Brain Stimulation 6 (2013) 545–553

Contents lists available at SciVerse ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

Repetitive Deep Transcranial Magnetic Stimulation Improves Verbal Fluency and Written Language in a Patient with Primary Progressive Aphasia-Logopenic Variant (LPPA)

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ARTICLE INFO

Article history:
Received 21 March 2012
Received in revised form
25 September 2012
Accepted 30 September 2012
Available online 2 November 2012

Keywords:
Repetitive transcranial magnetic stimulation (rTMS)
H-coil
Primary progressive aphasia logopenic variant (LPPA)
Dorsolateral prefrontal cortex (DLPFC)

ABSTRACT

Background: To date, no therapies are available for the logopenic variant of primary progressive aphasia (LPPA). Even though deep repetitive transcranial magnetic stimulation (rTMS) may improve cognitive functions in some neurodegenerative disorders, no previous studies investigated its effects in patients with LPPA.
Objective: Our aim was to investigate the effects on cognitive function of high frequency rTMS (hf-rTMS) delivered over the left dorso-lateral prefrontal cortex (DLPFC) through a coil designed for deep rTMS, compared to a SHAM stimulation, in a right-handed patient with LPPA.
Methods: The patient presented a progressive language impairment (phonological errors in speech and naming, impaired single word retrieval and sentences repetition) and predominant left perisylvian atrophy and hypoperfusion. He received four stimulation cycles (two REAL and two SHAM) each of whom lasted 20 min for 5 consecutive days. Patient's performances in frontal, visuo-spatial and linguistic tasks were evaluated before and after each stimulation session. Test scores after REAL were compared with those obtained at baseline and after SHAM.
Results: We found a temporary and highly significant improvement in the linguistic skills (both oral and written tasks) but not in the other cognitive domains tested, after REAL, but not SHAM stimulations.
Discussion: Hf-rTMS delivered over the DLPFC could improve language in LPPA by enhancing long-term potentiation and synaptic plasticity within the stimulated and interconnected areas involved in language network. Our findings might prompt future researches into the feasibility and efficacy of deep hf-rTMS as a therapeutic tool in progressive aphasia syndromes and other neurodegenerative disorders.

Background

Logopenic primary progressive aphasia (LPPA), also known as the logopenic variant of primary progressive aphasia (PPA), is the most recently described neurodegenerative disorder in the ambit of the slowly progressive aphasia syndromes [1,2]. Impaired single word retrieval and sentences repetition primarily due to phonologic short-term memory deficit [3], represent the core features of LPPA. Anatomically, brain atrophy accompanying LPPA has a perisylvian distribution, however a left temporo-parietal correlate has been emphasized in many structural and metabolic neuroimaging studies [2,4–6]. White matter changes within the left superior longitudinal fasciculus (mainly its temporo-parietal tract) and to a lesser extent in the arcuate fasciculus (AF) have also been described in LPPA even after gray matter atrophy is taken into account [7].

Previous studies suggested that LPPA is associated with a relatively high rate of patho-biological abnormalities consistent with Alzheimer's disease (AD) [4,8,9].

The limited benefit of linguistic rehabilitation in all PPA variants and the lack of pharmacologic therapies for these progressively worsening neurodegenerative disorders, impose the need for further research of alternative therapeutic strategies.

Financial disclosure and conflicts of interest: Dr. Alessandro Trebbastoni reports no biomedical financial interests or potential conflicts of interest. Dr. Ruggero Raccah serves as a scientific consultant for ATID (Advanced Technologies Innovation Distribution), which is Brainsway's distributor for Italy. Prof. Carlo de Lena reports no biomedical financial interests or potential conflicts of interest. Prof. Abraham Zangen is a key inventor of H-coils which were patented by the NIH and been licensed to Brainsway Inc., a company that produces these coils. Prof. Zangen serves as a consultant for and has financial interest in Brainsway Inc. Prof. Maurizio Inghilleri reports no biomedical financial interests or potential conflicts of interest.

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http://dx.doi.org/10.1016/j.brs.2012.09.014

Table 1
Neuropsychological test scores of the patient at baseline and at the end of the study.

Tests	Scores	
	Baseline	End of study
Mini-mental state examination (MMSE)	26	25
Instrumental activities of daily living scale (IADLs)	5	5
Activities of daily living scale (ADLs)	6	6
Clock drawing test (CDT)	2	2
Frontal assessment battery (FAB)	9.7[a]	9.7[a]
Verbal phonemic fluency test (FAS)	8[a]	6[a]
Bucco-lingual praxis test (BL-A)	19	–
Ideo-motor praxis test (IM-A)	19	–
Rey's 15-item auditory verbal memory test-learning	21.7[a]	–
Rey's 15-item auditory verbal memory test-recall	5	–
Visual search	31.7	–
Digit span	5.75	–
Corsi block-tapping test (CBT)	3.5[a]	–
Rey's picture-copy	22[a]	–
Rey's picture-recall	3.2[a]	–
Token test	21.5[a]	–
Boston naming test (BNT)	54	–

[a] Abnormal values, adjusted for age and education.

