Generalization of the effects of phonological training for anomia using structural equation modelling: a multiple single-case study

Paolo Vitali[1,2], Marco Tettamanti[2], Jubin Abutalebi[2], Ana-Inés Ansaldo[1], Daniela Perani[2], Stefano F. Cappa[2] and Yves Joanette[1]

[1] Centre de recherche, Institut universitaire de gériatrie de Montréal, Québec, Canada & Faculté de médecine, Université de Montréal

[2] Scientific Institute San Raffaele Hospital & University Vita-Salute, Milano, Italia

Correspondence should be addressed to:

Paolo Vitali

Centre de Recherche - Institut universitaire de gériatrie de Montréal

4565, ch. Reine-Marie, Montréal, Québec, Canada H3W 1W5

Tel: +1-514-3403540 ext. 4700; Fax: +1-514-3403530

E-mail: paolo.vitali.1@ulaval.ca

ABSTRACT

Structural Equation Modelling analysis of three longitudinal er-fMRI sessions was used to test the impact of phonological training and of the generalization process on the pattern of brain connectivity during overt picture naming in two chronic anomic patients. Phonological training yielded a positive effect on the trained material. Six months after the training, a generalization of the positive impact on the untrained items was also observed. Connectivity analysis showed that training and generalization effects shared paralleled cortical patterns of functional integration. These findings may represent the neurophysiological correlate of the traininginduced cognitive strategies for the compensation of anomia.

INTRODUCTION

Word-finding impairment (anomia) is the most common aphasic symptom, and one of the most frequent targets of language rehabilitation. Several studies examined the impact of different approaches to rehabilitation of naming in aphasic patients (for a detailed review, see Nickels, 2002). One approach focuses on the phonological stages of lexical retrieval. Phonological tasks - such as repetition of the target, rhyming tasks, as well as phonological (and orthographic) cueing of picture naming - have been extensively used as therapy for word-retrieval impairments. There is growing evidence that phonological therapy can be highly successful on word retrieval, resulting in long-term improvements of trained items (Miceli, Amitrano, Capasso, & Caramazza, 1996; Nettleton & Lesser, 1991). While the majority of studies did not find a generalization of phonological training effect to untrained items (Basso, Marangolo, Piras, & Galluzzi, 2001; Hillis & Caramazza, 1994; Laganaro, Di Pietro, & Schnider, 2006; Miceli et al., 1996; Nettleton & Lesser, 1991) some studies showed beneficial effects from initial phoneme cueing aid that generalized to untrained items (Best, Howard, Bruce, & Gatehouse, 1997; Best & Nickels, 2000; Bruce & Howard, 1987; Fink, Brecher, Schwartz, & Robey, 2002; Howard, 1994; Raymer, Thompson, Jacobs, & Le Grand, 1993; Robson, Marshall, Pring, & Chiat, 1998). Many factors could account for this discrepancy of results about the generalization effects of phonological therapy in treating anomia, including differences in the phonologically-based approach, differences among the treated patients, and differences in the duration and the intensity of the therapy (Hinckley & Craig, 1998).

Functional imaging studies of neuroplasticity during aphasia treatment are just beginning. The few functional studies addressing the neural effects of language training indicate that the improvement of trained material is associated with two possible neuronal mechanisms: the reactivation of left hemispheric perilesional areas (Belin et al., 1996; Leger et al., 2002) and/or the recruitment of right homologous brain regions (Blasi et al., 2002; Crosson et al., 2005; Musso et al., 1999; Peck et al., 2004). Although the role of left and right hemisphere in aphasia recovery following treatment is still a matter of discussion, recent studies suggest that the neuronal mechanisms of recovery may depend on the lesion size and aphasia severity. Specifically, it has been proposed that more severely impaired patients with larger lesions may have to rely on the right hemisphere for some types of processing, while less severely impaired patients with smaller lesions may be able to use remaining left-hemisphere mechanisms to support good recovery (Crosson et al., 2007). A previous fMRI study by our group (Vitali et al., 2007) compared the pattern of brain re-organization following phonological training in two patients with anomia engaged in a naming task. In agreement with the hypothesis mentioned above, we observed that the patient with a smaller lesion showed left perilesional reactivation post-training, including the left inferior frontal gyrus and the left supramarginal gyrus, while the patient with complete destruction of Broca's area showed a post-training activation in the right homologous frontal region.

