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THESIS

THE NEURAL MECHANISMS UNDERLYING RECOVERY OF APHASIA IN PATIENTS WITH LEFT HEMISPHERE STROKE

S.S.D. MED/34

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ABSTRACT

Aphasia is a severely disabling disorder. In Italy, approximately 150.000 individuals suffer from aphasia following a stroke. Although most individuals regain at least some language functions, between 30 and 43% of those affected remain severely aphasic 18 months after stroke. Among the different language functions, word-finding difficulties are the most frequent, pervasive and persisting disorder. Therefore, naming in normal individuals and naming disorders in individuals with aphasia have consistently been an area of interest for many researchers. Several studies have clarified many aspects of the anatomo-functional architecture of the cognitive/linguistic processes involved in naming, and have begun to tackle the problems inherent in the recovery of naming disorders after stroke. However, some theoretical and clinical issues remain underspecified. In particular, the relative role of ipsilesional and contralesional areas is still debated.

My PhD research program intends to evaluate the time course of recovery of language functions in patients with aphasia, as well as determine the neural underpinnings involved in the recovery of aphasia in patients with left hemisphere stroke, by means of an rTMS and fMRI study.

INTRODUCTION

Aphasia is a severely disabling disorder. In Italy, approximately 150.000 individuals suffer from aphasia following a stroke. Clinical evidence shows that aphasia typically tends to improve over time (De Renzi Faglioni, 1975; Vignolo, 1964, Kertez et al, 1979) and that this recovery can continue for many years (Basso, 1995; Pradhat-Diehel, 2001). With regards to the pattern of recovery of the different language functions, studies agree that auditory comprehension is usually the first function recovered (Basso, 1995), followed by the recovery of spontaneous speech language , which generally recovers less than auditory comprehension . A critical issue is the long-term recovery of aphasia. Current knowledge regarding the recovery of aphasia after stroke is based on observations limited to the first years post-stroke. Investigating this important issue may have important implications for aphasia rehabilitation.

Although most subjects regain at least some language functions, between 30 and 43% of those affected remain severely aphasic 18 months after stroke. Among the different language functions, word-finding difficulties are the most frequent, pervasive and persisting disorder. Therefore, naming in normal individuals and naming disorders in individuals with aphasia have consistently been of interest to many researchers. Several studies have clarified many aspects of the anatomo-functional architecture of the cognitive/linguistic processes involved in naming and have begun to tackle the problems inherent in the recovery of naming disorders after stroke. However, some theoretical and clinical issues remain underspecified. In particular, the relative role of ipsilesional and

contralesional areas is still debated. Behavioural studies have repeatedly demonstrated,that speech-language treatment (SLT), targeted to the specific deficit shown by the individual with aphasia , can induce long-lasting recovery from aphasia (for review, see Basso, 2004). These studies present and discuss behavioural data at length, and give detailed information on the training techniques used during SLT. They help establish that the recovery of language following SLT is causally related to treatment, and is not merely an aspecific effect of cognitive stimulation. However, behavioural studies do not provide fine-grained information on the neural correlates of damage and of its impact on treatment. Neuroimaging data, even though inconclusive in regards to the neural underpinnings of treatment-induced neuroplasticity, have provided interesting information on the neural mechanisms underlying spontaneous recovery of language and on those that are active in the damaged brain. Results clearly suggest that language recovery involves changes in both hemispheres.

An fMRI study on 14 patients who recovered from aphasia within the first year from onset (Saur et al, 2006) suggests that brain reorganization goes through three phases: 1) strongly reduced activation of left hemisphere (LH) language areas in the acute stage; 2) up-regulation and recruitment of right-hemisphere (RH) homologues of damaged areas in the sub-acute stage; 3) normalization of activity in the language network (i.e.decreased excitability of contralesional areas and increased recruitment of perilesional tissue, which correlates with language recovery) in the chronic stage. The picture observed in patients with chronic aphasics is more difficult to interpret. In these subjects, language tasks

result in complex patterns of perilesional and contralesional activation, the latter often occurring in regions that are homologues of those damaged in the language-dominant hemisphere (Cornelissen et al, 2003; Fridriksson et al, 2006; 2007; Leger et al, 2002; Meinzer, 2006; Musso et al, 1999; Small et al, 1998; Vitali et al., 2006). Several observations suggest that activity in contralesional RH regions may not play a positive role in the subject's performance. For instance, in an fMRI naming experiment with a small group of individuals with aphasia, activation was observed in the left perilesional areas during correct responses, and in the right inferior frontal gyrus during semantic errors (Postman-Caucheteux et al, 2010). In light of these and similar observations, it has been argued that RH mechanisms may support language recovery in the acute phase, but may be an inefficient, and perhaps even a maladaptive strategy in the long term, possibly hindering neural recovery (Price & Crinion, 2005).

Consistent with this possibility, several observations suggest that even though RH activation is often documented in chronic aphasia, perilesional LH activation shows a closer correlation with functional recovery (eg, Rosen et al, 2000; Heiss & Thiel, 2006; Meinzer et al, 2008). The possibility that maladaptive RH hyperactivation reduces language recovery has prompted the use of repetitive transcranial magnetic stimulation (rTMS) in an attempt to improve language disorders in individuals with chronic aphasia. It was reasoned that if the right hemisphere (RH) is hyperactive in individuals with chronic aphasia and inhibits residual function in the left hemisphere (LH), reducing its activity should

"release" LH networks and be conducive to improving language skills in patients with chronic aphasia (Naeser et al. 2005; Martin et al., 2009; Martin et al., 2010). Martin et al. (2005) showed that repetitive slow-frequency TMS (rTMS) over the anterior portion of the RIFG, for 5 days/week for 2 consecutive weeks, improved naming deficits and reduced naming reaction times in 4 individuals with chronic aphasia.

Although promising, these results have significant limitations. The studies were conducted on single cases and did not include a control group. Therefore, it remains unclear how often low-frequency rTMS over the RH homologue of Broca's area is required to successfully recover language functions. The main methodological limitations of these studies are that a) only single cases or very small patient samples have been studied; b) the effects of the experimental treatment cannot be clearly distinguished from spontaneous recovery or from a placebo effect, as control groups were not considered; c) all studies included non-fluent aphasics, with the exception of a single case, and thus no reliable data on other types of aphasia are available; d) no studies tried to combine the effects of rTMS with functional imaging procedures in order to evaluate the neural changes induced by rTMS. More recently, neuroimaging investigations have also studied language recovery. These studies clearly show that specific speech language training can modify the patterns of neural activation in subjects with aphasia, even in the chronic stage of the disorder (eg, Cornelissen et al, 2003; Fridriksson et al, 2006; Leger et al, 2002; Musso et al, 1999; Small et al, 1998), as well as provide neurobiological information of unprecedented

detail. However, they typically include only generic statements on the behavioral dimensions of the disorder and on SLT.

AIMS OF THE PROJECT

As previously mentioned, the long-term recovery of aphasia still remains a critical issue in the aphasia literature. Current knowledge regarding aphasia recovery after stroke is based only on observations limited to the first years after stroke. Thus, improving knowledge on this important issue may have important implications for aphasia rehabilitation.

Furthermore, the failure to retrieve object names in the presence of spared knowledge about the same objects (pure anomia) is the most frequent, pervasive and persistent aphasic deficit across clinical forms of aphasia, at all stages of evolution. Behavioral studies show that pure anomia can be improved by both low-frequency rTMS over the RH homologue of Broca's area and speech language therapy, but the neural substrate underlying recovery is unclear. In particular, the relative role of ipsilesional and contralesional areas is still debated.

The aims of the project are as follows:

- To characterize the time course of recovery of the different language functions in a patient with left hemisphere stroke. For this purpose, the long-term outcome (25 years) of language was studied in a young patient with global aphasia.

- To evaluate if and to what extent slow inhibitory rTMS treatment enhances naming abilities as compared to sham rTMS. The study was carried out according to a randomized control trial design in patients suffering from

chronic aphasia. The first group (experimental group) underwent an rTMS protocol while the second group (control group) underwent a sham rTMS protocol. Patients were evaluated 1 month after completing the treatment protocol in order to evaluate if the above changes were stable over a 1-month period.