In the last decades many studies employed repetitive transcranial magnetic stimulation (rTMS) as a therapeutic approach to asses cognitive functions improvements in patients with neuropsychiatric disorders [10–12]. rTMS is a non-invasive technique used to stimulate the brain. This technique is based on the creation of predetermined magnetic fields which alternate rapidly. The magnetic fields cause electrical induction in the brain cells that consequently induce action potentials. Magnetic stimulation of specific brain areas is generated by discharging high intensity alternating currents into a coil positioned on the patient's scalp. High frequency rTMS (hf-rTMS) can positively influence neuronal networks by inducing long-lasting effects on neuronal excitability and synaptic plasticity [13–15] in the stimulated areas and interconnected brain regions [16–20].

A recent meta-analysis of publications about the effect of hf-rTMS on cognitive function [10] found interesting data supporting improvement in some cognitive domain. Several studies analyzed changes in cognitive performances after hf-rTMS in Alzheimer's disease (AD) [11,12,21–25] or in elderly patients with subjective memory complaints [26], but only one case report on a PPA patient has been reported in the literature [27]. Many of these previous works described improvements on verbs productions [27], naming [21,22] and auditory sentence comprehension [23] after delivering hf-rTMS over the left prefrontal cortex, but hf-rTMS effects on writing has not yet been investigated in the literature.

In our case report we explored for the first time whether hf-rTMS, delivered deeply at 20 Hz frequency, improves linguistic skills in oral and written language in a patient with a diagnosis of LPPA. Given the crucial role of prefrontal cortex in language processing and on the basis of previous researches on the effects of hf-rTMS on linguistic performances in degenerative dementias [11,12,21–25,27], we chose the left dorsolateral prefrontal cortex (DLPFC) as the stimulation site.

To deliver TMS over the scalp, we employed the unique version of the Brainsway's H-coil (*Brainsway, Jerusalem, Israel*). Unlike the other coils used for TMS, the H-coil is designed to target larger and deeper areas of human brain because based on the principle of electric field summation that exhibits a significantly slower decay of electric field with depth [28–30]. The ability of the H-coil to deliver a broader stimulation of the left DLPFC could result much more effective than focal or superficial stimulation in promoting synaptic plasticity within the stimulated cortex and the interconnected areas by also activating subcortical white matter tracts (i.e. AF) affected in LPPA [7].

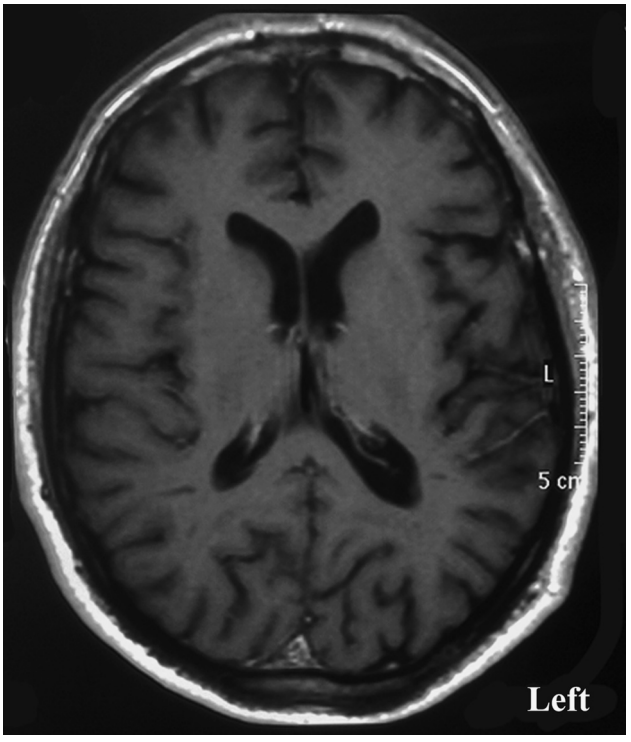

Figure 1. Patient's MRI of the brain. Structural image shows mild atrophy of the left perisylvian region.

Our aim was to provide initial evidence for safety and effectiveness of deep hf-rTMS as a potential tool in the treatment of language disorders. We hypothesized that the ability to stimulate deeper and larger brain volumes in a patient with such a neurodegenerative disease would increase the chances for enhancement in neuroplasticity in the associated widely spread neuronal networks.

Methods and materials

Case report

This is the case report of a 50-year-old, previously healthy, right-handed man (retired airline pilot; education: 18 years). The patient experienced the first symptoms in 2008: depressed mood and increased distractibility. Patient's wife described the onset of very mild language difficulties characterized by vocabulary simplification, babbling (initially intermittent) and occasional anomias on September 2009. Later, the same difficulties were also evident in written language. The clinical picture has progressively and slowly worsened with the emergence of social withdrawal, emotional flatness and apathy. A first brain magnetic resonance image (MRI) on December 2009 was normal and the patient was initially treated for depression. From November 2010 very mild difficulties in understanding more complex orders also appeared and on January 2011 he came to our attention. We firstly referred the patient to standard laboratory tests, serum vitamin B12, folate and thyroid hormone assay, electroencephalogram and a physical and neurological examination which were normal. Then he underwent a complete neuropsychological test battery (Table 1) and a morpho-functional study of the brain to assess cortical atrophy and perfusion deficits by means of MRI and single photon emission tomography (SPECT) scan. The neuropsychological evaluation showed the presence of short-term memory deficits in both verbal and visuo-spatial tasks, impairment of frontal functions, verbal comprehension and lexical phonological

