantly with regard to age [$t(22) = 0.26$, $P > 0.05$].

Results

We analysed both accuracy and vRTs using a repeated-measure ANOVA for each patient group (PNFA or SD) as the between-subject factor and site (sham, left and right) and stimulus type (actions or objects) as within-subject factors. *Post hoc* analyses (Fisher's least significant difference, LSD test) were performed. The results are expressed as the mean ± standard deviation or percentage, as indicated. Statistical significance was set at $P \leq 0.05$.

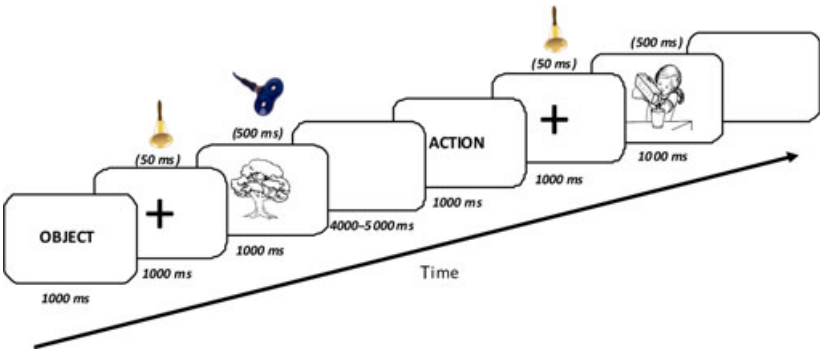

Figure 1 Schematic representation of the essential steps of the study design (see Methods for details).

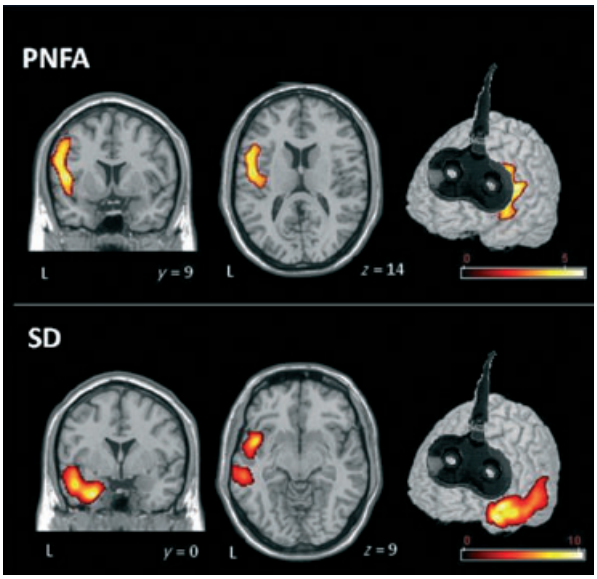

Figure 2 The figure represents reductions in regional cerebral perfusion (SPECT) and coil position, superimposed on 3D brain templates, in representative patients with Progressive non-fluent aphasia and semantic dementia compared with age-matched controls (n = 14) (Statistical Parametric Mapping, SPM8 analysis).The threshold was set at $P < 0.005$, uncorrected. L, left; R, right. The areas indicated in shades of yellow and red both indicate areas of hypoperfusion; yellow represents areas of maximum hypoperfusion.

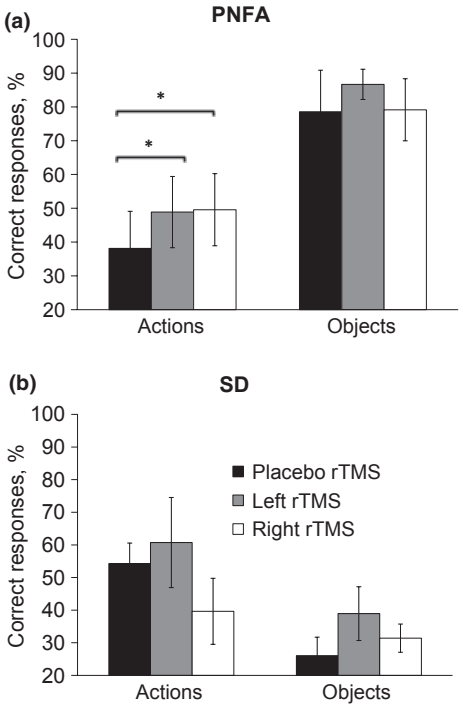

Figure 3 The mean naming performance during left or right dorsolateral pre-frontal cortex stimulation and placebo stimulation in patients with Progressive non-fluent aphasia (a) and semantic dementia (b). *P-value < 0.05.

Accuracy

The effect of rTMS of the DLPFC on object and action naming was analysed. In PNFA subjects, the repeated-measure ANOVA with site (placebo, left and right rTMS) as a factor demonstrated significant effects of stimulation [$F(2, 18) = 3.66$, $P = 0.04$]. Figure 3 shows the mean naming accuracy scores in each of the stimulation conditions for objects and actions.