- To show the neural mechanisms on which the potential clinical changes induced by phonological training are based. This was done by testing changes in hemispheric neural activity before and after the training by means of BOLD-fMRI in patients with aphasia.

OUTCOME OF APHASIA IN PATIENTS WITH STROKE

Current knowledge regarding aphasia recovery after stroke is based on observations limited to the first years post stroke. Studies on the recovery of aphasia report that the greatest degree of language recovery takes place in the first months after stroke (Lazar RM, 2008). Although the rate of recovery drops after 3 to 6 months, evidence of language improvement even 1 or 2 years after stroke has been reported in the literature (Naeser et al., 1990; Saur et al 2006). Only a small number of studies have followed patients with aphasia longer than 2 years post stroke (Lazar, 2008; Pradhat-Diehl et al, 2001; Naeser et al, 1998; Vitali et al, 2007). Therefore, current knowledge on the potential recovery of chronic aphasia is not sufficient. For the first time, the long-term outcome of language in a patient with global aphasia was studied (Smania et al., 2010). The patient was tested with a wide range of language, intelligence, and praxic abilities for 25 years after stroke.

Case description

In 1983, a 37-year-old man presented with an acute onset of right hemiplegia, hemianesthesia, and language disturbances. He was admitted to the Neurology Unit of the GB Rossi University Hospital, Verona –Italy. The computed tomography scan of his brain revealed a large ischemic cortical and subcortical lesion in the left middle cerebral artery territory. The patient had no risk factors for cerebrovascular disease and no previous history of cerebrovascular attacks. He was right handed and had 13 years of education. He underwent language

rehabilitation for 2 years; 5 times per week in the first 6 months and then 3 times per week until the end of the second year. For many years his only speech production was the nonsense word "musi." Details of his brain lesion are presented in Figure I. He was tested with the Milan Language Examination (MLE) (Organizzazioni Speciali, 1974), the Token Test (De Renzi e Faglioni, 1978), the Raven Test (Raven JC, 1962), and tests for oral, ideational, and ideomotor apraxia (Smania N., 2000) at 3 weeks, 2 and 6 months, and 1, 2, 3, 10, 21, and 25 years poststroke. An additional examination performed 3 years after stroke showed that spatial memory (Corsi Block- Tapping test (De Renzi e Nichelli, 1975) (span = 5, supraspan = 8) and selective attention (Spinnler e Tognoni,1987) (total score = 42/60) were within normal ranges. Verbal memory was not testable because of the severity of his aphasia.

Statistical analysis

Milan Language Examination data were analyzed by means of descriptive analysis and a linear regression model [score= a +ß log (time)] to estimate the trend of the Milan Language Examination data over time. The Spearman's test was performed between the main language functions (comprehension, repetition, naming, event description, reading) by computing the raw scores of speech naming and event description and the mean scores of comprehension, repetition, and reading items of the MLE ($P < .05$). Statistical analysis was performed with R Package 2.8.1.

Results

The MLE and other neuropsychological test data are given in Table 1. The MLE linear regression model showed a significant improvement in each language function (Comprehension $R2 = 81.85$, Repetition $R2 = 96.67$, Naming $R2 = 79.13$, Reading $R2 = 78.68$, Event description $R2 = 60.36$) over time. The rate of improvement was estimated at 1 year (Comprehension 70%, Repetition 50%, Naming 0%, Reading 0%, Event description 0%), 3 years (Comprehension 84%, Repetition 62%, Naming 24%, Reading 25%), and 25 years after stroke (Comprehension 100%, Repetition 85%, Naming 45%, Reading 46%, Event description 15%). Significant correlations were found between time changes in these language functions: Comprehension– Repetition ($r = .928$, $P < .001$), Naming–Reading ($r = .994$, $P < .001$), Repetition–Naming ($r = .867$, $P < .001$), and Repetition–Reading ($r = .874$, $P < .001$).

Discussion

Results showed that recovery of global aphasia after stroke is not limited to just the first years following onset but can extend for even more than 1 decade. Overall, 3 main periods of recovery could be identified (Figure II). The first period (first year after stroke) was characterized by recovery of verbal comprehension and word repetition, the second (1-3 years) by emergence of naming and reading, and the third (3-25 years) by a progressive improvement of previously emerged functions, as well as the appearance of spontaneous speech (event description).

To illustrate the time course of recovery found in this patient, each main language function tested by the MLE will be discussed separately (Figure II).

Auditory comprehension was the first function to show recovery, in particular in the first years (Naeser et al, 1990). However, different patterns of comprehension recovery were evident, depending on the contextual content of the tasks used. In the MLE comprehension subtests, in which the patient was challenged with simple and contextualized tasks (i.e., indicate which figure represents the everyday object verbalized by the speech therapist), the patient showed a rapid recovery, approaching normal performance in a 1-year time frame. On the contrary, a slower and more progressive recovery of performance occurred in the Token Test (Saur et al 2006; Selnes et al., 1983), which consists of very decontextualized and unusual verbal comprehension tasks (i.e. touch 1 or more tokens of different sizes and/ or colors; Table 1).

Repetition also had its greatest rate of recovery in the first year, paralleling the trend of comprehension improvement. After the first year, repetition continued to slowly improve, reaching its highest level after 10 years.

Naming of a visual item, which implies the ability to autonomously transform a visual–structural representation into a phonological output (Saur et al 2006), merged between 1 and 3 years after stroke and progressively improved, reaching 45% of performance in 25 years. It should be noted that reading had a trend of recovery equivalent to that of naming (Figure 2), suggesting that reading and naming may share elements of their neural substrates (Marsh EB, Hillis AE, 2005). Spontaneous speech ("Event description" in Table 1) emerged

many years after stroke, first documented at 10 years, and then slightly improved over time. Although spontaneous speech production was limited to a few high-frequency words (house, bread, beard, etc), this complex language task implies that the patient reached the skill of autonomously selecting a lexical representation from semantics, accessing the phonological word form, motor programming, and planning of articulation to say the word (De Leon et al., 2007). The most challenging question is to understand why this patient demonstrated such improvements in the long-term. In the first years after stroke, we hypothesize that improvements may have been influenced by language rehabilitation, which took place 5 days per week in the first 6 months and then 3 times per week until the end of the second year (Moss et al., 2006).With regard to the progressive recovery seen in the long term, other factors, such as the patient's strong motivation and active social participation, (Hinckley et al., 2001) may have played an important role. Indeed, motivation may have continuously stimulated the patient to express himself and to practice his linguistic abilities outside the rehabilitative context (Hinckley et al., 2001). Other important factors possibly contributing to the recovery process may be the patient's young age (Laska et al., 2001; Lazar et al., 2008) and the presence of relatively spared residual cognitive functions, such as memory and attention (Hillis AE, 2006). This condition may have produced a favorable foundation for the continued acquisition of new language abilities. Evidence emerging from the present case report may have implications for rehabilitation of language disorders after stroke. First, the results suggest that the time window for

possible improvement in global aphasia may be much wider than previously believed. Based on this, it could be hypothesized that patients may benefit from language stimulation over the long term. Moreover, the behavioral changes seen in this patient suggest that care programs in patients with chronic aphasia should take into account not only conventional aphasia training approaches but also other types of stimulation, such as the stimulation of various nonlinguistic cognitive abilities (Hillis AE, 2006; Seniòw et al., 2009) and the creation of a context within a person's everyday life that provides a sense of motivation and permits social interaction (Hinckley et al., 2001). The main limitation of this case report is that since it was based only on clinical examination, it is not possible to identify how functional brain changes were involved in the process of long-term language recovery. In conclusion, the present study highlights that in patients with global aphasia there may be some potential for the emergence and improvement of linguistic functions even many years after stroke.