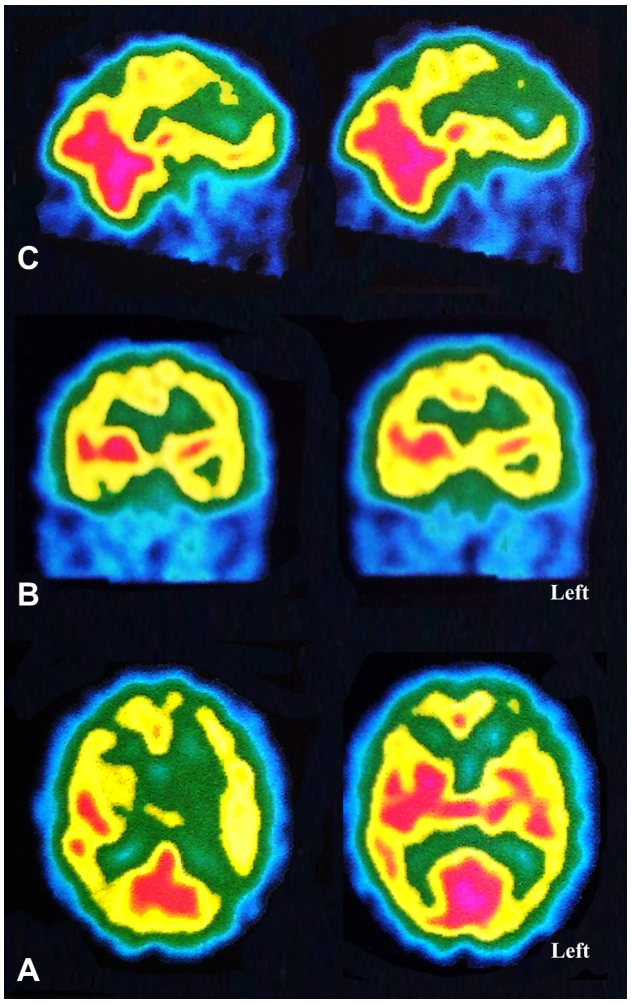

Figure 2. Sagittal (A), coronal (B) and frontal (C) brain slices of patient's (99m)-Tc-HMPAO SPECT scan. Functional images show diffuse decrease in perfusion (fronto-temporo-parietal regions bilaterally), more specifically in the left hemisphere within fronto-parietal and posterior temporal cortex.

production deficits. A more complex linguistic analysis showed a slow rate in the spontaneous speech with frequent pauses due to word-finding problems, occasional anomias and rare phonetic and phonemic paraphasias, without frank agrammatism, other motor speech errors (such as speech apraxia) or disprosody. The patient suffered also from moderate word retrieval (in spontaneous speech and confrontation naming) and sentence repetition deficits associated to a mild impairment in sentence comprehension (influenced by sentences' length and grammatical complexity). Spontaneous written production was characterized by short sentences, the presence of repetitions and occasional paragraphias (phonetic and phonemic) with syntax disruption, but no frank agrammatism. Regarding the motor aspects of written production, the patient had a normal handwriting and he was normally able to perform a written text. Reading aloud was preserved, but did not respect the prosody and punctuation with scarce understanding of the text, whereas he had no difficulties in single word comprehension. The MRI of the brain revealed a very mild atrophy of the left fronto-temporo-parietal junction (Fig. 1) whereas the SPECT scan (Technetium-99m hexamethylpropylene amine oxime-99mTc-HMPAO SPECT) showed a severe and diffuse cortical perfusion deficits of greater magnitude at the level of the left fronto-parietal and posterior temporal regions (Fig. 2).

On the basis of above mentioned clinical and morpho-functional data, we diagnosed a logopenic variant of primary progressive aphasia (LPPA) [2,3].

Experimental procedure

For studying the effects of hf-rTMS on cognitive functions in our patient with LPPA, we used the Brainsway's H-coil designed to target deep cortical areas. This cooled coil enables effective stimulation of all cortical layers and closest subcortical regions both at the top of cerebral convolutions and at the bottom of cerebral sulci under a larger site of stimulation [28–30]. TMS was administered over the left DLPFC by the H-coil connected to a Magstim Rapid^2 stimulator (Magstim, Whitland, UK). The coil was placed inside a specific helmet that allowed keeping the coil fixed on the scalp, over the target site during each stimulation cycle. Stimulation intensity was set at 100% of resting motor threshold for the first dorsal interosseous in the left hemisphere, but the coil was moved 6 cm forward, above the DLPFC, in proximity of the middle (MFG) and inferior (IFG) frontal gyrus over the Broca's areas 44 (BA44) and 45 (BA45) [31]. The limits of anatomical localizations based on scalp coordinates in the absence of neuro-navigation devices have to be taken into account, so the specific target area was also checked by means of the patient's MRI scan. We acquired many coronal and sagittal scans after placing fiduciary markers over the scalp. In this way, it is considered that the H-coil can stimulate a wide area of the left prefrontal cortex widely involved in language [32–38] and memory processing [38–42]. The patient randomly received two effective (REAL) stimulations and two placebo (SHAM) stimulations as control (each cycle: 20 min/day for 5 consecutive days) over a period of 69 days. Each daily stimulation session consisted of 30 consecutive trains delivered every 30 s; each train consisted of 50 stimuli delivered at a frequency of 20 Hz (i.e., a total of 1500 pulses during a 20-min session). The protocol fulfills with the safety norms published for this technique [43,44]. The inter-cycle interval was about fourteen days long (Fig. 3). Placebo stimulation was performed with a sham coil placed in the same Brainsway helmet (active or sham modes are determined by a switch controlled by a card reader) that produces a similar acoustic artifact and some scalp sensation but does not induce an effective field inside the brain due to a special arrangement and non-tangential orientation of the sham coil windings leading to field cancellation. To carefully test cognitive effects of the brain stimulation, we employed a brief neuropsychological test battery (mini mental state examination-MMSE, frontal assessment battery-FAB, phonological

