A Case Study of Primary Progressive Aphasia: Improvement on Verbs After rTMS Treatment

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This case-report shows that high frequency repetitive Transcranial Magnetic Stimulation (hf-rTMS), applied to the left prefrontal cortex, may improve the linguistic skills in Primary Progressive Aphasia (PPA). The patient’s performance was evaluated on a battery of language production and memory span tasks, before and after two hf-rTMS treatments and one SHAM treatment. We observed a significant and lasting improvement of the patient’s performance on verb production following the application of hf-rTMS versus Baseline and SHAM conditions. This finding suggests that hf-rTMS may directly strengthen the neural connections within an area of metabolic dysfunction and encourages the use of rTMS as an alternative therapeutic tool for neurodegenerative forms of aphasia.

Introduction

In Primary Progressive Aphasia (PPA), language is the only area of prominent dysfunction for at least the first 2 years of the disease, whereas core memory functions remain largely preserved (Mesulam, 2003).

The positive impact of linguistic rehabilitation on PPA is limited, as the gradual progression of the disease—along with a progressive deterioration of language skills—is intrinsic to its natural course.

The Transcranial Magnetic Stimulation (TMS) technique is a non-invasive procedure that has been used to treat neuropsychiatric diseases ranging from Parkinson’s (Pascual-Leone et al., 1994) to neglect (Brighina et al., 2003). The hypothesis behind these studies is that rTMS is able to normalize the neural activity in cortical areas of metabolic dysfunction. When applied in trains, repetitive TMS (rTMS) may have an excitatory or inhibitory effect on the neurons of the targeted area, that lasts beyond the duration of the train itself (Pascual-Leone et al., 1998). The specific effect depends on the stimulation parameters that are selected. In particular, low-frequency rTMS (lf-rTMS, ≤ 1 Hz) is proven to decrease cortical excitability, whereas high-frequency rTMS (hf-rTMS) is proven to increase cortical excitability (Pascual-Leone et al., 1998).

Both rTMS parameters have been used to address questions about the neural organization of language functions.

Low-frequency rTMS may be considered as a counterpart of the research on language deficits. This is because a train of pulses at 1 Hz frequency suppresses the excitability of the targeted region, in effect creating a “virtual lesion” that may transiently interfere with cognitive processing (Pascual-Leone et al., 2000).

It has been reported that this type of stimulation may cause arrest of both overt (Stewart et al., 2001; Epstein, 1998; Pascual-Leone et al., 1991) and covert speech (Aziz-Zadeh et al., 2005), as well as fine-grained dissociations between word-categories such as nouns and verbs (Shapiro et al., 2001).

High-frequency rTMS has been shown to facilitate many language-related tasks, including oral word associations (Bridge and Delaney, 1989), digit span (Duzel et al., 2005) and picture naming (Topper et al., 1998; Mottaghy et al., 1999). Previous results on normal subjects have also demonstrated an effect of facilitation specific for action word naming following hf-rTMS (20 Hz) of the left prefrontal cortex (Cappa et al., 2002).

The main objective of this study was to verify whether hf-rTMS, when applied on the damaged area of the left hemisphere, may improve the linguistic skills of a PPA patient.

Methods

Case Study

The patient was a 60-year-old right-handed man recruited from the Department of Clinical Neuroscience of the University of Palermo, Palermo, Italy.

The MRI scan showed a bilateral atrophy in the fronto-temporal region more pronounced on the left hemisphere.

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As revealed by the neuropsychological evaluation, the patient's performance on linguistic tasks (Rey's list-DR, Token test and semantic and phonemic verbal fluency) was below the normal range, whereas the performance on tasks assessing the integrity of other cognitive functions (MMSE, FAB, Raven progressive matrices, visual search, and Rey list-IR) was normal.

Given that speech and language skills had deteriorated for more than 2 years without evidence of non-linguistic cognitive deficits, the patient met the criteria for PPA (Mesulam, 2001).

A further assessment of his linguistic abilities (Miceli et al., 1994) revealed a selective impairment on Verb as opposed to Noun production with no difference across modalities (Correct %: Oral Nouns 86.6%; Written Nouns 81.8%; Oral Verbs 50%; Written Verbs 54.5%).

This finding converges with previous results showing a selective and progressive deficit for oral or written production of verbs in PPA (Hillis et al., 2002).

Indeed, there is now accumulating evidence on the role of left prefrontal cortical areas in verb processing, coming from neuropsychological (Bak et al., 2001; Berndt et al., 1997; Cappa et al., 1998) as well as neuroimaging studies (Dehaene, 1995; Raichle et al., 1994; Wise et al., 1991).

More recently, some rTMS studies pointed to a specific role of the left inferior frontal gyrus, just anterior and superior to Broca's area, for verb processing (Shapiro et al., 2001).

On the basis of the patient's difficulties on verbs, his lesion site, and the documented role of the left inferior frontal gyrus for verb processing, we targeted this region for stimulation.

We asked whether hf-rTMS may improve the patient's performance on verb production.

The study was conducted according to the Declaration of Helsinki (41st World Medical Assembly, 1990).

