Training-induced brain remapping in chronic aphasia: a pilot study

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ABSTRACT

Background: The neural correlates of training-induced improvements of cognitive functions after brain damage remain still scarcely understood. In the specific case of aphasia, although several investigations have addressed the issue of the neural substrates of functional recovery, only a few studies have attempted to assess the impact of language training on the damaged brain.

Aims: The main goal of this study was to examine the neurobiological correlates of improved picture naming performance in two aphasic patients who received intensive and specific training for a chronic and severe phonological anomia.

Methods & Procedures: In both participants, picture naming performance was assessed before and after phonological cueing training. Training-induced changes in patients' performance were correlated to brain activity patterns as revealed by pre- and post-training event-related functional Magnetic Resonance Imaging scanning.

Outcomes & Results: Training-induced improvement was observed concurrently with changes in the brain activation patterns. Better performance was observed in the patient with the smaller lesion, partially sparing Broca's area, who showed a left perilesional reactivation. Conversely, the patient with complete destruction of Broca's area showed a post-training activation in the right mirror frontal region.

Conclusions: The results show that, even in the chronic stage, phonological strategies may improve impaired naming and induce cerebral reorganization.

INTRODUCTION

Our knowledge of how the brain recovers after an acute stroke, and how different types of intervention can affect functional recovery remains limited. Spontaneous recovery after brain damage has generally been ascribed to the functional reactivation and reorganization of the brain. With regard to language disorders following left hemispheric damage, several studies have demonstrated the fundamental role of perilesional areas in efficient and long-term recovery.[1 2 3 4 5] Other investigations have also highlighted the capacity of the right hemisphere (RH) to take over impaired linguistic abilities, especially auditory comprehension, after damage to the dominant left hemisphere (LH).[6 7 8 9 10]

There is increasing evidence, in particular from the field of recovery of motor functions, that specific training can modulate the cortical reorganization resulting in an improved clinical outcome.[11] However, the neural correlates of training-induced improvements of cognitive functions after brain damage remain still scarcely understood. In the specific case of aphasia, although several investigations have addressed the issue of the neural substrates of functional recovery,[12 13 14] only a few studies have attempted to assess the impact of language training on the damaged brain.[15 16 17 18 19 20]

An important role of the RH is suggested by the study of Musso[16] who investigated with positron emission tomography (PET) the neural correlates of intensive verbal comprehension training in a group of aphasics. Post-training comprehension performances were positively correlated with the pattern of regional cerebral blood flow in the right homologues of Wernicke's area and of Broca's area. Moreover, Blasi[17] found that the learning of a stem-completion task was associated with specific response decrements in the right frontal and occipital cortex, rather than in the left-sided network engaged by normal subjects. Training-induced effects were prevalent in the RH also in a recent study of "intentional" therapy.[20]

Other investigations, however, suggest that the engagement of spared left hemispheric regions is also crucial. An influential PET study by Belin[15] involved patients with chronic non-fluent aphasia, who had shown considerable improvement in repeating words after the introduction of additional rehabilitation training with melodic intonation therapy (MIT). Improvement in word repetition with MIT intonation was concomitant with a RH deactivation and a significant increase of left frontal areas. The authors argued that the right-sided activations mediating defective word repetition with natural intonation might reflect a "maladaptive" functional reorganization, due to the presence of the left lesion itself, while actual recovery mediated by MIT training might be associated with the reactivation of left-hemispheric undamaged structures. Support for this hypothesis comes also from a recent study of the effects of repetitive transcranial stimulation to the RH.[21] Interference with right-sided Broca's area resulted in improved picture naming in three patients with chronic aphasia. Léger[18] compared the results of functional magnetic resonance imaging (fMRI) during a naming task pre- and post-rehabilitation in a patient with prominent phonological errors in speech production. The main difference between the two studies was a re-activation of perilesional left hemispheric areas, in particular the Broca's region and the supramarginal gyrus, in the post-treatment study.