The role of the inferior frontal and inferior parietal regions in aphasia recovery following phonological treatment has been shown in previous neuroimaging studies addressing phonological treatments for impaired lexical retrieval (Cornelissen et al., 2003; Fridriksson, Morrow-Odom, Moser, Fridriksson, & Baylis, 2006; Leger et al., 2002; Vitali et al., 2007). Although this pattern of recovery was observed for phonologically trained items, it is still unknown whether this effect could be observed also in the case of generalization to untrained items.

In this study, we addressed this crucial point by adopting a functional integration approach, which is complementary to the functional specialization logic used by classical neuroimaging studies of therapy-driven recovery of aphasia. Functional integration refers to the interactions among specialized neuronal populations, and investigates how these interactions depend upon the cognitive context. Integration within a distributed system is usually understood in terms of effective connectivity, which refers to the influence that one neuronal system exerts over another, either at a synaptic (i.e. synaptic efficacy) or population level (Friston, 2002). It may be measured, among other tools, by Structural Equation Modelling (SEM) of fMRI data over time. SEM of fMRI time series estimates the effects (in terms of modulation of connection strengths) of experimental manipulation on connectivity among brain regions within specified constraints, based largely on consideration of anatomical connectivity of the brain (Buchel & Friston, 2000; Buchel & Friston, 1997).

In the present study, we compared the impact of phonological training for anomia and of the associated generalization effect to untrained items on the pattern of effective connectivity related to improved overt picture naming in two chronic anomic patients (S.A. and G.R.). We performed a SEM analysis of fMRI time-series measured in the two aphasic participants, in order to evaluate the inter-regional covariance and to test the training- and generalizationinduced changes in coupling among brain regions of interest (ROIs) activated during an overt picture naming task. The aim of the study was: 1) to verify a possible modulation of the connection strengths among cerebral regions associated with improved picture naming performance following specific anomia training; 2) to characterize the specific contributions of training and generalization process to naming improvement in terms of effective connectivity. In both patients, ROIs activity was measured in three longitudinal event-related (er) fMRI sessions, shortly before and after the training, as well as six months later. Due to the different aetiology (traumatic vs. vascular) and lesion size, the SEM analyses were performed at the single subject level and the two patients were therefore treated as separate single cases.

MATERIALS AND METHODS

Participants

Two monolingual, Italian-speaking brain-lesioned individuals (S.A. and G.R.) with chronic nonfluent aphasia, characterized by persistent and severe naming deficits, participated in the study (see Table 1 for participants' demographic and clinical data). Language abilities were evaluated by means of standardized tests by a neurologist with expertise in aphasia (JA) and a speechlanguage pathologist. The two participants gave their written informed consent before entering the study, according to the Declaration of Helsinki (BMJ 1991; 302: 1194). This research was approved by the local Ethics Committee.

Case 1: S.A.

S.A., a 24-year-old right-handed man, suffered a closed head injury (CHI) one year before being enrolled in the study, resulting in right hemiparesis and aphasia. The lesion involved the left prefrontal cortex and the white matter underneath the fronto-parieto-occipital regions (Fig. 1). Before being enrolled in the present study, the patient was evaluated by a behavioural neurologist (JA) and a speech-language pathologist with expertise in aphasia syndromes as part of his clinical evaluation. In the language assessment, S.A. had a non-fluent and effortful speech, characterized by agrammatism, telegraphic language and mild speech apraxia. The most prominent language impairment was a severe naming deficit, mainly characterized by anomias, phonological paraphasias and difficulties in retrieving word forms. Word repetition and comprehension impairments were mild. The patient was thus diagnosed as non-fluent aphasic. S.A. was re-evaluated nineteen months post-onset, after the experimental phonological rehabilitation, between probes # 4 and # 5 of the present study (see experimental procedure section). The patient showed a still severely impaired language profile, with some improvements compared to the initial evaluation (Aachener Aphasie Test). The results of this second evaluation are reported in Table 2. Globally, the speech was still non-fluent, effortful, and telegraphic. The fluency tests still revealed word retrieval impairments. However, naming abilities showed significant improvements over the time.

Case 2: G.R.