Application of rTMS

A Cadwell high-frequency magnetic stimulator equipped with a water-cooled figure-of-eight coil (each loop 4.5 cm in diameter) was used.

Magnetic stimulation was applied at 90% of the motor threshold (MT) at 20 Hz frequency. MT was determined at the hot spot of the right FDI muscle as the minimum stimulus intensity able to elicit a motor evoked potential (MEP) of at least 50 µV in 5 or more of 10 consecutive stimulations. Ten trains of 40 pulses each, separated by a 30-sec pause, were applied daily for five consecutive days. The stimulation intensity was 56% of the maximum stimulator output. To target the region in the proximity of the inferior midfrontal gyrus, we positioned the coil on the scalp according to the coordinates used by Shapiro et al., (2001) – 6 cm anterior and 1 cm ventral from the motor spot for the first dorsal interosseous muscle in the left hemisphere. This point was also checked by means of the patient's MRI scan (see Figure 1).

Fig. 1. Axial MRI scan of the patient, with the arrow indicating the position of the TMS coil.

However, the limits of anatomical localizations based on scalp coordinates in the absence of a frameless stereotactic system have to be taken into account. This is particularly true in a case of frontal lobe atrophy.

The position was marked on a tightly fitting Lycra cap worn by the patient.

We also included a condition of SHAM stimulation as a control, with the coil angled 90°on the edge of a single wing over the same site and with the same stimulation parameters used for real rTMS.

A treatment consisted in a 5-day application of rTMS or SHAM stimulation according to the parameters described above.

The patient underwent two rTMS and one SHAM treatments in the following order: real rTMS – SHAM rTMS - real rTMS. Each new treatment started when the performance of the patient was at a level not significantly different from the Baseline for 2 consecutive sessions (see below). The testing stopped at the fourth session after the last rTMS treatment, because the patient began a pharmacological therapy.

This study was performed in close adherence to TMS safety guidelines (Wassermann, 1998).

Experimental Tasks

The test battery administered to the patient included, in the following order:
a. two sentence-completion tasks (18 trials each) with sentences lacking a verb. In the first task, we manipulated the tense of the verb (present – compound past – future; e.g., Oggi io mangio una mela. Ieri io … una mela lit., ‘Today I eat an apple. Yesterday [I ate [lit. have eaten]] an apple’); in the second task we manipulated the person of the verb (e.g., Io suono la chitarra. Maria [suona] la chitarra ‘I play the guitar. Maria [plays] the guitar’);
b. two sentence-completion tasks (eighteen trials each) with sentences lacking a noun (e.g., In cucina ho un forno. In cucina ho due [forni] ‘I have an oven in the kitchen. I have two [ovens] in the kitchen’), or a determiner (e.g., Ho sbucciato [la] banana ‘I pealed [the –fem, sing] banana’);
c. two memory span tasks with series of pseudo-words or numbers respectively. For the pseudoword task, there were 12 trials of 3 pseudo-words each (2 bissilabic and 1 trisilabic). For the number task, there were 12 trials of 4 numbers each. In 1/3 of the trials there were 1-digit numbers, in 1/3 of the trials there were 2-digit numbers, in 1/3 of the trials there were half 1-digit and half 2-digit numbers.

The patient was asked to repeat each sequence, as pronounced by the experimenter. We reasoned that the rTMS delivered on the targeted area should only affect the patient's performance on verb tasks—Noun production was already at ceiling and memory should be unaffected by the treatment.

Procedure

The experimental tasks were administered to the patient: (I) In 2 separate baseline sessions before the beginning of the rTMS treatment. This was done in order to control for possible learning effects; (II) in six sessions after the first real rTMS treatment; (III) in 2 sessions after the SHAM rTMS treatment; (IV) in four sessions after the second real rTMS treatment.

The patient was tested by the second author who, at the time of testing, was blind to the hypothesis.

The whole experimental battery was administered to the patient in each testing session. The first testing-session post-rTMS or post-SHAM was performed one or two days after the end of the treatment. The patient did not receive any type of stimulation (real or SHAM) during the whole period of testing. The between-session interval was set at 15 days (Figure 2).

Results

Responses that differed from the targets as well as no-responses were scored as errors. For all the completion tasks, we assigned the score of “1” to correct responses, and the score of “0” to errors. For the memory span tasks, we assigned one point to each number/pseudoword that was repeated correctly. Thus, the scores ranged from 0 (=0 correct) to 3 (=all pseudo-words correct) or 4 (=all numbers correct).

Repeated-measure ANOVAs were performed on these values, by separately considering the patient's performance on Verbs, Nouns, Pseudo-words and Numbers. For Nouns and Verbs, there were two variables: Session (13 levels: data from the two baseline sessions were collapsed as they were perfectly comparable – see Figure 3) and Task (2 levels: Tense vs. Person for verbs, Noun Number vs. Determiner Number for nouns).

For Pseudo-words and Numbers only the variable Session was considered.

Verbs. The main effect of Session was the only significant effect (F(12, 408) = 3.3, p = .0002). This effect was due to an increased performance after both real rTMS treatments. Duncan post-hoc comparisons revealed significant differences between the first four sessions post-first rTMS treatment vs. Baseline (p < .01) and both post-SHAM sessions (p < .05); and between the first 3 sessions post-second rTMS treatment vs. Baseline (p < .05) and both post-SHAM sessions (p < .05. Figure 3).