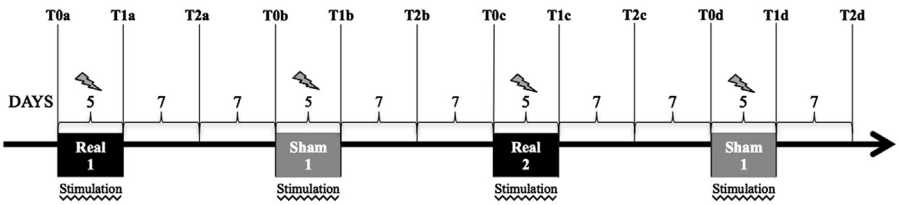

Figure 3. Study design.

Table 2
Number of words generated by the patient within 1 min in the PLF test (verbal phonemic fluency).

	REAL			SHAM		
	Before	After	7 days after	Before	After	7 days after
Cycle I	5	**11**	8	8	6	7
	5	**12**	7	7	6	5
Cycle II	8	**13**	8	7	7	5
	7	**11**	6	6	6	6
Mean ± SD	6.25 ± 1.5	**11.75**[a] ± **0.95**	7.25 ± 0.95	7 ± 0.81	6.25 ± 0.5	5.75 ± 0.95

The scores were obtained twice (inter-tests interval: 6 h) before (T0a and T0c), after (T1a and T1c) and seven days after (T2a and T2c) REAL stimulation cycles and before (T0b and T0d), after (T1b and T1d) and seven days after (T2b and T2d) SHAM stimulation cycles. Significance of the bold numbers: $P < 0.05$.
[a] The scores significantly improve after REAL, but not SHAM, stimulations.

verbal fluency test-PLF, clock drawing test-CDT and block design test-BDT) for the assessment of frontal functions, visuo-spatial functions and verbal fluency, with a more specific evaluation of the written language. Because of the limitation of clinical data obtained from a single patient and in order to statistically analyze the effects of REAL rTMS vs. SHAM stimulation in the patient, the neuropsychological evaluation was repeated twice (inter-tests interval of 6 h) before (T0a, T0b, T0c and T0d), within 24 h after (T1a, T1b, T1c and T1d) and 1 week after the stimulation session ended (T2a, T2b, T2c and T2d) (Fig. 3). In order to investigate phonemic verbal fluency in the patient, we used the PLF test, the Italian standardized version [45] of the verbal fluency test developed by Arthur Benton and colleagues in 1976 [46]. The patient was instructed to generate as many words as possible beginning with letters "P", "L" and "F" within a 1-min period for each letter, excluding proper nouns such as people's, city and country names and the same word with a different suffix. Regarding the written language, the patient was asked to write about an episode of his own life, a sort of "creative writing". No other restrictions were given and so he could write the same one or a different episode every time. He received 15 min for this task each time. Linguistic analysis of written text was carried out on the basis of the grammatical rules of Italian language. We firstly proceeded with a quantitative analysis of the text. We estimated the number of words, lines and sentences written by the patient at each time-points. Then we qualitatively analyzed the text for semantic errors (errors in the relation between signifiers, such as words or phrases, and what they stand for), grammatical and syntactical errors (errors in the rules and principles that govern the sentence structure and the composition of phrases and words) including paragraphias and neologisms. Therefore we estimated four ratios for the statistical analysis: number of total errors (semantic, syntactical and grammatical)/written lines (*E*/*L*), number of total errors (semantic, syntactical and grammatical)/written words (*E*/*W*), number of semantically wrong sentences (sentences with at least one semantic error)/total written sentences (Sem/S) and number of syntactically wrong sentences (sentences with at least one syntactical error)/total written sentences (Syn/S). The patient underwent the four stimulation sessions in the following order: REAL–SHAM–REAL–SHAM (ABAB design) (Fig. 3). We also asked the caregiver to refer us about any changes in patient's daily living activities before and after each stimulation. The neuropsychologist, the patient and the caregiver were in blind about the administration of REAL or SHAM stimulation. The study was conducted according to the Declaration of Helsinki (1990) and the local Ethical Committee approved the experimental procedures.

Statistical analysis

All the neuropsychological test scores (MMSE, FAB, PLF, CDT, BDT, *E*/*L*, *E*/*W*, Sem/S and Syn/S) obtained at each time-point (2 scores in total for each session) were compared by using an ANOVA for repeated measures with time (baseline T0 vs. post stimulation T1 and T2) and type of stimulation (REAL vs. SHAM) as main factors of analysis. We also compared data at baseline before REAL and SHAM (paired samples *t*-test) in order to evaluate that clinical status before each session was similar. *P* less than 0.05 was considered significant.

