Original Paper

European Neurology

Eur Neurol 2016;76:12–18
DOI: 10.1159/000447399

Received: March 8, 2016
Accepted: May 27, 2016
Published online: June 25, 2016

Left Prefrontal Repetitive Transcranial Magnetic Stimulation in a Logopenic Variant of Primary Progressive Aphasia: A Case Report

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Key Words
Logopenic primary progressive aphasia · Repetitive transcranial magnetic stimulation · Alzheimer's disease · Language · Neuropsychology · Single photon emission CT

Abstract
Background/Aims: High frequency repetitive transcranial magnetic stimulation (hf-rTMS) improves language skills in Alzheimer's disease (AD). We report the use of hf-rTMS in a patient with logopenic primary progressive aphasia (LPPA) due to AD. ***Method:*** hf-rTMS was applied to the left dorsolateral prefrontal cortex of a LPPA patient. Cerebral perfusion, neuropsychological and linguistic performances were evaluated before and 1 month after hf-rTMS. ***Results:*** The tolerance was good. Improvements on linguistic (fluency, naming, lesser paraphasia) and cognitive skills (Mini Mental State Examination, verbal memory free recall, speed processing) and cerebral perfusion were observed. ***Conclusion:*** hf-rTMS can be used in LPPA patients. A procognitive effect persisting several weeks after stimulation in LPPA patients was suggested and should therefore be evaluated in a clinical trial as an adjunctive therapeutic tool.

Introduction

Logopenic primary progressive aphasia (LPPA) is a syndrome characterized by a slowly progressive, isolated anomia with slow speech rate, word-finding pause, phonological loop dysfunction and left temporoparietal brain atrophy due to neurodegenerative disease [1, 2]. Alzheimer's disease (AD) is the most common neuropathology underlying LPPA [2]. No medication has proven to be effective for LPPA. Current treatment of LPPA is based on linguistic therapies [3]. During high frequency repetitive transcranial magnetic stimulation (hf-rTMS) sessions applied on the right or left dorsolateral prefrontal cortex (DLPFC), improved performance on picture naming and other language-related tasks have been observed in both healthy subjects and AD patients [4–7]. We reported a possible improvement in cognitive skills maintained for 1 month following hf-rTMS treatment applied on the left DLPFC in an AD patient [8]. A case of agrammatic primary progressive aphasia treated with hf-rTMS applied on the left DLPFC also showed improvement in a verb completion task after the hf-rTMS treatment [9]. Furthermore, Trebbastoni et al. [10] reported the case of an LPPA patient treated by hf-rTMS delivered

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over the left DLPFC (a total of 7,500 pulses for 5 consecutive days) whose linguistic skills improved just after stimulation and returned to baseline 7 days after the stimulation. No linguistic therapy was associated with hf-rTMS in this study. Other studies suggest that neuropsychological and linguistic improvements in AD patients are maintained for several weeks or months after hf-rTMS treatment of either the left or right DLPFC [6, 11, 12]. Therefore, we hypothesized that a more intense hf-rTMS stimulation on the left DLPFC compared to Trebbastoni's study [10] (a total of 40,000 pulses for 5 consecutive days) as an add-on therapy to linguistic therapies could improve both lexical access and the effect of linguistic therapies in LPPA patients. The resulting cognitive and metabolic improvements may persist for 1 month. We report the use of hf-rTMS as an adjunctive treatment to linguistic therapies on an LPPA patient.

Materials and Methods

The local Ethics Committee of the University Hospital of Besançon gave its approval to conduct the protocol and the patient gave informed written consent.

Neuropsychological and linguistic examinations were administered, and cerebral perfusion single photon emission CT (SPECT) was performed before hf-rTMS treatment at baseline (Time 0) and 1 month after the last stimulation session (Time 1). A second language evaluation was conducted 3 months after the last stimulation session (Time 2).

Cognitive and Linguistic Examinations

The linguistic tests consisted of the following: a sentence comprehension assessment with a Verbal Comprehension Test; a Picture Naming Test with 80 items (PNT80); word, non-word and sentence repetition; Isaac Set Test; phonological and categorical fluency tests [13–17]. All tests were performed in French. PNT80 was also performed in German (same pictures).

Neuropsychological tests consisted of the following: Mini Mental State Examination (MMSE), Mattis Dementia Rating Scale, Crossing-Off Test, Trail Making Test part A, Stroop Test, Free and Cued Recall Test 16 items (different version at Time 0 and Time 1), Forward Digit Span, Backward Digit Span, Delayed-Matched Sample in 48 items (DMS48) (different version at Time 0 and Time 1) [18–22].