None of these studies dealt with a direct correlation between brain activity and single behavioral responses, and thus the evaluation of the impact of language rehabilitation on recovery was only partial. Our study represents the first use of a single-case, event-related (er-) fMRI approach to examine the functional correlates of training-induced improvement in overt picture naming in aphasic patients. The event-related paradigm is the only type of fMRI design that allows one to relate behavioral performance (i.e., hit or defective overt retrieval) to the pattern of brain activation.

Impaired word retrieval (anomia) is one of the most prominent and widespread aphasic deficits, and is often the focus of rehabilitation. Most often, the therapy consists of providing phonological cues to facilitate word retrieval. Phonological cueing has been suggested to be effective especially in patients with defective retrieval of the word form (i.e., phonological anomia).[22]

We, thus, assessed picture naming performance before and after phonological cueing training, in two participants with chronic aphasia who presented severe phonological anomia. Training-induced changes in patients' performance were correlated to brain activity patterns as revealed by pre- and post-training er-fMRI scanning.

Given the heterogeneity between aphasic individuals with anomia, emphasis was placed on single-subject analysis of the results since training-elicited mechanisms are not necessarily uniform among anomic patients.[23] The advantage of a multiple single-case longitudinal design is that individual confounds can be kept under control, since each participant becomes his or her own control.

In this respect, our hypothesis was that training-induced improvement following a specific approach would be associated with activations in the areas surrounding the lesion or in the RH areas homologous to the damaged LH regions.[12] Given that there is a general agreement concerning the crucial role of Broca's area in lexical retrieval,[24] the effects of the training on the activation of Broca's area were specifically examined.

MATERIALS AND METHODS

Participants

Two chronic aphasic subjects (patient 1 and patient 2) with extensive LH lesions participated in the study. Their demographic and clinical information is summarized in Table 1. The two subjects gave their written informed consent before entering the study. This research was approved by the local Ethics Committee.

(Table 1 about here)

Patient 1

Patient 1, a 24-year-old right-handed man, suffered a closed head injury (CHI) one year before being enrolled in this study, resulting in right hemiparesis and aphasia. One year after the CHI, and after several months of global and unspecific language therapy, patient 1's speech was still non-fluent and effortful, characterized by speech apraxia, agrammatism, and telegraphic language. Extensive linguistic assessment conducted with a standardized aphasia protocol[25] at the time of the present study revealed a severe impairment on word repetition with relatively preserved comprehension abilities. The most prominent language impairment observed was a severe naming deficit, characterized by the difficulty to retrieve word forms.

Patient 2

Patient 2, a 53-year-old right-handed man, suffered an extensive LH stroke, which caused a right-sided hemiplegia and global aphasia, four years before being enrolled in the study. Patient 2 never received a structured speech therapy during the four years that preceded the present study even if some improvement in his language abilities, especially verbal comprehension, occurred. When patient 2 was enrolled in the present study, he still presented a right-sided hemiparesis and a language deficit characterized by non-fluent speech, agrammatism, good word repetition, and restored verbal comprehension, as revealed by an extensive linguistic assessment conducted with a standardized aphasia protocol.[25] Once again, the main language impairment was a severe anomia due to the difficulty to retrieve word forms.

Experimental procedure

The experimental pictures were determined on an individual basis from a series of standardized pictures of concrete objects that the patients were asked to name when enrolled in the present study.[26] A number of stimuli that patients could not name were selected from this data set. Half of the selected pictures were used as training material for anomia training (training set), whereas the other half were employed as an untrained control condition (control set). Items were matched for word length, number of syllables and frequency in the Italian.[27] Moreover, we selected a set of pictures that the patients could name either spontaneously or after being phonologically cued with the first syllable of the target word (spontaneous set).

Training consisted of repeatedly cueing patients with the initial syllable of the target word, and subsequently adding missing syllables, until the correct answer was produced. Phonological training started after acquisition of a first pre-training er-fMRI session, and was administered daily in 1-hour sessions for both patients until the participants achieved a score of 50% on picture naming with the training set. Specifically, this required eight weeks of training for patient 1, and four weeks of training for patient 2, after which the second, post-training er-fMRI was performed.