THE NEURAL MECHANISMS UNDERLYING RECOVERY OF APHASIA: EFFECTS OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (r-TMS) IN PATIENTS WITH LEFT HEMISPHERE STROKE

Functional imaging studies of patients with chronic aphasia suggest that recovery of language can take place in a pre-existing, bilateral network, with an up-regulation of undamaged areas and a recruitment of perilesional tissue and homologue right language areas (Saur et al., 2006). Repetitive transcranial magnetic stimulation (rTMS) has been proposed as a feasible and safe therapeutic and investigative instrument in cognitive disorders resulting from stroke (Mally J, Stone TW., 2007). This device is mostly used for its inhibiting properties over the unaffected hemisphere of patients with stroke. The scientific justification of this approach is based on functional neuroimaging studies which show that in motor and cognitive disorders resulting from stroke a long-term over activation of the unaffected hemisphere could correlate with a poor functional recovery (Saur et al., 2006). It was assumed that this hyperactivity of the unaffected hemisphere could have an inhibitory effect over the affected hemisphere, hindering possible residual mechanisms of neural recovery. On this basis, it was hypothesized that inhibition over the unaffected hemisphere as a result of rTMS could possibly release recovery processes within the neural network sub serving language functions. Two preliminary studies in patients with chronic nonfluent aphasia showed that 10 sessions of 1Hz rTMS application to the right Broca's homologue led to improvement in the patients' ability to name pictures (Martin et al., 2004; Naeser et al., 2005).

However, as previously reported, further research is warranted to demonstrate the effectiveness of rTMS in the treatment of aphasia. In particular, future studies should include multiple baseline language testing pre-rTMS, as well as a sham rTMS control group.

The aim of this study was to evaluate if and to what extent slow inhibitory rTMS treatment enhances naming abilities, compared to sham rTMS.

METHODS

Patients

Ten right-handed subjects with chronic aphasia caused by left hemispheric stroke were enrolled. MRI confirmed the diagnosis of stroke.

Inclusion criteria were: (1) single left ischemic stroke at least 1 year prior to enrollment; (2) aphasia with a mild-moderate comprehension impairment; (3) no evidence of language recovery in the month prior to enrollment; (4) at least 10% correct responses on the picture naming battery.

Exclusion criteria were: (1) any clinically significant or unstable medical condition; (2) severe auditory comprehension deficit; (3) severe perceptual or widespread cognitive deficit; (4) history of substance abuse, (5) any neuropsychiatric comorbility; (6) contraindications to rTMS and MRI.

Subjects were recruited among outpatients referred to the Speech Therapy Department of the GB Rossi University Hospital (Verona). They signed informed

consent forms to participate in the study.

Six patients were considered eligible to participate in the study. Two patients (one in the experimental group and one in the control group) were excluded from the study because they discontinued the treatment program. Thus, two patients in each group completed the study (for details see Figure III).

Aphasia diagnosis was established by means of the Aachener Aphasia Test (AAT) (Luzzatti et al., 1987): two patients (F.C. and M.M.) had to some degree recovered from non fluent Broca's aphasia to anomic aphasia (Luzzatti et al., 1987); one patient (N.I.) had moderate nonfluent Broca's aphasia, and one (T.T.) had severe nonfluent, global aphasia.

Patient F.C was a 57-year-old right handed male 1 year post stroke, and patient M.M was a 71-year-old right handed male 2 years post stroke. At preliminary testing they had non-fluent aphasia, pure anomia and agrammatic speech. The structural MRI scan showed a left frontal lobe lesion in the anterior branches of the left middle cerebral artery that included the left cortical Broca's area and the white matter deep to it (Figure IV).

Patient F.C. had no sensorimotor deficits in the right upper extremity, while M.M. had right hemiparesis.

Patient N.I. was a 54-year old female 3 years post stroke. She had non-fluent aphasia, pure anomia and agrammatic speech. The structural MRI scan showed a cortical and subcortical lesion in the left middle cerebral artery (Figure IV) and she had a right hemiparesis.

The most severe patient, T.T., was a 56-year old right handed female 3 years post stroke. She had severe non-fluent aphasia with anomia. The structural MRI scan showed a large cortical and subcortical lesion in the branches of the left middle cerebral artery (Figure IV). The lesion involved the fronto-parietal and temporal lobes (Figure IV) and she had severe right hemiparesis.

Demographic and clinical patients' features are reported in Table II.

All patients received no speech therapy treatment in the six months prior to enrollment in the study, nor did they receive any speech therapy during the study. Written informed consent was obtained from all participants before her/his inclusion in the study.

After preliminary testing, each patient was assigned to the experimental or control group, based on a simple randomization scheme. The experimental group underwent rTMS treatment while the control group underwent sham-rTMS.

Each patient completed a behavioral evaluation three times: before treatment (T0), immediately after treatment (T1) and at follow-up (1-month) (T2).

The experimental behavioral procedures included the short version of the Batteria per l'Analisi dei Deficit Afasici (BADA; Miceli et al., 2004) and the naming test (108 items).

Experimental behavioral procedures

- *Battery for Aphasic Deficit Analysis (BADA) (Miceli et al 2004)*

A 36-task language battery which allows a detailed analysis of language disorders evaluating sublexical, lexical-semantic, syntactic and phonological working memory functions. There is a full-length version of the battery (BADA-F), and two abbreviated versions (BADA-1 and BADA-2). Each of the abbreviated versions include half of the stimuli included in the BADA-F and their stimuli are fully matched for psycholinguistic variables. The BADA-1 is administered at T0, one of the abbreviated versions at T1, and the other at T2. The variety of tasks in the BADA allows the measurement of changes in a wide range of language abilities that may benefit from treatment.

- *Picture naming test.*

One hundred and eight stimuli generated from the standardized set of 260 pictures from Snodgrass and Vanderwart (1980). The list contains items from three separate semantic categories (animals, vegetable, tools and furniture). During each evaluation session the stimuli are presented on a laptop using three different randomized orders. Once the picture is shown, the subject is asked to name it as soon as possible. The total number of pictures named correctly is measured. During the 3 weeks prior to the start of treatment, the patient is tested 3 times on three separate days in order to collect a baseline.

In order to ensure that anomia results from damage to lexical knowledge (poor naming but normal stimuli comprehension) as opposed to from damage to conceptual knowledge (represented by difficulties in both comprehension and naming), three word picture verification lists were generated. Each list consists of 36 pictures taken from the Snodgrass and Vanderwart picture naming test, and an additional 72 pictures semantically or not semantically related to the target picture . The patient is asked if he/she recognizes the picture shown, and is required to answer "yes/no". During the 3 weeks prior to the start of treatment, the patient is tested 3 times on three separate days. A different list was used during each evaluation session.

Treatment procedures

Each participant received 10 treatment sessions, 5 days/week, for 2 consecutive weeks. Treatment was carried out on an outpatient basis. No speech language therapy other than that included in the study protocol was administered until T2.

rTMS procedures

The target area for real and sham rTMS was identified by means of a neuronavigator system during MRI acquisition, based on morphological

functional data. The stimulation point was fixed by a marker using a stereotactic neuronavigation system (BrainVoyager, Brain Innovation BV, The Netherlands).

For real rTMS, stimulation was applied at 1-Hz frequency for 20 min (1200 pulses) at 90% of the motor threshold (left, 1st dorsal interosseus muscle) (Rossini et al, 1994), using a Super-Rapid High Frequency MagStim Magnetic Stimulator and a figure 8-shaped coil (MagStim, NY). A frameless stereotaxic system (BrainVoyager, Brain Innovation BV, The Netherlands) guided the position of the TMS coil on the patient's scalp. Coil orientation was held constant across sessions and subjects, at approximately 45°. For sham rTMS treatment, a sham coil was placed at the same site.

Statistical analysis

Descriptive analysis and non-parametric tests were used to compare results at T0, T1 and T2. Post-hoc paired Wilcoxon tests were used to compare T0 and T1, and T0 and T2. The level of significance for multiple comparisons was adjusted according to the Bonferroni procedure. To compare the effects of treatments in the two groups, the Mann-Whitney test was used. For this purpose, the differences in performance at T0-T1-T2 were considered for each task.

Results

BADA results are detailed in Table III.

Picture naming test results collected before treatment, immediately after treatment and at follow-up are detailed in Table IV.