SPECT Examination

Cerebral perfusion SPECT examination was performed with 99mTc-ECD radiotracer at Time 0 and 99mTc-HMPAO radiotracer at Time 1 (because of stockout of ECD). A visual analysis was applied using a homemade semi-quantitative SPECT visual rating scale developed in an LPPA population with both 99mTc-HMPAO and 99mTc-ECD radiotracers (intraobserver concordance >90% and kappa >0.7; interobserver concordance >70% and quadratic weighted kappa >0.41) [23]. The scale ratings are grade 0 (normal uptake in the territory, i.e., between 70 and 100% of the maximum pixel value), grade 1 (low uptake in a small territory, i.e., between 50 and 70%), grade 2 (low uptake in a large territory, i.e., between 50 and 70%) and grade 3 (no uptake, i.e., <50%).

Application of hf-rTMS

The patient was treated by rTMS for 10 stimulation sessions of 20 min each spread over 1 week, with 2 sessions per day on consecutive working days. A Magstim Super rapid (Magstim Company Ltd., Whitland, Wales, UK) [24] with an air cooling figure-of-eight coil was used. The hf-rTMS was administered at 10 Hz for 5 and 25 s between train, and 100% of the motor threshold (because of the risk of seizure in AD [25]) over the left DLPFC per session (2,000 stimuli per session), with the coil angled tangentially to the head. The left prefrontal cortex hf-rTMS stimulation site was determined by measuring a 5 cm anterior and parasagittal line from the hand motor area.

Assessing Change in Cognitive Test Performance

Percentages of improvement from baseline (Time 0) were calculated by dividing the difference in the score (Time 1 – Time 0) by the score at Time 0 (baseline) (e.g., (Time 1 – Time 0)/Time 0 × 100). A positive percentage score meant that performance increased. In this study, an improvement score had to change by at least 20% from baseline to be considered significant [26].

Results

Case Report

The patient was a 66-year-old right-handed German/French bilingual woman with a high level of education who was selected from the Memory Center of Research and Resources of Besançon. The symptoms had begun 5 years previously and were characterized by a progressive, isolated anomia. After 2 years of speech therapy, a language and neuropsychological evaluation showed a slight decline with an increase in anomia, phonological paraphasia and length-dependent comprehension difficulties in both oral and written language and isolated verbal short-term and working memory impairment. No depressive symptoms or behavioral abnormalities were observed (assessed by an experienced psychiatrist, EH). Basic and instrumental activities of daily living were preserved. Neurological examination and MRI were normal but SPECT imaging (HMPAO-SPECT) detected left frontotemporoparietal hypoperfusion. Cerebrospinal fluid biomarker analysis (Innogenetics®) revealed decreased levels of Aβ1–42 (310 pg/ml; normal >500 pg/ml), and increased levels of tau (491 pg/ml; normal <100 pg/ml) and of phosphorylated tau (72 pg/ml; normal <60 pg/ml) suggesting an AD profile. These clinical, imaging and biological findings led to the diagnosis of LPPA according to Gorno-Tempini criteria [1, 2]. Linguistic therapy began 2 years before rTMS and continued

Table 1. Linguistic and cognitive performances at baseline (Time 0) and 1 month (Time 1) after the hf-rTMS treatment. Linguistic performance 3 months (Time 2) after the hf-rTMS treatment.

Cognitive function tested	Language and neuropsychological test	Time 0	Time 1	Time 1 – Time 0 improvement, %	Time 2	Time 2 – Time 0 improvement, %
Oral language	PNT80 (French) (/80)	69	72	4.4	70	1.4
	Picture Naming Test (German) 80 items (/80)	71	74	4.2	73	2.8
	Isaac Set Test (number of words)	24	28	17	27	12.5
	Categorical fluency (2 min; number of words)	10	21	110*	16	28.5*
	Phonological fluency (2 min; number of words)	14	20	43*	14	0
	Word repetition (/25)	25	25	0	24	–4
	Non-word repetition (/8)	8	6	–25*	6	–25
	Sentence repetition (/3)	1	1	0	1	0
Overall cognitive efficiency	MMSE (/30)	5	27	8	ND	ND
	Mattis Dementia Rating Scale (/144)	132	130	–1.5	ND	ND
Speed processing and executive function	Crossing-Off Test (Index)	196	204	4	ND	ND
	Trail Making Test part A (sec)	53	32	40*	ND	ND
	Stroop Test: reading (number of words)	70	91	30*	ND	ND
	Stroop Test: color naming (number of words)	34	51	50*	ND	ND
	Stroop Test: interference (number of words)	14	40	186*	ND	ND
Verbal memory	Free and Cued Recall Test 16 items, free recall (/48)	26	29	11.5	ND	ND
	Free and Cued Recall Test 16 items, total recall (/48)	47	48	2	ND	ND
	Forward Digit Span	3	3	0	ND	ND
	Backward Digit Span	3	3	0	ND	ND
Visual memory	DMS48, %	100	100	0	ND	ND