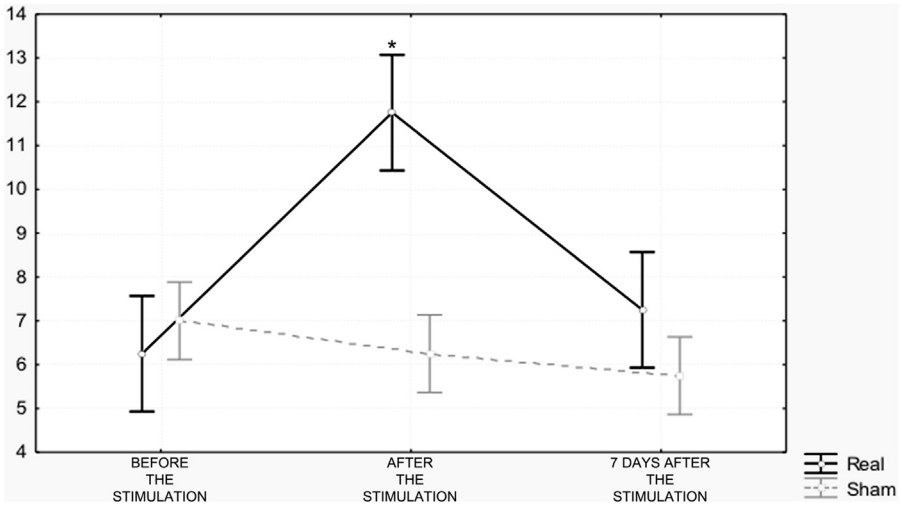

Figure 4. Figure shows the effects of REAL (continuous line) vs. SHAM (dashed line) hr-rTMS on the PLF test scores. Note that the REAL but not the SHAM stimulation significantly improves the PLF test scores immediately after stimulation (*).

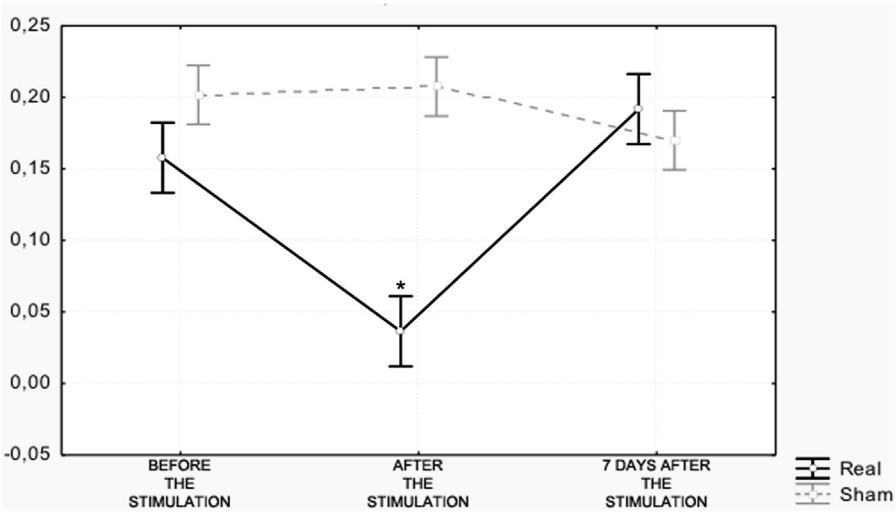

Figure 5. Figure shows the effects of REAL (continuous line) vs. SHAM (dashed line) hr-rTMS on the total number of semantic, syntactical and grammatical errors in the written texts measured as errors/written words ratio (*E*/*W*). Note that the REAL but not the SHAM stimulation significantly decreases the *E*/*W* ratio immediately after stimulation (*).

Results

No side effects or adverse events related to the electrophysiological stimulation procedures were reported. The patient referred an improvement of linguistic skills and written language after each REAL stimulation session, but not after SHAM sessions. He reported a slight improvement in the word retrieval and more facility in doing crossword puzzles.

Statistical analysis of neuropsychological scores showed a significant improvement in the linguistic tasks after REAL but not after SHAM stimulations. Regarding the verbal phonetic fluency as measured by PLF test, in fact, the patient obtained best scores after effective stimulation ($F(4, 16) = 8.72$; $P = 0.0006$) (Table 2) (Fig. 4). Regarding writing, the patient wrote about a different event each time. Statistical analysis shows a highly significant reduction in the number of total errors (syntactical, semantic and grammatical) as measured by *E*/*L* ($F(4, 16) = 11.82$; $P = 0.00012$) (Fig. 5) and *E*/*W* ($F(4, 16) = 14.26$; $P = 0.00004$) (Fig. 6) ratios, in the written task after REAL cycles. We also found a highly significant decrease in the number of semantically and syntactically wrong sentences in the text as measured respectively by Sem/S ($F(4, 16) = 6.03$; $P = 0.0037$) (Fig. 7) and Syn/S ($F(4, 16) = 9.98$; $P = 0.0003$) (Fig. 8) ratios after effective stimulations (Fig. 9). No significant differences in the number of words ($F(4, 16) = 1.19$; $P = 0.35$), lines ($F(4, 16) = 0.39$; $P = 0.8$) and sentences ($F(4, 16) = 2.11$; $P = 0.12$) written in the specific 15 min-long task were found before and after each cycle. No significant differences between the score obtained after the first (T1a) and second (T1c) REAL stimulation also appeared. These results seem to be specific for language as the other scores tested (MMSE, FAB, BDT and CDT) did not differ before and after REAL and SHAM rTMS. Stimulation cycles left any motor aspects of written production unchanged in the patient. Beneficial effects in verbal and written language observed after the end of effective stimulation cycles tend to disappear within seven days (Fig. 9). The neuropsychological scores tested before REAL (T0a and T0c) and SHAM (T0b and T0d) sessions were similar ($P = 0.1218$). The patient's global cognitive state remained substantially stable over the study period (Table 1). Furthermore, no significant learning or practice effects appeared at each time-points (Table 2).