Nouns. The main effect of Task was the only significant effect (F(1,34) = 8.5, p = .007). This effect reveals that the patient fared significantly better on the Determiner than on the Noun task, independently of the treatment.

Memory tasks. The variable Session did not reach significance, either for Pseudo-words or Numbers.

Discussion

This case study is the first to report lasting improved linguistic skills following application of hf-rTMS treatment in a PPA patient.

The application of rTMS to the anterior midfrontal gyrus resulted in a significant improvement of the patient's performance on verbs, as compared to both baseline and SHAM conditions.

Fig. 2. Schematic representation of the times of the study.
On the other hand, no difference was observed between SHAM and baseline conditions.

This observation supports the view that the patient's improvement was a TMS-specific effect.

Moreover, the lack of any modification of the patient's performance in the memory tasks seems to speak in favour of a language-specificity of the reported rTMS effects.

Unfortunately, our data do not allow us to adjudicate between the language-specificity or, more narrowly, the verb-specificity of the rTMS treatment.

This is because the SPAN tasks administered to our patient were both non-language and non-verb tasks. In addition, the only other linguistic tasks included in the battery were concerned with nouns, and the patient's performance on nouns was at ceiling, hence unaffected by TMS.

Alternatively, one could make the argument that, since the tasks were repeated by using the same items, the language improvement could be reduced to an a-specific learning effect.

This is unlikely, however. Critically, we used an ABA design (rTMS-SHAM-rTMS) and found an effect on linguistic performance of the first rTMS treatment, no effect of SHAM treatment, but an effect (again) of the second rTMS treatment.

Likewise, this pattern of performance cannot be accounted for by the hypothesis of a deterioration of language skills, independently of rTMS.

If, at the time of SHAM treatment, the patient's performance were deteriorated to the point where any treatment—TMS or SHAM—would be fruitless, the second rTMS treatment would have been ineffective. But in fact this was not the case.

Nevertheless, we cannot exclude an impact of language deterioration on the patient's performance. The most obvious effect to be attributed to language deterioration is the different duration of the benefit between the first and the second rTMS treatment.

In the case of the first treatment, it spanned over 4 sessions, whereas in the case of the second treatment, it spanned over 3 sessions (at the fourth session, the performance did not drop to baseline levels, but the difference was no longer significant).

Leaving aside artefactual motivations that may well be responsible for this finding, one would make the prediction that, by prolonging the duration of the treatment, one could prolong the benefit as well. Follow-up studies should be devoted to test this prediction by manipulating the duration of the TMS treatment as well as other parameters of the protocol.

The mechanisms by which 20 Hz rTMS applied to the anterior portion of the left midfrontal gyrus led to improved ability on verbs are largely unknown.

We hypothesize that the rTMS treatment, by modulating cortical activity, was able to increase the excitability of the targeted area. Possibly, this modulation may have re-established the normal equilibrium of the activation levels between areas deputed to linguistic tasks and other neighboring areas that were shown to be abnormally activated in PPA patients engaged in linguistic tasks (Sonty et al., 2003).

Unfortunately, at this time, we cannot say whether our hf-rTMS protocol really excited the L-midfrontal gyrus of our patient. We hypothesize that this occurred, but we have no pre-rTMS and post-rTMS fMRI comparisons for him. Functional MRI comparisons would be critical for future research, in order to better understand the effects of rTMS on activation levels in specific regions of interest (ROIs), both local and remote from the site of rTMS.

The post-rTMS improvement in this PPA patient is particularly striking, because neurodegenerative forms of aphasia are not considered to have potential for improving.

Our findings complement the results by Naeser et al. (2005 a-b). These authors observed improved language abilities after inhibition of the right homologue of the Broca’s area in
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non-fluent post-stroke aphasics. A reasonable interpretation is that the connections of a given language-relevant region may be strengthened following the suppression of the homologue of that region, thus suggesting that low frequency-rTMS may possibly modulate the distributed, bihemispheric language network.

Our tentative study opens up the possibility that TMS, when applied at high frequency, may directly strengthen the neural connections within the damaged area in the left hemisphere.

This hypothesis nicely converges with recent results showing improved action naming performance following hf-rTMS in AD patients (Cotelli et al., 2006).

The real challenge for the efficacy of rTMS treatments is that in PPA, as well as in neurodegenerative disorders, differing from post-stroke aphasia, a progressive deterioration of language skills is intrinsic to the natural course of the disease.

The extent to which rTMS may counterbalance the natural trend towards linguistic deterioration in PPA is a question for future research. Although no treatment at the moment may be thought to be able to reverse the course of any neurodegenerative disease, our results suggest that TMS may be used as a therapeutic tool to slow down linguistic deterioration in PPA, and possibly in other forms of neurodegenerative aphasia.

Further explorations in this direction, besides their potentially relevant therapeutic impact, may greatly contribute to our understanding of the physiopathology of the neural circuits devoted to specific language functions.

References