Pathological score (<10th percentile or <1.5 SD); ND = not done; * significant improvement (>20%).

during and after the brain stimulation and remained at the same frequency and with the same procedure. Rehabilitation objectives were to intentionally exploit her residual semantic knowledge and to apply lexical retrieval strategies especially in spontaneous speech [3]. Her linguistic performances, after an initial improvement during the first months of logopedic rehabilitation, were then considered as stable by the logopedist for more than 6 months before hf-rTMS stimulation.

Safety

No adverse events were reported and stimulation sessions were well tolerated (no pain at the site of coil placement or headache and no seizure).

Linguistic and Neuropsychological Examination

At Time 0, speech evaluation (table 1) showed anomia, word finding difficulties, phonemic and semantic paraphasia without motor speech disorder. Sentence comprehension was length-dependent impaired. The neuropsychological evaluation (table 1) revealed impairment in speed processing, free recall of verbal memory tests and short-term memory. The MMSE score was below the normal range. At Time 1, improvements in cognitive and language tasks were observed. These improvements were more important in speed processing and lexical access tests (PNT, fluency). MMSE and verbal memory free recall performances that were pathological at Time 0 were normal at Time 1. Improvement in verbal fluency and reduced paraphasia were still observed 3 months after the last stimulation session (Time 2). A subjective cognitive improvement, especially on communication skills, cognitive speed and initiation, was also reported by the patient and her husband.

Cerebral Perfusion Examination

Cerebral perfusion SPECT examination showed a left frontotemporoparietal and striatal hypoperfusion at baseline (Time 0), and 1 month after hf-rTMS (Time 1), an increased left cortical (from grade 2 to grade 1 in the semi-quantitative SPECT visual rating scale) and basal (from grade 2 to grade 0 in the semi-quantitative SPECT visual rating scale) perfusion (fig. 1).