During er-fMRI acquisitions, all the pictures from the three experimental sets (spontaneous, training, control) were visually presented for 4,500 ms and subjects were asked to name them aloud. Recordings of the oral responses made by subjects permitted us to monitor their performances during scanning. Overt naming attempts were recorded using a non-magnetic microphone placed within the scanner head coil about 1 cm in front of participant's mouth connected via an optical cable to a laptop computer situated outside the scanner room. Vocal responses were recorded in .wav format during each fMRI run and scored off-line.

Er-fMRI acquisition and data analysis

Functional images (fifteen 6-mm-thick slice volumes, FOV = 280 x 280 mm, matrix 64 x 64) were acquired with a 1.5-Tesla General Electric Signa Horizon System using a gradient echo echoplanar pulse sequence (TE = 60 ms, TR = 2,000 ms). A standard T1-weighted sequence (1 x 1 x 1 mm^3 voxel size, matrix 256 x 256) was also used to acquire high-resolution anatomical images of patients' brains.

fMRI data were analyzed using a conventional statistical parametric mapping analysis (SPM-99: Wellcome Department of Imaging Neuroscience, London, UK).[28] Functional images were realigned and subsequently spatially normalized with respect to the MNI brain template,[29] by using the lesion-masking MATLAB routine devised by Brett and colleagues.[30] Finally, normalized images were spatially smoothed with an 8-mm full width at half-maximum, isotropic Gaussian kernel.

For each patient, a single statistical analysis combining the data from the first and second er-fMRI sessions was performed. Effects of interest (successful naming, sequences of phonemic approximations[31] and phonological/semantic errors) were independently modeled in the statistical design along with effects of no interest (anomias, that is, no overt response to a given item). These effects of no interest were modeled to covary out confounding effects and were not considered in the analysis.

In the pre-training er-fMRI session, simple main effects of errors (that is, sequences of phonemic approximations, phonological and/or semantic errors) and successful naming were calculated. In the post-training er-fMRI session, we assessed the anatomo-functional correlates of the training-induced improvement, by comparing brain activations associated with successfully named items of the training set and brain activations associated with successfully named items of the spontaneous set.

RESULTS

Task performance

The aphasic patients' performance before and after training is summarized in Table 2.

(Table 2 about here)

Table 3 reports the percentage of correct responses before and after training on the training, control, and spontaneous sets.

(Table 3 about here)

In the case of patient 1, a dramatic decrease in the number of anomias following training was observed during the second fMRI scanning session, concurrently with a behavioral improvement on picture naming. In patient 2, phonological training resulted in a significant reduction in errors during the second fMRI scanning session, while an increase in the number of anomias was observed. On the other hand, in the latter patient correct naming performance was stable as assessed behaviorally. However, after intensive training, both patients showed a significant naming improvement on the training picture set, which generalized neither to the control set nor to the spontaneous set.

Functional magnetic resonance imaging results

Brain activity associated with errors

The neural activity corresponding to errors in lexical retrieval was assessed only during the first er-fMRI session. The goal was to describe the neural substrate related to the production of errors observed before training. Patient 1's sequences of phonemic approximations and semantic/phonological errors were associated with activity in the left inferior frontal gyrus (IFG) (see Table 4 and Figure 1A). The activation of the IFG during the production of semantic/phonological errors and phonemic approximations was also observed in patient 2, but in this case on the RH alone, and together with the right precentral gyrus (PreCG), the right middle frontal gyrus (MFG), and the left hippocampus. Patient 2 also presented bilateral activations in the cingulate cortex (see Table 4 and Figure 2A).