G.R., a 53-year-old right-handed man, suffered from an extensive left hemisphere stroke, which caused a right-sided hemiplegia and global aphasia, four years before being enrolled in the study. The thrombotic brain infarction involved the left middle cerebral artery, and determined a lesion in the fronto-temporo-parietal areas, extending to the temporo-parieto-occipital junction (Fig. 1). Five and ten months post-stroke, the patient was extensively evaluated as part of his clinical assessment. Results are reported in Table 3. Five months post-stroke, G.R. presented a non-fluent motor aphasia characterized by stereotyped and perseverative spontaneous language, with oral comprehension limited to single words and simple sentences. Written production and comprehension were severely impaired. Ten months post-onset, G.R. showed minimal improvements at the level of oral production, in particular in repetition tasks and spontaneous language. No significant naming improvements were reported over time. The patient still presented a clinical profile of severe non-fluent motor aphasia. When G.R. was enrolled in the present study (four years post-onset), he still presented a rightsided hemiparesis and a language deficit characterized by frequent anomias, non-fluent telegraphic speech, agrammatism, relatively good single word repetition and comprehension, as revealed by an extensive linguistic assessment conducted with a standardized aphasia protocol (BADA, Miceli, Laudanna, Burani, & Capasso, 1994). The clinical picture did not show significant improvements compared to the last evaluation performed three years before.

Experimental procedure

We performed a multiple single-case study on the efficacy of a specific therapy for impaired word-retrieval, including three separate pre-training testing sessions of picture naming. The first two behavioural sessions were performed at the time of the patients' inclusion in the study (baseline probes # 1 and # 2) and the third one consisted in the pre-training fMRI session (baseline probe # 3).

During the first two behavioural sessions, both patients were tested twice (baseline probes # 1 and # 2) on a series of 260 standardized pictures of concrete objects (belonging to different categories: tools, animals, vegetables, etc.) (Snodgrass & Vanderwart, 1980) in order to establish the degree of spontaneous recovery, to verify naming performances consistency, and to determine the experimental pictures on an individual basis. A number of stimuli that participants could not name in both testing sessions were selected (the number of stimuli selected for S.A. and G.R. are reported respectively in Table 4 and 5). Half of these selected pictures were used as training material for anomia training (training items), whereas the other half were employed as an untrained control condition (control items). For both patients, the two lists (training and control items) were matched in terms of word length (S.A.: 5.25 ± 1.12 vs. 5.25 ± 1.80; G.R.: 7.11 ± 2 vs. 6.5 ± 2.15), number of syllables (S.A.: 2.25 ± 0.44 vs. 2.35 ± 0.67; G.R.: 3 ± 0.77 vs. 2.83 ± 0.99) and frequency of occurrence in Italian (S.A.: 1.5 ± 0.76 vs. 1.55 ± 0.76; G.R.: 2 ± 1.08 vs. 2.17 ± 1.04) (De Mauro, Mancini, Vedovelli, & Voghera, 1993). The syllabic structure was comparable and included the most common consonant-vowel (CV, CCV, VCC) and stress (penultimate, antepenultimate) patterns for Italian. Moreover, we selected a set of pictures that the participants could spontaneously name in both sessions (spontaneous items). Due to the limited number of items spontaneously named by S.A., his spontaneous item set included the only item that he could name as well as other 17 items he could consistently name after phonological cuing of the first syllable in the probe conditions # 1 and # 2 (see Table 4). This was done in order to have comparable conditions for the two participants. The subsets of items derived from the baseline probes # 1 and # 2 were then employed in the third testing session (pre-training er-fMRI session, baseline probe # 3) and in the post-training er-fMRI sessions (probes # 4 and # 5).

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. The one-hour training sessions were conducted by a speech-language pathologist and were performed five days a week. No session was skipped by the patients. Phonological cueing training started after acquisition of a first pre-training er-fMRI session (baseline probe # 3). Only the dataset of training items was presented during each training session. The training was concluded when the patients were able to name at least 50% of the training set items. Specifically, this required eight weeks of training for S.A., and four weeks of training for G.R., after which the second, posttraining er-fMRI was performed (post-training probe # 4). A final er-fMRI session was acquired six months after the end of the training (follow up probe # 5). Between functional sessions two and three, participants did not receive any structured anomia or language rehabilitation.