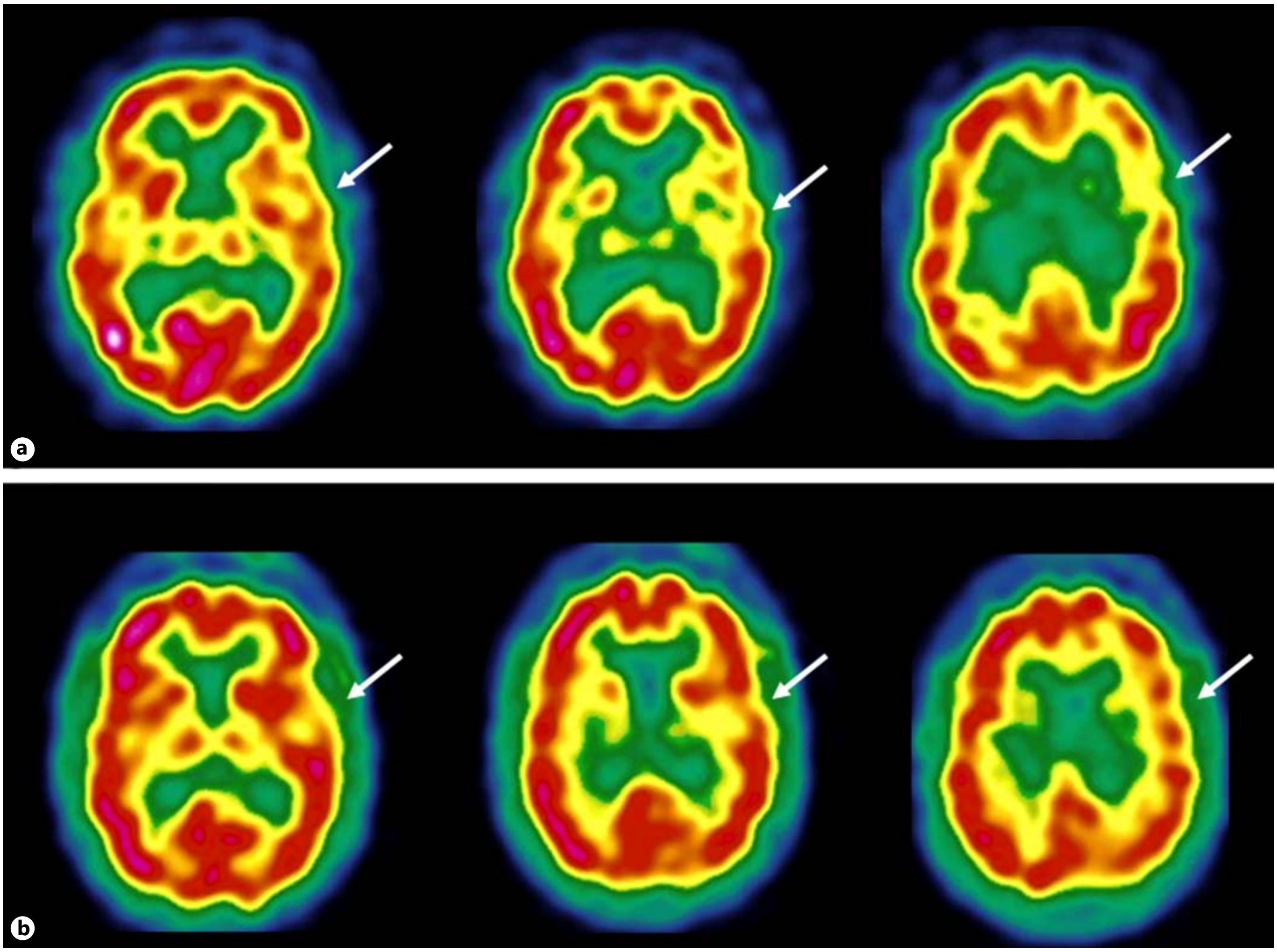

Fig. 1. Cerebral perfusion SPECT before (**a**, Time 0, with 99mTc-ECD radiotracer) and 1 month after (**b**, Time 1, with 99mTc-HMPAO radiotracer): hf-rTMS showed an increased cerebral perfusion in the left frontotemporoparietal cortex (from grade 2 to grade 1 in the semi-quantitative SPECT visual rating scale) and the left striatum (from grade 2 to grade 0 semi-quantitative SPECT visual rating scale; white arrow) 1 month after hf-rTMS treatment.

Discussion

This case report suggests a good tolerance of hf-rTMS and a potential sustained effect on language and cognitive skills after 1 month following hf-rTMS treatment applied on the left DLPFC in an LPPA patient. The choice of the target of hf-rTMS and stimulation parameters were based on previous studies focused on AD and PPA that suggest a positive and sustained effect of hf-rTMS applied on the left DLPFC. Finocchiaro et al. [9] were the first to report a possible long-lasting effect of hf-rTMS applied to the left DLPFC on language performance in patients with a probable agrammatic variant of PPA. The hypothesis was that hf-rTMS may strengthen the neural connections within the damaged area in the left hemisphere. Trebbastoni et al. [10] observed only an immediate effect of rTMS applied on the left DLPFC in linguistic tasks. Our results suggest that hf-rTMS has an effect in an LPPA patient on linguistic tasks but also in other cognitive domains that persists for at least 1 month.

LPPA is not a purely linguistic disorder as the verbal short-term and working memory deficits induce difficulties in many neuropsychological tests [27, 28]. In addition to linguistic modification observed in our case report, other neuropsychological performances such as speed processing and verbal memory free recall were also improved after hf-rTMS. As the raw MMSE score (25/30) suggested a mild AD stage, the preserved activities in daily living suggested only a prodromal stage of atypical AD. Initial MMSE performance was underestimated by the language and short-term memory component highly involved in this test (verbal encoding impairment was 1/3, mental calculation difficulties 4/5 and language disorders 6/8) [27]. In addition, our patient also had a high level of education and was bilingual. Therefore, she probably presented a high cognitive reserve and preserved cognitive and neural compensatory capabilities that hf-rTMS might have boosted. A later intervention in patients with more impaired cognition and/or less reserve might not have improved cognitive performances as much. As it was proposed for other clinical trials in AD, a comparison of the hf-rTMS effect between prodromal or mild stage of neurodegenerative disorders and more severe forms should be considered in future clinical trials to evaluate the optimal timing for brain stimulation.