(Table 4 about here)

Brain activity associated with correct pre-training responses

Due to the insufficient number of successful naming events (n = 1), spontaneous naming by patient 1 was not considered. Picture naming by patient 2 was associated with activations in the right PreCG, the right IFG, the right MFG, and the right insula. The left precuneus was also activated (see Table 5 and Figure 2B).

(Table 5 about here)

Brain activity associated with training-induced performance improvement

Both patients activated after training the supramarginal gyrus (SMG) in the left inferior parietal lobule (IPL), and the pars triangularis of the IFG (patient 1 in the LH, but patient 2 in the RH). Furthermore, similar activations were observed in the precuneus (on the left for patient 1, and on the right for patient 2), and in the right posterior cingulate cortex. Patient 1 also showed an activation of the anterior portion of the left insula, the left middle temporal gyrus (MTG), the left temporo-occipital junction, and the right hippocampal gyrus. Instead, patient 2 showed an activation of the left MFG and the left superior frontal gyrus (see Table 6 and Figures 1B and 2C).

(Table 6 about here)

(Figures 1 and 2 about here)

DISCUSSION

The main goal of this study was to examine, in two cases of severe and chronic aphasia, the neurobiological correlates of improved picture naming performance following intensive phonological training.

We studied two aphasic patients characterized by different behavioral and neuropathological profiles. Despite the variation, both patients benefited from the phonological training. The functional results indicated that two different processes contributed to the naming improvement: the restitution of function in crucial areas surrounding the lesion, and the contralateral compensation in homologous regions, suggesting that specific anomia training can lead to cerebral reorganization in chronic and severe aphasia.

As expected, both patients improved naming on the training set, without generalization to the untreated items. This is in agreement with several investigations reporting that treatments for word-finding impairments produce clear effects on the treated items, while generalization to untreated items is often absent, or – when occurring - less robust than the item-specific effects.[32] However, the cases were not comparable with respect to the overall performances in the task or to the brain activity patterns. Given that the patients were different in age, etiology of brain damage and lesion size, these differences might explain the different courses and the different activation patterns. Each patient is thus discussed separately.

Patient 1

Naming improvement after training was grater in the younger patient (patient 1) with the smaller lesion due to CHI, partially sparing Broca's area. In the case of CHI lesions, spontaneous recovery effects may extend until one year post-onset, and the overall prognosis is related to age.[23] These favorable prognostic factors might have contributed to naming recovery in patient 1. Nevertheless, our findings showed that phonological training was specifically effective, since significant post-training improvement in naming was noted on the trained picture set only. This result underlines that, in some cases, phonological strategies could be useful to improve impaired picture naming, even in the chronic stage.

From the standpoint of brain activity, this patient showed a left perilesional reactivation following the training, involving the pars triangularis of Broca's area. The role of Broca's area in phonological processing is well-known.[33] The preservation of Broca's area in patient 1 may have enhanced the impact of phonological training. It must be however underlined that the activation of the left IFG during error production paralleled the left IFG activation during training-induced correct naming, and may be similarly related to demands for lexical selection and retrieval.[34] Patient 1 also displayed training-induced modifications in the SMG portion of the left IPL. This area is another crucial component of the phonological loop of verbal working memory, in particular for phonological storage.[35] It is thus likely that this patient adopted phonological compensatory strategies for successful lexical retrieval (see Léger[18] for a similar interpretation).

Additionally, there was an activation of the right hippocampal region, which may reflect the memory consolidation processes for lexical items.[36] Therefore, the present results are in agreement with the hypothesis that the word-learning system as a whole might play a role in anomia rehabilitation.[37]

Patient 2

Naming performance during the post-training fMRI session was more complex for patient 2. The improvement was also significant on the training picture set, but it was less prominent than in patient 1, and it was accompanied by an increase in anomic events along with a dramatic reduction in error rates.

A number of factors can be evoked to explain the less prominent improvement after training in patient 2. He was older than patient 1, and had a larger lesion of different - ischemic - nature. Furthermore, his training started 3 years later, and was shorter.