During er-fMRI acquisitions, all the pictures from the three experimental sets (spontaneous, training, control) were visually presented for 4500 ms and participants were asked to name them aloud. Oral responses were recorded on audio files and analysed offline. The noise of the scanner was filtered out from the audio files by means of the software Soundforge, until the responses were clearly intelligible. In order to avoid observer bias, the naming performance was independently scored by two researchers (PV and MT) and a neuropsychologist not involved in the study with expertise in language and aphasia. The naming responses were scored as correct only if they were entirely correct, i.e. without any phonological or semantic paraphasia.

er-fMRI acquisition parameters 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 (GE Healthcare, USA) using a gradient echo echoplanar pulse sequence (TE = 60 ms, TR = 2000 ms). Standard T1- weighted MRI brain scans were also acquired for each participant in 120 axial planes with 1 mm^3 isotropic voxels. The images were reconstructed using Analyze package (Biomedical Imaging Resource Mayo Foundation). The volume of the brain damage was used to create a “lesion mask”, in order to protect the whole brain normalization process from undue warping caused by cost-function effects when damaged brains are matched to normal templates (Brett, Leff, Rorden, & Ashburner, 2001). Spatial pre-processing and normalization of images in the standard stereotactic space devised by the Montreal Neurological Institute (Friston, Ashburner, Poline, Frith, & Frackowiak, 1995) were performed using SPM99 (Wellcome Department of Cognitive Neurology, University College London: http://www.fil.ion.ucl.ac.uk/spm/spm99). For each participant, a single statistical design combining the data from the three er-fMRI sessions was created. Trained, control and spontaneous successful naming across sessions was modelled in the statistical design.

Structural Equation Modelling: single-case analysis

In the choice of the ROIs for the estimation of effective connectivity, we considered the areas of the language brain network involved in normal naming (Demonet, Thierry, & Cardebat, 2005) and in language recovery (Price & Crinion, 2005). The anatomical network included brain areas in the left hemisphere along with their right homologues: the Ba 45 portion of the inferior frontal gyrus (IFG) (Broca’s area *pars triangularis*), the insula, the middle temporal gyrus (MTG) (Ba 21/37), and the Ba 40 portion of the inferior parietal lobule (IPL) (the supramarginal gyrus, SMG) (see Table 6). For each subject, within this network of areas, we localized the ROIs’ stereotaxic coordinates on the basis of the maximum peak of significance in the fMRI single-subject results. Specifically, the regions were defined as 5 mm radius spheres, with the maximum peak as the centre of the sphere. The maximum peak of each region was significant at $p < 0.001$ (uncorrected) in the SPM{F} analysis for all effects of interest. Left Ba 45 (IFG) and insula were not included in the SEM analysis of G.R. because they fell into the lesioned area (Table 6).

The principal component of the adjusted (for effects of interest) BOLD signal in every ROI was entered as an observable quantitative variable into the SEM model for the analysis of effective connectivity. To model the influence of training and generalization process on the connection strengths between ROIs, we also included two modulator variables that modulate how changing conditions alter the connectivity between two areas. The first modulator variable (the training variable) defines trained and untrained successful picture naming events. Specifically, naming performances on control and spontaneous items were entered as a unique untrained condition in the SEM model. This was done for two main reasons. Firstly, the main goal of the analysis was to compare the items that were trained with the items that were not trained, i.e. control and spontaneous conditions. Moreover, from a statistical point of view, this gave us more statistical power because of the inclusion of a greater number of stimuli in the untrained condition. We attributed a value of -1 to the “untrained context” (correctly named items of the control and spontaneous sets) and +1 to the “trained context” (correctly named items of the training set). The second modulator variable (the time variable) defines the fMRI acquisitions temporal order. We attributed respectively values 1, 2, and 3 to the first, second, and third er-fMRI sessions. Both experimental covariates were convolved by a canonical haemodynamic response function. The convolved training variable was multiplied by the activity (in terms of BOLD signal) in the source area to form a first-order interaction term. The latter term was subsequently multiplied by the convolved time variable to form a second-order interaction term. Residual variance for every variable within the model was modelled by a reciprocal connection from each node to itself. Direct connections between variables within the model were unidirectional to ensure robust estimates.