The within subject analysis performed by the Wilcoxon test showed no significant difference on the number of pictures correctly named immediately after treatment and at follow-up.

The between subject analysis performed by the Mann-Whitney test showed that the experimental and control group had no significant differences in performance.

Discussion

Preliminary results in four patients with aphasia showed that the application of 1Hz rTMS to the right Broca's homologue area could lead to a similar degree of improvement as in the sham rTMS. The slow inhibitory rTMS treatment performed resulted in slight improvements in the number of pictures correctly named in both the experimental and control group after treatment, but these differences were not significant. At 1-month post treatment no significant changes were found. In contrast, Naeser and collegueaus (2005) reported significant improvement in picture naming (and in reaction time) at 2 months post-rTMS, with lasting benefits noted at 8 months in three patients. The Authors hypothesized that the application of 1Hz rTMS to an anterior portion of R Broca's homologue may suppress this area and then modulate the prefrontal/temporo-parietal connections important for picture naming. It is

likely that the suppression of the right Broca's homologue in these patients may promote better modulation in the right hemisphere, as well as in the remaining left hemisphere temporo-parietal language structures important for naming (Price et al., 2001). Previous functional imaging studies performed before and after speech therapy have suggested that "new" left hemisphere activation may be particularly important in patients who have shown good responses after treatment (Cornelissen et al., 2003; Musso et al, 1999). It is possible that functional imaging studies performed before rTMS treatments would be necessary to better understand which patients had a real iperactivation of the right Broca's homologue area and are suitable for slow inhibitory rTMS treatment. In this light, it is possible that patients who underwent real rTMS did not improve in naming tasks because they had no hyperactivity in the right hemisphere, with consequently scarce rTMS effects.

However, the comparison between the rTMS and the sham rTMS group suggests that rTMS may have limited effects in treatment of naming disorders in aphasia. Considering that the study involved only four patients, further research on large patient samples is warranted in order to confirm these preliminary data. It is important to note that none of the patients in the experimental group had any side effects, thus confirming that rTMS appears to be a safe procedure.

In both groups, all patients and their care-givers reported a significant improvement in daily life communication. In the experimental group this effect could be caused by the possible role of rTMS in improving mood with a consequently improvement in their communicative abilities (Mally et al., 2007;

Rossini et al., 2005). Although no specific outcome measures for mood disorders was included in this study, it is possible that this effect occurred in patients treated with rTMS. It is interesting to note that similar effects were found in the sham rTMS group.

Future studies with patients with aphasia should perform fMRI before and after a series of rTMS treatments. This would demonstrate whether rTMS alters activation in specific cortical regions of the bi-hemispheric neural network for naming and other language behaviors, thus aiding our understanding of the mechanism of action of rTMS.

THE NEURAL MECHANISMS UNDERLYING RECOVERY OF APHASIA IN PATIENTS WITH LEFT HEMISPHERE STROKE: AN fMRI STUDY.

Project in collaboration with Centre of Mind/Brain Sciences (CIMeC) Functional Neuroimaging Laboratory (LNiF)- Mattarello-Italy

Failure to retrieve object names despite the presence of spared knowledge about the same objects (pure anomia) is frequent in aphasia. It has been repeatedly demonstrated that speech-language therapy (SLT), targeted to the specific deficit shown by the individual with aphasia, can induce long-lasting recovery from aphasia (Basso, 2004). These studies present and discuss mainly behavioral data, and provide detailed information on the training techniques used during SLT. They help establish that language recovery following SLT is causally related to treatment, and is not merely an aspecific effect of cognitive stimulation. However, behavioral studies do not provide fine-grained information about the neural correlates of damage and of its impact on treatment. In addition, the neural substrate underlying recovery is unclear. In particular, the relative role of ipsilesional and contralesional areas is still debated. The neural underpinnings of phonological training in three patients with aphasia in the chronic stage after stroke, by means of BOLD-fMRI, were investigated.

METHODS

1. Patients

Eight right-handed subjects with chronic aphasia caused by left hemispheric stroke were enrolled. The diagnosis of stroke was confirmed by MRI. Inclusion and exclusion criteria were the same as previously described (see methods). Inclusion criteria: (1) single left ischemic stroke at least 1 year prior to enrollment; (2) aphasia with a mild-moderate comprehension impairment; (3) no evidence of language recovery in the month prior to enrollment; (4) at least 10% correct responses on the picture naming battery.

Exclusion criteria: (1) any clinically significant or unstable medical condition; (2) severe auditory comprehension deficit; (3) severe perceptual or widespread cognitive deficit; (4) history of substance abuse, (5) any neuropsychiatric comorbility; (6) contraindications to MRI 4T.

Patients were recruited among outpatients referred to the Speech Therapy Department of the GB Rossi University Hospital (Verona) and the CIMeC Unit (Trento), the Santa Maria del Carmine Unit (Rovereto). They signed informed consent forms to participate in the study.

Eight patients were considered eligible to participate in the study. Two patients were excluded because they did not meet inclusion criteria, while one patient declined to participate. Five patients were included in the study and three of them completed the post treatment analysis (Figure V).

Case description

The first patient (CFI) was a 58-year old right-handed male, 2 years post stroke. At preliminary testing, he had non-fluent aphasia, with pure anomia and agrammatic speech. The structural MRI showed a lesion involving the left hemisphere, in particular in the anterior branch of the middle cerebral artery (inferior and medial frontal gyri, insula and putamen). He had no sensorimotor deficits.

The second patient (RLO) was a 38-year old right-handed female, 5 years post stroke. At preliminary testing, she had non-fluent aphasia with pure anomia and agrammatic speech. Her structural MRI showed damage similar to that of the first patient, involving the anterior branch of the middle cerebral artery. She was affected by right hemiparesis.

The third patient (PPE) was a 65-year old right handed male, 27 years post stroke. His speech was severely non-fluent and agrammatic with pure anomia. The structural MRI showed a large lesion involving the entire territory of the middle cerebral artery. Lesion mapping showed involvement of Brodmann's areas 22, 21, 20, 37, 44, 6, 6s, 4, 40, 39, 3, 1, 2, 5, and 7 (MRIcron software, see http://www.mricro.com/mricron). The time course of aphasia recovery in this patient has been reported and described in literature (Smania et al., 2010). He was affected by right hemiparesis.

Pictures of patients' lesions are shown in Figure VI. Diagnosis of aphasia was established by means of the Batteria per l'Analisi dei Deficit Afasici (BADA; Miceli et al., 2004).

Demographic and clinical patients' features are reported in Table V.

Each patient completed a behavioral evaluation before treatment (T0) and the day after the end of treatment (T1). Written informed consent was obtained from all participants before her/his inclusion in the study.

Evaluation procedures and materials

a. Preliminary naming procedure

Three-hundred black-and white drawings were presented 3 times for oral naming. Sixty drawings were selected: 20 easy (E) stimuli, always named correctly; 40 difficult (D) stimuli, always named incorrectly. The latter stimuli were divided in two fully matched subsets: a 20-item, difficult/trained subset (DT) to be used for phonological training, and a 20-item, difficult/untrained (DU) subset, serving as the control. Treatment focuses on one subset, while the other serves as the control.

b. Experimental behavioral procedures

1) Batteria per l'Analisi dei Deficit Afasici (BADA) (Miceli, G., Burani, C., Capasso, R., Laudanna, A. Bologna, EMS, 2004) (for details see methods in chapter X) The short version of the BADA was administered before treatment. The variety of

tasks in the BADA allows the measurement of changes in a wide range of language abilities that may benefit from treatment.

2) Picture naming test. It includes 80 stimuli known to be difficult for the subject, based on the results from the preliminary naming procedure (see section a.). Matched subsets of difficult items were prepared, and treatment focuses on one subset, while the other serves as control.