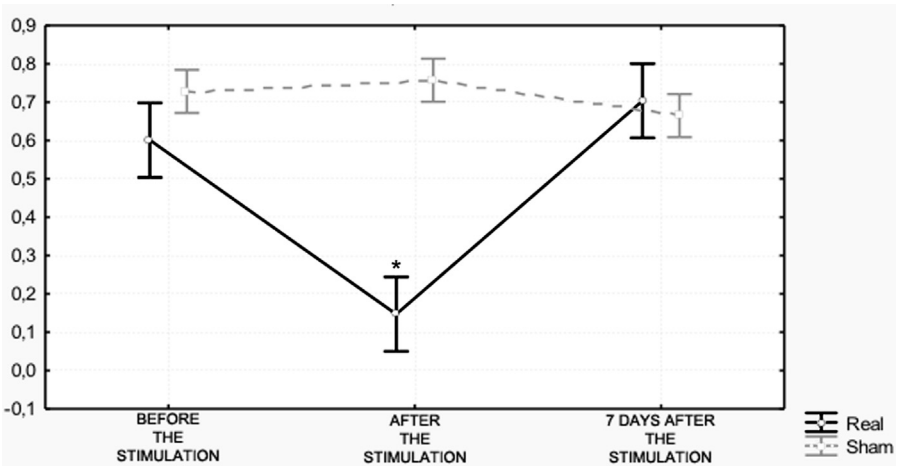

Figure 6. Figure shows the effects of REAL (continuous line) vs. SHAM (dashed line) hr-rTMS on the total number of semantic, syntactical and grammatical errors in the written texts measured as errors/written lines ratio (*E*/*L*). Note that the REAL but not the SHAM stimulation significantly decreases the *E*/*L* ratio immediately after stimulation (*).

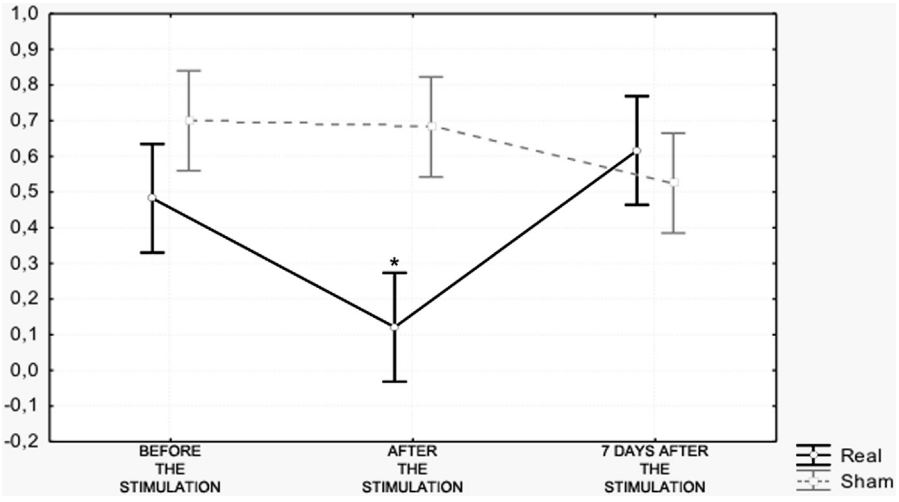

Figure 7. Figure shows the effects of REAL (continuous line) vs. SHAM (dashed line) hr-rTMS on the semantically wrong sentences in the written texts measured as semantically wrong sentences/total written sentences ratio (SEM/S). Note that the REAL but not the SHAM stimulation significantly decreases the SEM/S ratio immediately after stimulation (*).

Conclusion

In this case report we demonstrated that the employment of hf-rTMS delivered over the left DLPFC, in a patient with a diagnosis of LPPA, led to an improvement in phonemic verbal fluency and written language after REAL, but not SHAM stimulations. We indeed found a significant increase in the PLF test scores and a highly significant reduction in the number of syntactical, semantic and grammatical errors written by the patient after the application of effective stimulation, as compared to both baseline and SHAM conditions.