Additionally, patient 2 was already much better at picture naming than patient 1 during the pre-training session, and, thus, the training impact might have been reduced by a ceiling effect.

In patient 2, Broca's area was completely destroyed by the ischemic lesion, and, additionally, pre- and post-training RH activations observed with the same patient suggest a permanent functional impairment of the LH. It is possible, thus, that in patient 2 the damage to Broca's area may have reduced the impact of phonological training, this approach being more suitable for tapping into the LH's phonological processing abilities. In patient 2, we observed an activation of "mirror" right frontal regions after training. This right-sided activation, involving the right homologous of Broca's area, may indicate compensatory activation of RH areas.[2 6] Therefore, it might be the case that, in patient 2, the right homologous of Broca's area mediated successful, though non-optimal, lexical retrieval. This finding supports the hypothesis that after LH damage, preexisting language areas in the RH are reactivated and may play an important role in aphasia recovery.[3 6 8] One alternative explanation, partially applying to the brain changes observed in patient 1 too, is that the increased IFG activation after training, particularly since it was associated with increased anomias in patient 2, could also reflect increased articulation or increased effort, similarly to the increased activity in the right homologous of Broca's area (in Broca's proper for patient 1) during semantic/phonological errors and phonemic approximations. This interpretation is not fully supported by behavioral observations in the two patients, whose oral production at picture naming, after training, was clearly faster and less effortful on the trained picture set.

It is also possible that the post-training activation of the right IFG in patient 2 was linked not only to a lesser degree of training-induced improvement but also to a change in retrieval strategy, which might account for the lower number of errors and the larger number of anomias in this participant. Thus, the training approach may have favored a change from a lexical-semantic to a phonological strategy during picture naming. The latter strategy forces the patient to search for and utter only the correct item, and to discard alternatives (i.e., errors). Given the reduced phonological competence of the RH, patient 2 was not always successful in accessing the target, and thus an anomic event occurred.

Patient 2 also offers interesting insights into the specific patterns of activation associated with errors in naming. Indeed, it is thanks to the event-related methodology employed in this study that we were able to detect the pattern of brain activity related to erroneous naming. The strong bilateral activation of the anterior cingulate cortex which was observed might reflect cognitive control and attentional processing. One of its most prominent roles is detecting and signaling the occurrence of conflicts in information processing and, more specifically, to develop an error-likelihood signal.[38]

Spontaneous naming was associated with an almost exclusively right-sided brain activation, engaging the RH homologue regions of the LH regions involved in word retrieval tasks in the healthy population. The MFG is involved in a multitude of cognitive functions, including action and speech initiation, and executive and word retrieval processes. The activation of the right PreCG and the right insula may reflect speech output and articulatory planning, respectively, i.e. those vocal movements associated with word forms.[33]

The study has a number of limitations which must be considered in the interpretation of the results. In particular, since repeated fMRI studies were not done in the absence of treatment, it is unclear whether the functional changes were due to the treatment itself, or could simply be attributed to repeating the study after practice of the task.[39] Moreover, recent studies of motor and speech recovery indicate that some of the activations (particularly in the hemisphere contralateral to the lesion) observed in post-stroke recovery may not reflect activity that is important to the task, but rather “maladaptive” activation unrelated to functional performance. In fact, inhibition of some such areas of activation with rTMS can result in improvement of the task.[21] It must be however underlined that our findings in patient 2 seem not to support this alternative view, as the enhanced engagement of right-sided brain regions observed in this patient after training paralleled the behavioral improvement. Additionally, our results are in strong agreement with previously reported results regarding recovery mechanisms in aphasic patients,[1 18 6 8 16] and are in line with longitudinal studies indicating that the damaged brain can show plastic changes even several years post-onset.[40]

On a general note, we think that multiple single-subject er-fMRI study is a promising method to investigate the recovery process taking place in individual subjects, which should be put to test in other patients using additional training approaches.

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COMPETING INTERESTS

The authors declare having no competing interest.