Treatment procedures

Each participant received 10 treatment sessions, 5 days/week, for 2 consecutive weeks. Treatment was carried out on an outpatient basis. No speech language treatment other than that included in the study protocol was administered during the study

Phonological training of DT stimuli was administered for 10 consecutive days, in 1-hour sessions. During each session, the DT subset was presented 10 times, in different randomizations. The patient was asked to name each stimulus. When he failed to do so, a phonemic cue was provided (initial sound, then initial syllable, then first two syllables, and so forth), until the correct response was produced.

fMRI procedures

During the fMRI procedures the patient was required to name the 60 drawings

selected by the preliminary naming procedures. They were administered during three event-related BOLD fMRI sessions, performed with a 4T scanner. Drawings were presented for 4500 ms and the patient was asked to name them. Overt naming attempts were recorded via a nonmagnetic microphone placed within the scanner head coil about 1 cm in front of the participant's mouth, connected via optical cable to a laptop computer situated outside the scanner room. Vocal responses were recorded in ".wav" format during each fMRI run and were scored off-line.

fMRI naming sessions took place 1 month before training (T0), immediately before training (T1), and immediately after training (T2). During each session, the patient was asked to name the 60 stimulus drawings (naming task) or say a pre-learned pseudo-word in response to a squiggle (control task). Activations yielded by the E, DT and DU subsets at T0, T1 and T2 were contrasted.

The fMRI took place at the Centre of Mind/Brain Sciences (CIMeC)-Functional Neuroimaging Laboratory (LNiF) Mattarello-Italy). fMRI acquisition and Data Analysis Functional images were acquired with a Bruker MedSpec 4Tesla MRI performed by the Functional Neuroimaging Laboratory (LNiF) of CIMeC.

RESULTS

Behavioral data

In all patients behavioral analyses showed no changes between T1 and T0 (pre-treatment). In contrast, the same analyses showed significant changes between T2 and T1. Differences were restricted to trained stimuli (DT) and they did not generalize to untrained stimuli (DU). Naming accuracy was significantly greater at T2 than T1. The patient PPE showed an impressive effect after treatment. Before treatment he was unable to name any items and after treatment he was able to name all of them, despite being treated 27 years after stroke.

Neuroimaging data

Before training neuroimaging analyses showed no changes between T1 and T0. In the first fMRI naming session all patients showed a great activation in the left hemisphere, in particular in the perilisional areas. After training the difference between the activation while naming treated versus not treated difficult to name items was evaluated. Results showed that activation patterns were different.

In CFI, DT stimuli yielded multiple perilesional foci of significant increase of BOLD signal at T2 compared to T1.

In RLO, DT stimuli yielded multiple ipsilesional and midline (precuneus and posterior cingulate) foci of significant increase of BOLD signal at T2 compared to T1.

In PPE, DT stimuli yielded only controlesional foci of significant increase of BOLD signal at T2 compared to T1. For details see Figure VII.

Discussion

Results show that phonological training improves "pure anomia", even in patients with chronic aphasia. In accordance with data from previous studies, these effects were restricted to treated stimuli and no effects were seen for untreated materials. Patients underwent ten 1-hour phonological training sessions during which the patient was required to name 20 preselected stimuli. For each patient sixty drawings were selected from the preliminary naming procedure: 20 easy (E) stimuli, always named correctly; 40 difficult (D) stimuli, always named incorrectly. The latter stimuli were divided in two fully matched subsets: a 20-item, difficult/trained subset (DT) to be used for phonological training, and a 20-item, difficult/untrained (DU) subset, serving as the control. After training, all patients improved the number of pictures named correctly among the treated stimuli. In particular, patient PPE showed an impressive effect. Before treatment he was unable to name any difficult items and after treatment he was able to name all of them, despite being treated 27 years after stroke. These data are confirmed by previous studies that demonstrate that

speech-language therapy (SLT), targeted to the specific deficit shown by the individual with aphasia, can induce recovery from aphasia (Basso, 2004).

It remains to be seen if, for how much, and for how long improvement persists and/or can be enhanced by neuromodulation tecniques (rTMS and tDCS). Combining electrical stimulation (rTMS or tDCS) with speech therapy sessions may further promote language improvement by promoting the up-regulation of undamaged areas and recruiting perilesional tissue and homologue right language areas (Saur et al., 2006).

The fMRI data show that before training all patients had a great activation in the left hemisphere and in particular in the perilisional areas. After training the difference between the activation while naming treated and non-treated difficult to name items was measured and different types of activation were observed.

The first patient (CFI) showed an activation of the perilesional neural tissue subserving spared naming abilities. The second patient (RLO) showed an ipsilesional (not just perilesional) and midline activation involving the precuneus and the posterior cingulate gyrus. The third patient (PPE) showed an entirely contralesional activation.

All patients showed item-specific recovery after training. However, activation patterns were different. So even though before treatment all patients had activation in the perilesional area, after treatment the activation varied greatly. A possible explanation or this heterogeneous activation in regions within the "language area" of the ipsilesional and contralesional hemisphere could be that

the relative role of the two hemispheres in recovery may change in different individuals/patients as a function of various factors such as intrahemispheric lesion site, lesion side, lesion size and time post-onset. Furthermore, it could be argued that areas outside the language network may be involved in the recovery of language deficits: aside from perilesional and homologue language-associated regions, functional integrity of domain-unspecific memory structures may be a prerequisite for successful aphasia recovery. Their role, however, is yet to be understood.

CONCLUSIONS

The long-term outcome of language shows that the time span for recovery of language functions in global aphasia after stroke may be much longer than previously documented. Furthermore, the recovery of a given function could pave the way for the recovery of others. Preliminary results in four patients with aphasia showed that application of 1 Hz rTMS to a portion of Right Broca's homologue area could lead to similar degrees of improvement as in sham rTMS. Thus, data obtained leads to consider carefully the effect of TMS in enhancing naming abilities in aphasia. Further research on a larger patient sample is warranted in order to demonstrate the effectiveness of rTMS in the treatment of aphasia.

Functional data confirms that phonological training improves "pure" anomia, even in patients with chronic aphasia. Furthermore, results suggest that remodelling of cortical functions is possible even years after a stroke. The behavioural gain seems may be mediated by brain regions that had been partially deprived from input after the initial stroke. It remains to be seen if, how much, and for how long improvement persists or can be enhanced by neuromodulation techniques. The fMRI study shows that, even in the chronic stage after a stroke, language reorganization is a dynamic process, which may involve heterogeneous activations in regions within the "Language area" of the ipsilesional and contralesional hemisphere. The relative role of the two hemispheres in recovery may change in different subjects as a function of factors that are yet to be identified.

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TABLES AND FIGURES

Table I. Results of neuropsychological examination.

		Time from stroke								
		3 w	2 mo	6 mo	1 y	2 y	3 y	10 y	21 y	25 y
Milan Language Examination										
Speech	event description	0	0	0	0	0	0	1	2	2
	naming	0	0	0	0	10	20	35	55	50
Comprehension	words	40	55	80	95	100	100	100	100	100
	wsr	10	40	80	80	90	90	100	100	100
	sentences	10	10	45	90	75	100	100	100	100
Repetition	letters	0	80	90	100	100	100	100	100	100
	syllable	80	80	70	90	100	100	100	100	100
	words	0	0	35	35	50	70	80	95	95
	neologism	0	0	20	50	30	30	50	80	80
	sentences	0	0	0	20	0	0	30	60	40
Writing	Text (letter)	unable	unable	unable	unable	unable	unable	unable	unable	unable
	naming	0	0	10	15	25	25	25	30	40
Reading comprehension	words	0	75	100	100	100	100	100	100	100
	wsr	0	70	70	75	90	95	100	100	100
	sentences	0	0	80	80	80	80	80	80	100
Reading	letters	0	0	10	20	20	20	40	75	60
	syllable	0	0	0	0	15	50	50	70	70
	words	0	0	0	0	0	15	50	70	70
	neologism	0	0	0	0	0	0	20	20	30
	sentences	0	0	0	0	0	0	20	40	40
Dictation	letters	0	90	80	100	100	80	90	100	100
	syllable	0	20	0	70	90	60	80	100	100
	words	0	0	0	10	10	10	30	50	35
	neologism	0	0	0	0	0	10	10	10	10
	sentences	0	0	0	0	0	0	10	10	10
Copying	words	0	70	100	100	100	100	100	100	100
	M-m	0	10	50	95	100	95	100	100	100
Other neuropsychological tests										
Token Test		7	7	10	14	18	22	26	29,5	30
Raven's Test		ND	ND	ND	17	ND	18	ND	26	28
Oral apraxia		ND	15	15	20	16	20	20	20	20
Ideational apraxia		ND	6	12	14	14	14	14	14	14
Ideomotor apraxia		ND	63	60	69	65	52	ND	70	72

Explanatory notes:w= week; mo= month; y= year; wsr= word semantically related; ND= no data

Table II. Patients demographic and clinical patients' features.