The choice of hf-rTMS stimulation target and neuroimaging modification after treatment suggest a role of the left DLPFC in improvements of speed processing and lexical access observed in our LPPA patient. The mechanisms by which hf-rTMS applied to the left DLPFC improved speed processing and word retrieval are largely unknown. The DLPFC is particularly involved in episodic memory and executive functions [29, 30]. Neuroimaging findings might be explained by random variability between the 2 examinations and difference of fixation between the 2 radiotracers, which is a limitation of our study. However, 99mTc-ECD and 99mTc-HMPAO radiotracers are supposed to have relative differences in the uptake pattern between temporal and posterior cortical regions, but a quite similar uptake in frontal regions [31, 32], which was our region of interest in this study. Moreover, only an asymmetric modification was observed in the left hemisphere, which was stimulated and is a region of interest involved in language processing and especially in LPPA. The use of additional neural resources in the DLPFC and cortico-subcortical activation by hf-rTMS may counterbalance the degeneration in the language network caused by LPPA. Increased perfusion in the left hemisphere (in regions of interest known to be involved in LPPA) might reflect this mechanism and may correspond to additional neural plasticity induced by hf-rTMS and linguistic therapy. hf-rTMS may facilitate cognitive processes that depend partly on the DLPFC, such as improved attention and executive functions playing a role in lexical access strategies and the phonological loop.

Second, as intense hf-rTMS can modulate cortical excitability and neural plasticity, the association with linguistic therapies may potentiate the effect of both therapies and explain the long-lasting effect observed. The absence of concomitant linguistic therapy in the study by Trebbastoni et al. [10] who observed only a transient improvement (<7 days) by less intense hf-rTMS stimulation in an LPPA patient might support this hypothesis.

The changes observed in cognitive and language functions were not related to mood changes because our patient had no mood disorders before or after hf-rTMS [33]. One of the major limitations of our study is that no sham rTMS was used to exclude placebo effect in this feasibility study. These improvements could also be due to practice effects (PEs) because the patient was reassessed with the same test materials (except for the alternative version of FCRT and DMS48). The asymmetric neuroimaging modification observed on the left frontal regions might be explained by PE [34] or placebo effect [35]. However, few placebo effects and PEs were reported during sham stimulation in hf-rTMS studies on healthy subjects [7], AD [6] and PPA patients [9, 10]. Moreover, PE is considered as moderate (<16%) especially in linguistic tasks (<5%) in healthy subject with high-frequency testing (2, 6 and 9 weeks and 3 months) [36]. Several studies have demonstrated that PE is largely absent in patients with neurodegenerative disease and dementia, even for short test–retest intervals [37–40]. In order to limit PE, we did not carry out linguistic and neuropsychological examinations immediately after rTMS to observe the long-lasting effect 1 month after hf-rTMS. Moreover, it is worth noting that this effect is supposed to be more important during the first retest especially for cognitive speed (<5%) than at subsequent evaluations in which performances are relatively stable or slightly improved [41]. In our study, the linguistic performances at Time 2, the third evaluation, were lower than at Time 1, the second evaluation, suggesting that an effect other than PE was involved in the improvement observed at Time 1 and gradually faded at Time 2. If a strong test–retest effect was involved in our results, the Time 2 evaluations, conducted 3 months after brain stimulation after 2 previous cognitive examinations, would have shown an additional improvement or stability in cognitive performances.

Our case report can be considered as a feasibility study and raised questions that future clinical design should try to answer like the optimal disease stage for brain stimulation and the potential role of neuroimaging biomarkers to assess long-term effects of hf-rTMS on brain functioning. The scientific value of a single case, without control condition (sham stimulation) such as a crossover design, remains limited especially because the improvement observed might be due to placebo and PE. As reported by a European consensus guideline on the therapeutic use of rTMS in AD [42], further studies with randomized, double-blind, sham-controlled, crossover trials with neuropsychological and neuroimaging follow-up in a population of patients with LPPA are needed to confirm these results. These studies might use repeated evaluation before and after therapeutic intervention to evaluate and limit the impact of PE [43, 44] in the analysis of potential precognitive effect of hf-rTMS brain stimulation. The first evaluation can be excluded from the analysis in order to have a baseline that already has the major part of PE component before therapeutic intervention [41]. Repeated and delayed assessments after the therapeutic intervention might also help to discriminate the PE and delayed therapeutic effect as in our case report. The delayed assessment can be considered as a 'wash out' period. The delayed decrease in some performances suggested that the previously observed improvement was not only due to PE. However, it does not permit to exclude placebo effect. Functional neuroimaging evolution before and after brain stimulation might also be an interesting tool to assess the treatment in these future trials.

Conclusion

hf-rTMS was well tolerated in this LPPA patient and, therefore, should be evaluated by a clinical trial as an adjunctive therapeutic tool in the LPPA population. If the sustained neuromodulation and long-lasting procognitive effects are confirmed in future clinical trials, this would be useful to define new rehabilitation strategies. Further studies with specific design are required to confirm these results.

Disclosure Statement

The authors have no conflicts of interest to disclose. There was no funding for this work.

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