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Table 1. Demographic and clinical information on the anomic patients

Patient	Age (years) & handedness	Lesion type	Lesion site	Months post-onset
Patient 1	24 Right	Closed head injury	Left prefrontal cortex Left fronto-parieto-occipital white matter	12
Patient 2	52 Right	Ischemic stroke	Territory of left middle cerebral artery, involving fronto-temporo-parietal areas and extending to the temporo-parieto-occipital junction	48

Table 2. Patients' pre- and post-training behavioral data

Patient	Naming (%) on Snodgrass and Vanderwart test	Anomias 1st fMRI (%)	Anomias 2nd fMRI (%)	Correct naming 1st fMRI (%)	Correct naming 2nd fMRI (%)	Errors 1st fMRI (%)	Errors 2nd fMRI (%)
Patient 1	0.38	91.4	50.0	1.7	31.0	6.9	19.0
Patient 2	45.52	12.0	42.3	47.8	48.9	40.2	8.8

Table 3. Patients' pre- and post-training performance on the 3 experimental sets

T = training picture set; C = control picture set; S = spontaneous picture set; Delta % = difference in performance (%) between the 1st and 2nd er-fMRI sessions; ** = significant at p < .001; * = significant at p < .01; n.s. = non-significant.

Patient	Correct 1st er-fMRI (%)			Correct 2nd er-fMRI (%)			Delta %		
	T	C	S	T	C	S	T	C	S
Patient 1	0.0	0.0	5.5	75.0	0.0	16.7	**+75.0** X^2 = 30 **	+0.0	+11.2 n.s.
Patient 2	23.3	40.0	78.1	60.0	26.7	59.4	**+36.7** X^2 = 8 *	–13.3 n.s.	–18.7 n.s.

Table 4. Stereotactic coordinates and Z scores for brain areas associated with pre-training errors in patient 1 and patient 2

Brain regions (Brodmann area)	X	Y	Z	Z statistic
Patient 1				
Left inferior frontal gyrus (BA 47)	–56	+16	–12	3.26
Left inferior frontal gyrus (BA 45)	–62	+20	+4	2.93
Patient 2				
Left anterior cingulate cortex (BA 32)	–12	+12	+40	3.77
Left hippocampus	–20	–22	–16	3.87
Right precentral gyrus (BA 6)	+38	+2	+28	3.49
Right inferior frontal gyrus (BA 47)	+50	+26	–16	3.58
	+44	+40	–12	3.36
Right middle frontal gyrus (BA 11)	+20	+48	–16	3.25
Right cingulate cortex (BA 24)	+0	+34	–8	3.93

Table 5. Stereotactic coordinates and Z scores for brain areas associated with correct pre-training responses (i.e., spontaneous naming) by patient 2

Brain regions (Brodmann area)	X	Y	Z	Z statistic
Patient 2				
Left precuneus (BA 7)	–14	–60	44	3.76
Right precentral gyrus (BA 6)	+60	+2	+24	3.79
Right inferior frontal gyrus (BA 47)	+54	+22	–12	3.57
Right middle frontal gyrus (BA 10)	+26	+50	0	4.13
Right insula	+46	–4	+8	3.72