Patient	F.C.	M.M.	N.I.	T.T
Aphasia impairment	Mild/anomic	Mild/anomic	Moderate	Severe
Age (years), sex	55, M	71, M	54, F	56, M
Laterality	Right-handed	Right-handed	Right-handed	Right-handed
Education	Elementary school	Secondary school	Secondary school	Secondary school
Months post-stroke	15	24	36	36
Type of stroke	ischemic	ischemic	ischemic	ischemic
Side of lesion	LH	LH	LH	LH
Duration of speech language rehabilitation (months)	7	12	18	9

Legend: M= male; F= female; LH=left hemisphere

Table III: Battery for the analysis of aphasic deficits (BADA) scores at the pre-treatment evaluation.

B.A.D.A subtests			Patient			
			F.C.	M.M.	N.I.	T.T
Phonology	Discrimination	Auditory	53,3	3,3	30	46,7
		Auditory-visual	20	13,3	40	33,3
	Transcoding	Repetition	16,7	5,6	-	77,8
		Reading	21,7	0	-	95,7
Lexicon						
	Lexical decision	Auditory	5	0	30	45,5
		Visual	5	0	47,5	55
	Transcoding	Repetition	0	5	-	45
		Reading	10,9	0	-	55
	Word comprehension	Auditory	0	10	25	55
		Visual	5	10	10	45
	Action comprehension	Auditory	0	0	10	50
		Visual	0		20	70
	Pictures naming	Oral	0	0	46,7	93
	Action naming	Oral	0	0	64,3	78,6
	Naming on description	Oral	12,5	0	75	100
Grammar	Transcoding	Repetition	0	0	12	90

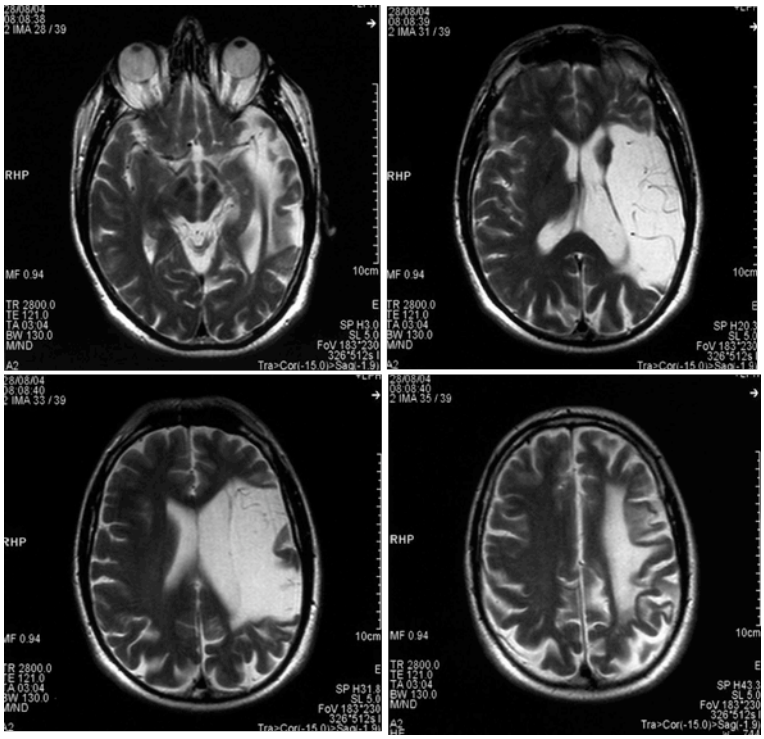
Data are expressed as percentage of errors.

Table V. Patients demographic and clinical patients' features.

Patient	**FCI**	**RLO**	**PPE**
Aphasia impairment	Mild/anomic	Moderate	Severe
Age (years), sex	58, M	38, F	65, M
Laterality	Right-handed	Right-handed	Right-handed
Education	Primary school	Secondary school	Secondary school
Years post-stroke	2	5	27
Type of stroke	ischemic	ischemic	ischemic
Side of lesion	LH	LH	LH
Duration of speech language rehabilitation (months)	7	12	9

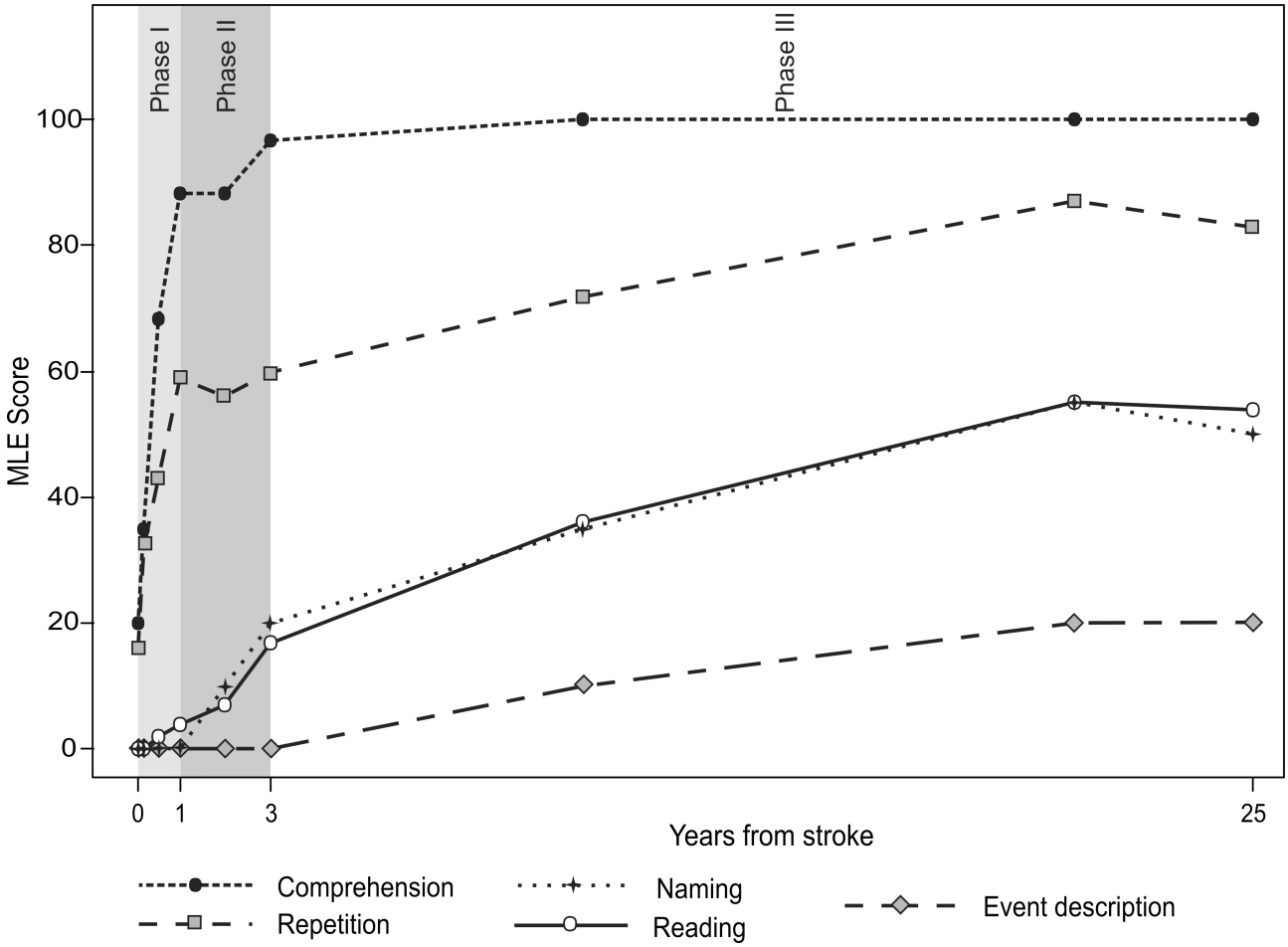
Legend: M= male; F= female; LH=left hemisphere

Figure I. Brain magnetic resonance imaging performed 21 years after stroke.