Action-naming performance during left (mean = 48.88 ± 6.3, $P = 0.036$) and right (49.57 ± 6.8, $P = 0.027$) DLPFC stimulation was enhanced in comparison with that observed during placebo stimulation (38.15 ± 6.9). Conversely, object naming performance did not differ significantly between the conditions (left, 86.68 ± 2.7; right, 79.14 ± 5.8; placebo stimulation, 78.57 ± 7.8).

The single-subject scores showed that 50% of patients with PNFA demonstrated bilateral effects in action-naming improvement, but 30% of the patients reported a selective right DLPFC effect, and 20% showed an improvement only after stimulation of the left DLPFC. The difference in individual scores for action naming during left and right DLPFC stimulation, as compared with placebo stimulation, are reported in Fig. 4.

In patients with SD, no facilitating effect of stimulation of the DLPFC on object and action naming was observed. In particular, no facilitation effect on action naming by stimulation of the right (39.60 ± 20.2) or the left (60.72 ± 27.6) DLPFC compared with the placebo condition (54.30 ± 12.6) was shown. Moreover, object naming performance did not differ significantly between the conditions (left, 38.93 ± 8.2; right, 31.43 ± 4.3; placebo stimulation, 54.28 ± 6.3).

Vocal reaction times

The analysis of vRTs did not yield significant results in patients with PNFA (actions: left 1653 ± 508, right 1678 ± 460, sham 1490 ± 448; objects: left 1325 ± 437, right 1332 ± 328, sham 1208 ± 299) or in patients with SD (actions: left 2833 ± 1106, right 3138 ± 1521, sham 3084 ± 1524; objects: left 2334 ± 896, right 4176 ± 2709, sham 2916 ± 868).

Discussion

In this work, we suggested that rTMS of the DLPFC had a facilitating effect on action naming performances in patients with PNFA. This was selectively observed in patients with PNFA and was absent in another primary

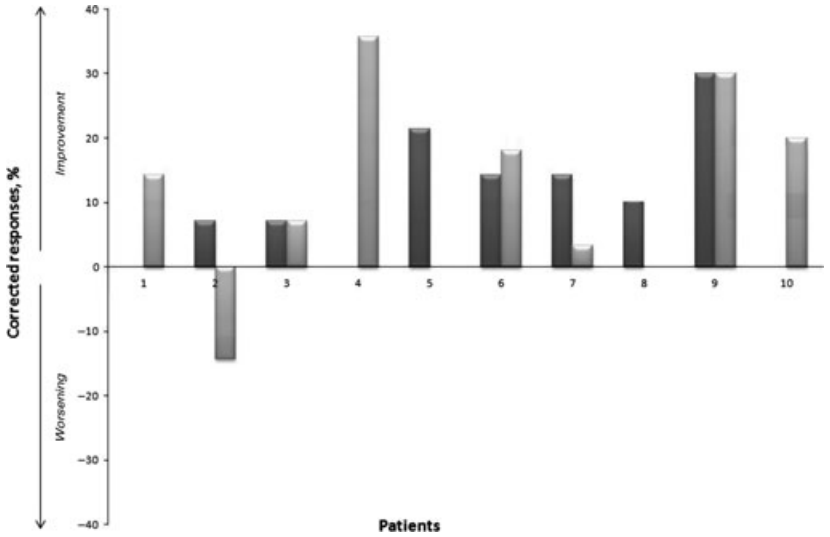

Figure 4 Single-subject naming performance during left (black) or right (grey) dorsolateral pre-frontal cortex stimulation as compared with placebo stimulation. An improvement or worsening of the percentage of correct responses with respect to placebo stimulation is reported for each subject. The presence of two columns denotes bilateral effects, whilst one column represents a right or left effect (the absence of one of the columns means no effect for that type of stimulation in that patient).

progressive aphasia (namely, SD). Moreover, an improvement in action naming was observed for bilateral stimulation of the DLPFC and was not limited to the stimulation of language-associated areas on the dominant side. A crucial role in supporting linguistic performance after left hemispheric damage has been traditionally assigned to the right hemisphere. Functional reorganization of the language system has already been described in primary progressive aphasia [25]. Functional neuroimaging in patients with PNFA revealed changes in language network connectivity rather than hypoactivity [26,27]. In this present study, we showed inter-individual differences in the effects induced by rTMS (bilateral, only right or only left effects). Several studies have demonstrated anatomical and functional interindividual differences during cognitive tasks [28–32]. A useful avenue in developing future interventions might be the combination of functional neuroimaging and non-invasive brain stimulation (rTMS or tDCS) to test treatment-specific changes in activation and connectivity. This method might provide additional insight into the language network and may also facilitate the development of innovative therapeutic strategies for patients with PNFA. Future research should employ larger samples of patients and long-term follow-up to maintain the induced effects.