Table 6. Training-induced patterns of brain activity in patient 1 and patient 2

Brain regions (Brodmann area)	X	Y	Z	Z statistic
Patient 1				
Left inferior frontal gyrus (BA 45/46)	–54	+34	+4	2.88
Left inferior frontal gyrus (BA 45)	–42	+22	+12	2.78
Left insula	–34	+4	0	3.53
	–34	+4	+4	3.09
Left middle temporal gyrus (BA 21)	–58	–68	+4	3.31
	–46	–36	0	2.71
Left temporo-occipital junction (BA 39/19)	–42	–80	16	2.81
	–36	–78	16	2.73
	–40	–76	12	2.44
Left inferior parietal lobule (BA 40)	–56	–48	+36	2.74
	–46	–40	+36	2.54
Left precuneus (BA 7)	–18	–64	44	3.42
Right posterior cingulate cortex (BA 30)	+10	–46	+12	3.77
Right hippocampal gyrus	+12	–40	0	2.81
	+26	–46	–16	2.68
Patient 2				
Left middle frontal gyrus (BA 9)	–44	+40	+32	3.02
Left middle frontal gyrus (BA 10)	–34	+50	–4	2.86
Left superior frontal gyrus (BA 9)	–6	+52	+36	2.65
Left superior frontal cortex (BA 10)	–18	+50	–8	2.93
Left inferior parietal lobule (BA 40)	–56	–46	+28	3.14
	–56	–46	+32	2.65
Right inferior frontal gyrus (BA 45)	+40	+24	+16	3.56
Right precuneus (BA 7)	+2	–60	+52	3.53
	+12	–66	+60	2.53
Right posterior cingulate cortex (BA 31)	+18	–42	+ 44	3.25
	+16	–44	+32	2.90

Legend for figures

Figure 1. Patient 1's cortical patterns of regional activity during picture naming. The statistical images are thresholded at *p*-level = .01 (uncorrected) in order to verify our *a priori* hypothesis regarding the involvement of Broca's area and its right homologue in lexical retrieval and in training-induced improvement. Results are superimposed onto transversal slices of the patient's T1*weighted normalized brain image.

A) Cerebral activation associated with failures in lexical retrieval during the pre-training fMRI session

B) Cerebral activation underlying training-induced improvement in naming performance

Figure 2. Patient 2's cortical patterns of regional activity during picture naming. The statistical images are thresholded at *p*-level = .001 (uncorrected) for A) and B), and at *p*-level = .01 for C) in order to verify our *a priori* hypothesis regarding the involvement of Broca's area and its right homologue in lexical retrieval and in training-induced improvement. Results are superimposed onto transversal slices of the patient's T1*weighted normalized brain image.

A) Cerebral activation associated with failures in lexical retrieval during the pre-training fMRI session

B) Cerebral activation associated with the pre-training spontaneous naming

C) Cerebral activation underlying training-induced improvement in naming performance

Figure 1

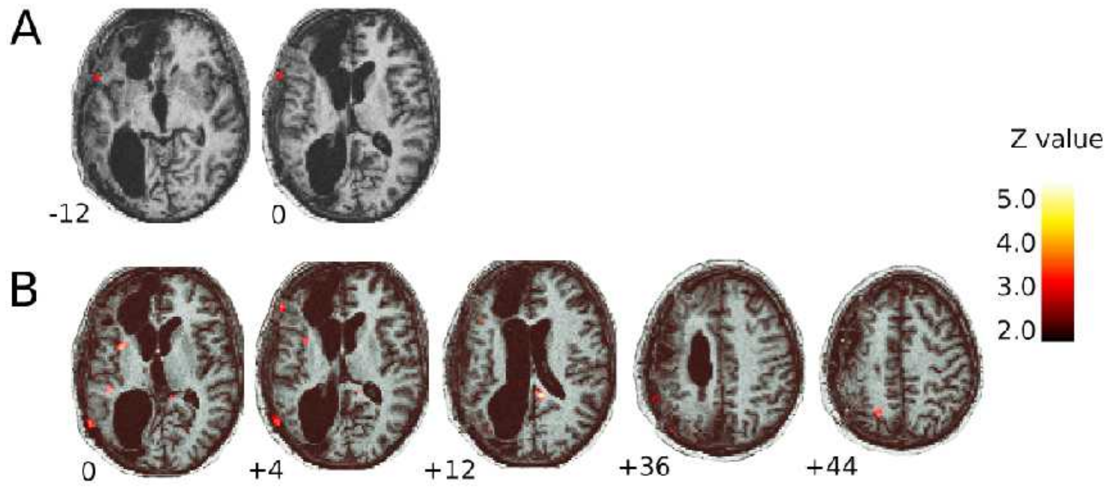

Figure 2