Lesion mapping showed involvement of Brodmann's areas 22, 21, 20, 37, 44, 6, 6s, 4, 40, 39, 3, 1, 2, 5, and 7 (MRIcron software, see http://www.mricro.com/mricron)

Figure II. Time course of recovery of language function over 25 years.



Abbreviation: MLE indicates Milan Language Examination.

Figure III: Flow Diagram of the study.

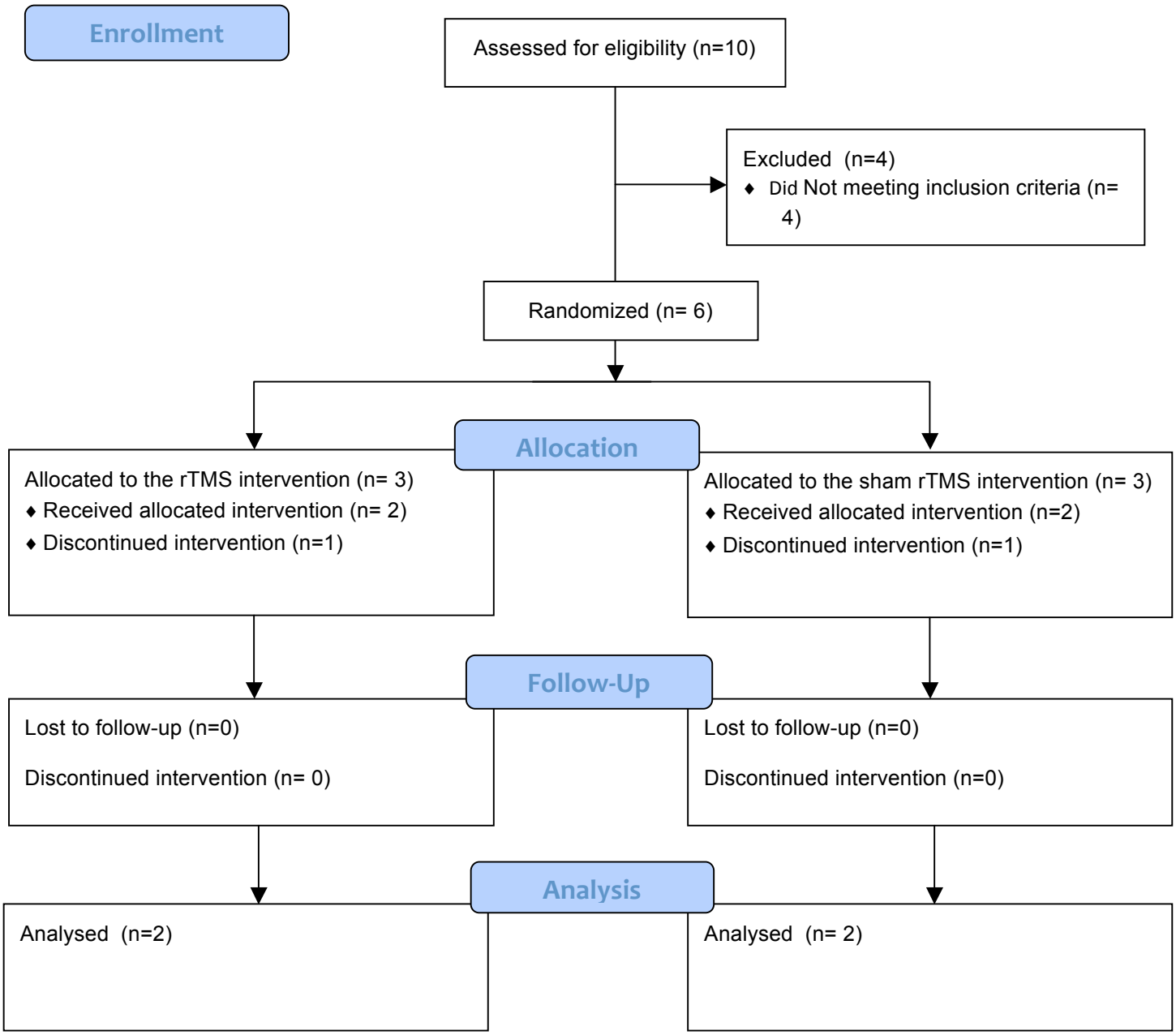


Figure IV. Structural MRI scan for each patient showing left hemisphere lesion.

FC (57-yr old, R-handed male; 1 yrs p-o). Non-fluent; pure anomia, agrammatic speech

MM (71-yr old, R-handed male; 2 yrs p-o). Non-fluent; pure anomia, agrammatic speech

NI (54-yr old, R-handed female; 3 yrs p-o). Non-fluent; pure anomia, agrammatic speech

TT (56-yr old, R-handed male; 3 yrs p-o). Severely non-fluent; anomia, agrammatic aphasia.