The evidences that LPPA is often due to AD pathology [4,8,9] may actually connect the present findings with previous results by Cotelli et al. [21–23], but no one else has tested before the effects of hf-rTMS on writing in degenerative dementias. The novelty of our results is that the hf-rTMS-related facilitation effect over the DLPFC highly involves writing process. The act of writing is a complex cognitive process characterized by high hierarchical organization and goal directed thinking [47] that highly involves prefrontal cortex [48,49]. We asked the patient to write a sort of real-life "creative writing". This task is known to activate DLPFC, mainly the left IFG and MFG, as well as motor associated areas and the temporal lobe in the posterior part of the superior temporal gyrus [50]. With the use of a connectivity based approach, DLPFC has been shown to physiologically interact with several frontal (i.e., ventrolateral prefrontal cortex), parietal (i.e., anterior superior parietal lobule) and temporal (i.e., superior temporal sulcus and superior temporal gyrus) areas depending on the context of the writing [51]. The choice to stimulate the left DLPFC within the IFG (BA44 and BA45) and MFG also depended on several previous evidences about the anatomy of language impairment in PPA. Cortical thinning in PPA patients is generally asymmetric and most severe in the perisylvian language region of the left dominant hemisphere as in our patient. In a recent paper by Rogalski and colleagues, reduced cortical thickness of IFG correlates to word fluency impairment and grammatical processing in sentence production [52]. The IFG, and in particular Broca's areas, has long been known to support language production [53] and comprehension processes [54,55]. At a linguistic level, the subregion BA44 is mainly involved in syntactic structure building, whereas BA45 in semantic processes [56,57]. In a morpho-functional recent study on PPA, Wilson and colleagues reported that the

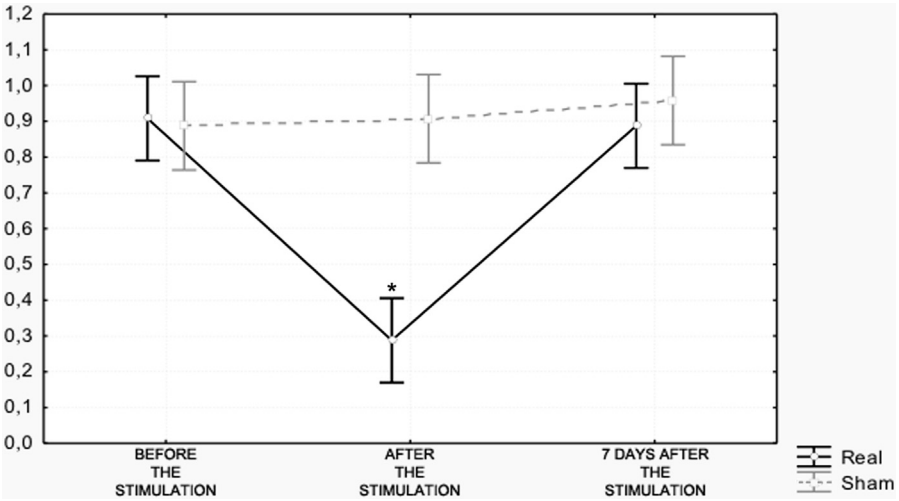

Figure 8. Figure shows the effects of REAL (continuous line) vs. SHAM (dashed line) hr-rTMS on the syntactically wrong sentences in the written texts measured as syntactically wrong sentences/total written sentences ratio (SYN/S). Note that the REAL but not the SHAM stimulation significantly decreases the SYN/S ratio immediately after stimulation (*).

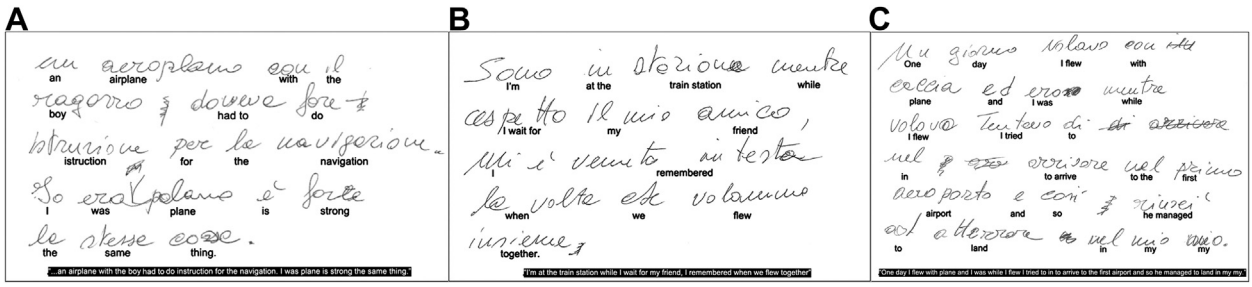

Figure 9. Figure shows three excerpts obtained from the texts written by the patient before (A), after (B) and seven days after (C) REAL stimulation (first cycle). Note that just immediately after the stimulation (B) an improvement in syntax, grammar and semantics appeared.

patients, in contrast to controls, showed low modulation within BA44 for processing syntactic complexity and this abnormal modulation correlates to the left dorsal IFG atrophy [58]. Previous researches also showed the importance of the white matter damages in relation to aphasia in PPA. Syntactic and semantic processing depends not just on cortical regions, but also on the white matter fiber bundles that connect them. There is increasing evidence that disrupted connectivity might be a significant contributing factor to language deficits in PPA [7,59]. In fact, syntactic processing depends on left frontal and posterior perisylvian regions, as well as on intact connectivity between them [59].