Furthermore, a facilitation effect after right or left DLPFC rTMS has recently been reported in older adults. The effect was comparable with that observed in our patients with PNFA [11]. In this recent paper, a shortening in vRTs was reported; in the present work, rTMS induced an increase in accuracy amongst patients with PNFA.

Moreover, our data are consistent with a previous work that reported an improvement in action-naming performance following left rTMS in a single PNFA case study [33]. The authors observed a significant and lasting improvement in action production following the application of high-frequency rTMS over the left frontal cortex vs. baseline and placebo conditions.

Progressive non-fluent aphasia is characterized by a more severe impairment in action retrieval than in object naming [34,35].

The observation of a severe impairment in verb retrieval in the case of PNFA is not unexpected. This variant is associated with a clinical picture that is reminiscent of Broca's aphasia and reflects prominent pathological involvement of the anterior language areas. Hillis *et al.* [35] reported a detailed investigation of action naming in a large sample of patients with this condition. They showed that the disorder is particularly severe in the oral modality, suggesting an impairment of modality-specific lexical representations. This is in accordance with the selective atrophy of left pre-frontal cortex that occurs in PNFA [2].

It is interesting to note that the neurological correlates of action naming impairment may also be relevant for the interpretation of related cognitive mechanisms. Relevant hypotheses include the possible relationship between verb-processing impairments and grammatical disorders, which are typically associated with frontal

damage [36], a link with executive dysfunction [37] and the relationship between verbs and action content.

Therefore, the improvement in action naming observed in the present study might be due to either specific stimulation of the DLPFC and its selective function in the naming of actions or to the baseline high proficiency in object naming, which did not permit any further improvement by rTMS.

The improved performances observed after DLPFC stimulation may reflect a facilitation of lexical retrieval processes because the naming disorder in PNFA is likely due to defective access rather than to the loss of semantic knowledge. Accordingly, we failed to observe rTMS facilitation during naming amongst patients with SD in whom semantic representations had deteriorated [35,38,39].

Taken together, these results support the hypothesis of a specific role of rTMS in access deficits. Several studies have demonstrated that an action-naming deficit in PNFA reflects inefficient access to semantic knowledge rather than a true loss of semantic representations [35]. The improvement in PNFA patient performance observed in the present study may reflect the facilitation of lexical retrieval processes, suggesting that the naming disorder in patients with PNFA is owing to defective access rather than to a loss of semantic representation [39]. The lack of an rTMS effect in patients with SD, in which semantic representations are considered to be degraded, would be in line with this hypothesis [40].

Finally, in the present study, we investigated facilitation effects by stimulating either the left or the right DLPFC. An improvement in action-naming performances after right DLPFC rTMS, beyond the expected effect of the stimulation to the left side, could be attributed to a compensatory mechanism based on the recruitment of right-hemispheric resources to maintain task performance in patients with PNFA. These findings are consistent with recent results obtained in healthy elderly and patients with Alzheimer's disease, in which stimulation of both DLPFCs improved naming more than did placebo stimulation [8,9,11].

The basis of the facilitative effects of rTMS on lexical retrieval remains unclear. High-frequency stimulation, as applied in the present work, results mainly in excitatory changes [13]. rTMS influences the activity of the brain centres close to and distant from the stimulated site, which may be due to strengthening of the synaptic activity of the surviving neurons in the stimulated network [41]. One 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 [12].

Therefore, transcranial magnetic stimulation–induced modulation might explain the beneficial results obtained in patients with PNFA and suggest that rTMS may produce a modulation, or even a rearrangement, of synaptic efficiency within a given network, which would in turn lead to more effective processing [42].

The major limitation in our study was the number of patients. The results reported here might suggest new possible therapeutic approaches in PNFA. The present preliminary results highlight the improvements induced by a single session of rTMS. Further studies are needed to conclusively demonstrate the therapeutic potential of the induction of long-term neuromodulatory effects using brain stimulation. Indeed, in Alzheimer's disease, it has been demonstrated previously that rTMS applied to the left DLPFC for 2 weeks consecutively provides persistent beneficial effects with respect to cognitive performance [43]. The use of repeated rTMS sessions could be used to investigate the long-term effects of the stimulation, which are particularly interesting in neurodegenerative patients. In light of the present findings, the same protocol might be applied to patients with PNFA to elucidate the long-term improvement in naming performance.

We acknowledge that these are preliminary findings. However, if confirmed in larger samples, these results could highlight the potential role of rTMS of the DLPFC in the modulation and facilitation of language performance in PNFA. They hold considerable promise for the design of new rehabilitation strategies in patients with neurodegenerative disease. Future studies to evaluate the utility of rTMS as a novel rehabilitation approach in PNFA are required.

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Disclosure of Conflict of Interest

The authors declare no financial or other conflict of interests.

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