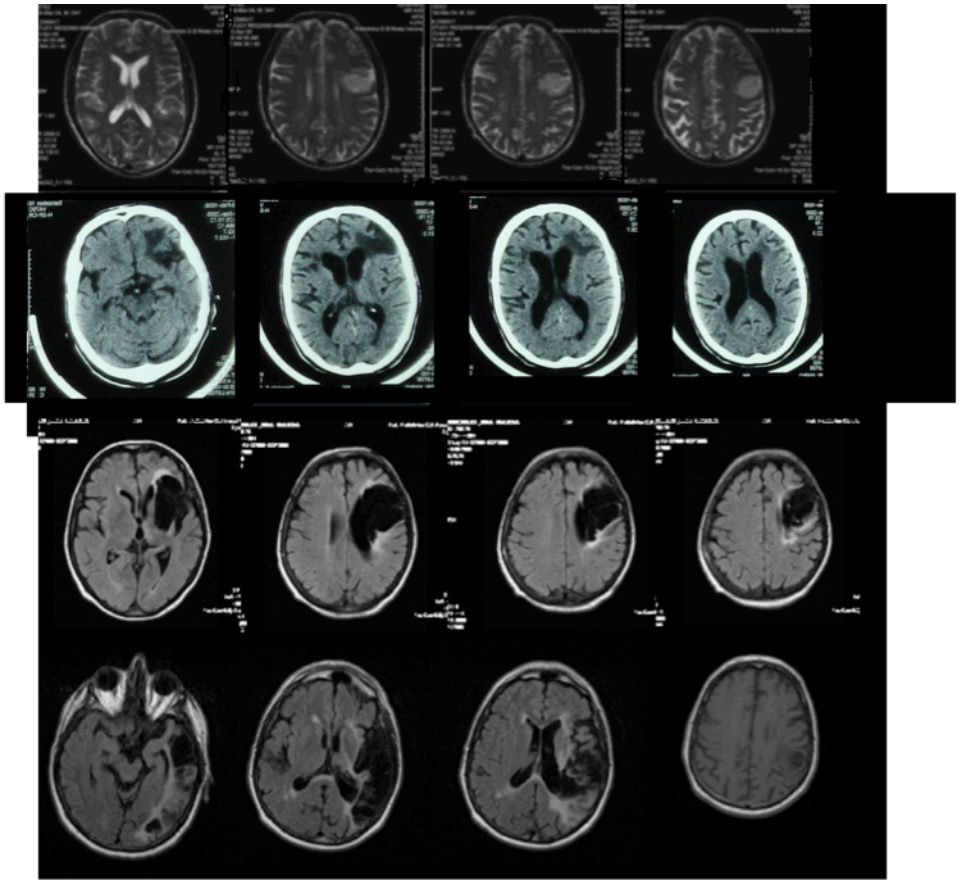


Figure V: Flow Diagram of the study

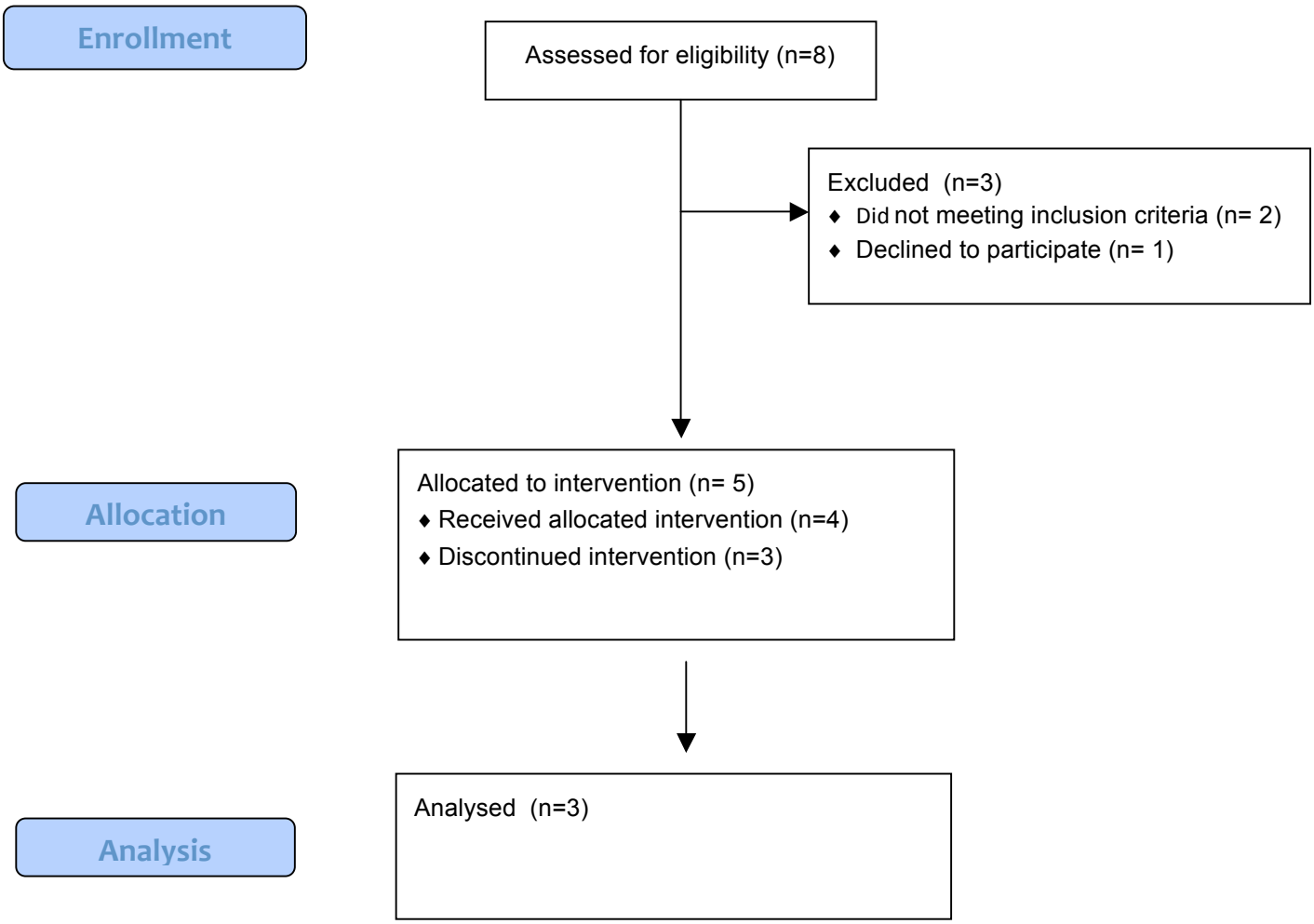
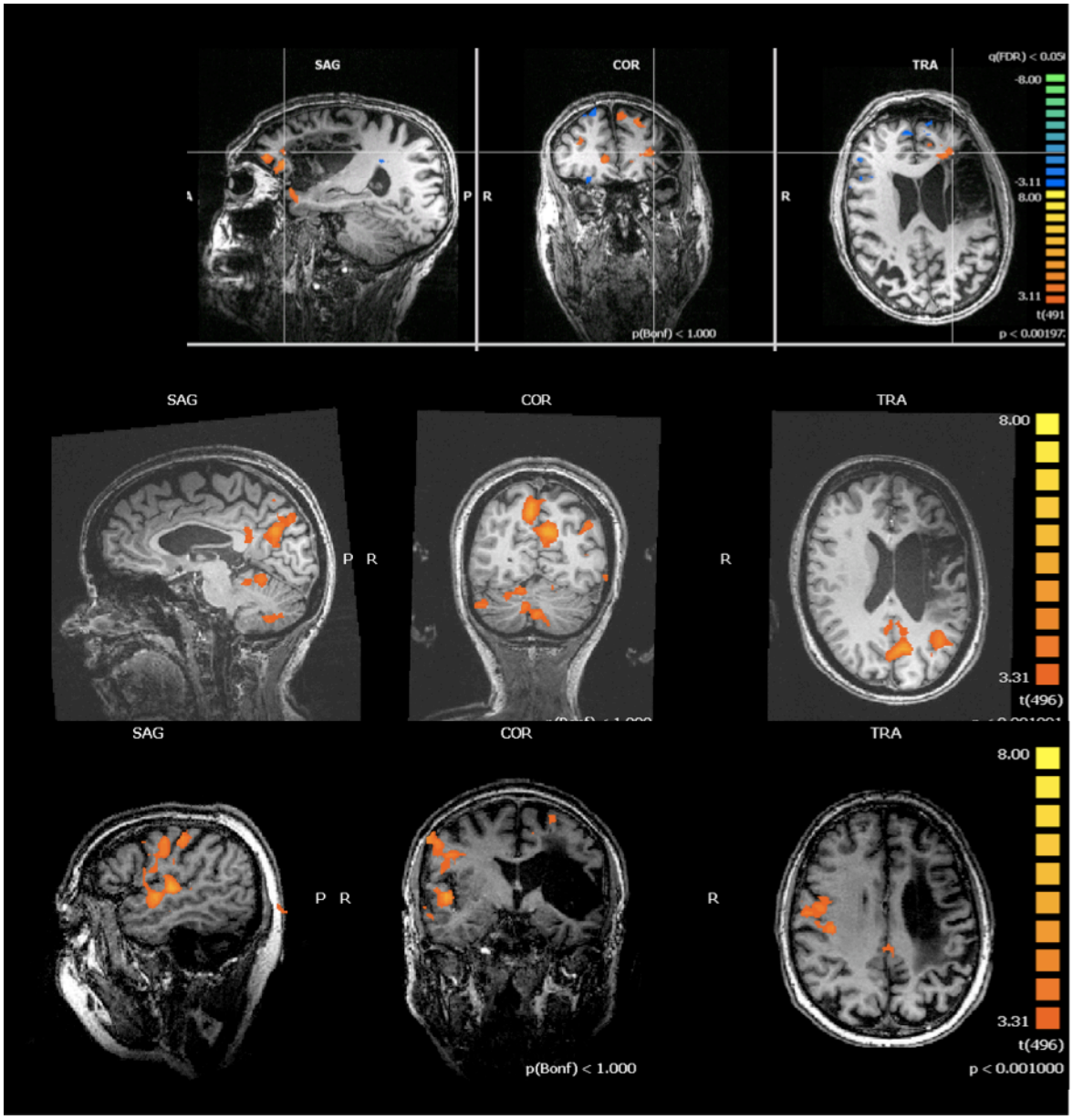


Figure VII. Activation observed after phonological training.



Comparison of the activation in response to Difficult-Treated versus Difficult-Untreated items. After treatment the first patient (CFI) showed entirely perilesional activation; the second (RLO) showed ipsilesional and midline but not perilesional or controlesional activation; the third patient (PPE) showed entirely controlesional activation.