Our results are in line with these previous morpho-functional evidences about the crucial role of IFG (Broca's region) [54–57] and its interconnecting fibers to posterior temporal lobe (Wernicke's area) via AF [59], in altered syntactic structure building and semantic processing in patients with PPA. The thorough linguistic analysis of written production in our patient, in fact, have shown that semantics and syntax improved after delivering effective stimulation through the Broca's cortex till the deep white matter bundles below (AF) in the left DLPFC. Even though the ability to write has been associated with the functional and structural integrity of several cortical regions (depending on the linguistic demands of the writing task) other than prefrontal areas in the language-dominant hemisphere, hf-rTMS deeply delivered over the DLPFC seems to bring a "qualitative" effect on writing. REAL stimulation of the left DLPFC, in fact, highly improved retrieval and selection of semantic information and syntactic processing, leaving unchanged other "quantitative" aspects of writing such as the control of action in space and the motor execution of writing mainly controlled in posterior parietal cortex, where a critical node in the somato-motor circuitry involved in writing lies [51]. After each stimulation the patient wrote the same amount of words and sentences, but he wrote them more correctly (syntactically and semantically) exclusively after REAL stimulation. It can be assumed that the effective stimulation, promoting synaptic plasticity, improves the ability to write in our patient by facilitating semantic and syntactic processing known to be altered in LPPA.

Notwithstanding the beneficial effects of REAL stimulation in our LPPA patient, the neurophysiological mechanism by which hf-rTMS delivered over the left DLPFC improves verbal fluency and the ability on semantics and syntax in written language remains unknown. It is also difficult to interpret the observed functional effects in terms of exact anatomical effects because there is no clear knowledge about spatial resolution of deep TMS. A recent diffusion tensor tractography study on the three variants of PPA showed lower fractional anisotropy in the temporo-parietal tract of the left superior longitudinal fasciculus and mild changes of diffusivity in the AF in LPPA patients when compared with healthy subjects [7]. It can be assumed that the deep hf-rTMS-dependent direct activation of the left DLPFC and its underactive (partially spared) subcortical interconnecting fibers (in particular the AF) that provide direct connection between the posterior and anterior cortical regions critical for language (regions of Broca and Wernicke), may enhance synaptic plasticity and then bring a widespread facilitation of the fronto-temporal network for language in LPPA. Since mild cortical atrophy on MRI coexists with severe and diffuse hypo-perfusion on SPECT scan in our patient, the benefits we found after REAL stimulation could therefore depend on the activation of spared, but low-functional pathways of this network. In this way deep hf-rTMS could partially restore or compensate the significant degree of functional plasticity within directly stimulated sites and interconnected (presumably via cortico–cortico and cortico–subcortical connections) brain areas improving patient's linguistic skills.

The other coils used for TMS in the clinic and research (round or figure-of-eight shaped), induce stimulation in cortical regions mainly just superficially from the windings. As the fields induced by these coils decrease rapidly as a function of depth, only very high intensities would allow functional stimulation of deep brain regions and such intensities would lead to undesirable side effects [43,44]. The H-coil, instead, has been developed to achieve effective stimulation of deeper brain regions promoting synaptic plasticity in the form of long term potentiation also in brain centers distant from the stimulated sites [29,60]. Hence, the ability to stimulate deeper and larger brain regions with the H-coils may be beneficial in LPPA because the target of stimulation is not localized in a very superficial and focal site in the cortex, but rather deeper cortical layers [1,2] and subcortical white bundles should be affected [7,59] and a larger volume of stimulation may be, then, more effective.

Another important finding of this paper is that the beneficial effects observed after REAL stimulation seem to be transient tending to disappear within 7 days. These data could suggest a short-lasting effect of hf-rTMS-dependent conditioning on neural networks in our stimulation protocol. To our knowledge, only one previous experimental evidence on AD patients revealed a long-lasting effect limited to sentence comprehension after hf-rTMS delivered over a much longer period (two weeks) [23]. The short-lasting effects we found in our patient could depend on possible different functional responses to hf-rTMS when delivered to modify a complex neural systems as the writing network is. The relatively brief period of stimulation (five consecutive days) in our protocol, could also justify our results. Hence, a longer period of stimulation could induce long-term neuro-modulatory effects much more useful for new rehabilitation strategies.

REAL stimulation significantly improved patient's performances in linguistic skills, whereas it left the other neuropsychological scores tested (MMSE, FAB, BDT and CDT) unmodified. These data integrate previous reports about the language-specificity of rTMS-effects when applied over the DLPFC [21–23]. Even though we did not use a frameless stereotactic neuronavigation system to localize the target area of stimulation, in fact, we are quite sure to

have stimulated a wide area of the left DLPFC, not merely subregions of BA44 and BA45, because the H-coil is able to stimulate large volumes under the windings [28–30,60].

Even though, we could not absolutely exclude the potential influence on performance that arises from practicing a task, our results seem to suggest no practice effects at each time-point over the study period (Table 2). Anyway, in order to limit any potential confounding factors due to practice or learning effects, we kept the same experimental condition at each time-point. Moreover the lack of any hf-rTMS effects on the other cognitive domains tested would suggest that no learning effects could explain our results.

Despite the limitation imposed by a single case study, our preliminary findings complement previous researches on hf-rTMS as a therapeutic tool in neurodegeneration [21–23,25–27]. Since no treatments are available in LPPA, the present case report indicates the need for further investigation into the potential clinical benefit of deep TMS over the DLPFC in LPPA and all the other forms of neurodegenerative aphasias. Such studies will evaluate whether longer and more intense stimulation periods will result in long-lasting beneficial effects and whether chronic maintenance TMS sessions are feasible.

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