The structural model was implemented by Lisrel 8.51 (Joreskog & Sorbom, 2001) using the weighted least squares algorithm with an asynchronic covariance matrix for non-normalized data (Higham, 1993) to estimate covariance that best predict the observed variance-covariance structure of the empirical data. Path coefficients - the estimated connection strengths between variables - were identified for every connection in the structural model. The significance of path coefficients for the interaction terms was tested at the individual subject level, i.e. running the SEM model separately for each subject. Statistical inferences about the path coefficients were based on the comparison of a free model with a model constrained to zero for the interaction term of interest (first or second order). The difference in goodness of fit between free and constrained models was expressed as chi-squared (X^2 difference test or likelihood ratio test, with degrees of freedom determined by the number of constraints, namely 1; X^2 difference threshold = 3,84, df = 1, $p < 0.05$) (Bollen, 1989). Under the null hypothesis that one area has the same influence over another either for trained/untrained context or across sessions, the free and constrained models do not differ in goodness of fit. If the models produced a significantly better fit when the interaction terms were not constrained to zero, then these pathways were considered to explain a greater quota of variance in the target variable. A significant training- and/or timedependent modulation of coupling between two cerebral regions indicated that the two areas have coherently increased or decreased their neural activity during task execution, but it is not possible to point out if this greater connectivity was a sign of an excitatory or an inhibitory influence, at synaptic level, of one area upon the other.

RESULTS

Behavioural results

Case 1: S.A.

As reported in Table 4, phonological training yielded an immediate positive effect on the training items (probe # 4 vs. probe # 3: Fisher's exact test, $p<0.001$), that was still present after 6 months post-training (probe # 5 vs. probe # 3: $p<0.001$). An effect of generalization was observed for both control (probe # 5 vs. probe # 3: $p=0.02$) and spontaneous (probe # 5 vs. probe # 3: $p=0.04$) items during probe # 5. The improvement in the spontaneous item naming performance observed in S.A. can be explained by the fact that this condition included a subset of items that could not be spontaneously named in the probes # 1 and # 2 (see the experimental procedure section).

Case 2: G.R.

As reported in Table 5, G.R. showed a significant effect of phonological training (training items probe # 4 vs. probe # 3: Fisher's exact test, $p<0.001$) that was still present after 6 months posttraining (probe # 5 vs. probe # 3: $p<0.001$). An effect of generalization was observed for control items during probe # 5 (probe # 5 vs. probe # 3: $p<0.01$).

SEM results

The activation patterns associated with the naming task in both patients were reported elsewhere (Vitali et al., 2007). Here we only report the results of the SEM analysis.

Case 1: S.A.

In S.A., correct picture naming on training items following phonological training was associated with an enhancement of connectivity between the following ROIs: - left IFG (in a region correspondent to Broca's area pars triangularis) and left IPL (in a region correspondent to the SMG); - right IFG and left IPL (and vice-versa); - right IPL and left MTG (see Fig. 2A). Conversely, correct picture naming on untrained items showed a pattern of effective connectivity mainly localized between ROIs within the right hemisphere: - IFG and IPL (and vice-versa); - MTG and IFG; - MTG and insula; - IPL and insula. Moreover, an enhancement of effective connectivity was observed between: - right IFG and left MTG; - right MTG and left insula (and vice-versa) (see Fig. 2B). It is noteworthy that six months post-training, when generalization to untrained material had occurred, untrained picture naming was accompanied by greater coupling between Broca's area pars triangularis and the left IPL (see Fig. 2C).

Case 2: G.R.

In G.R., correct picture naming on training items following phonological training was associated with modulation of path-strengths between the following ROIs: - left IPL and right insula (and vice-versa); - left IPL and right MTG; - right MTG and right IFG (and vice-versa); - right IPL and right MTG (and vice-versa) (see Fig. 3A). Conversely, untrained picture naming was associated with enhanced connectivity between left MTG and left IPL (and vice-versa) (see Fig. 3B). Generalization to untrained items was accompanied by time-dependent connectivity changes between the following ROIs: - left IPL and right MTG; right IPL and left MTG (and vice-versa); - right MTG and left MTG; - right MTG and right IFG (and vice-versa) (see Fig. 3C).

DISCUSSION

The purpose of the present study was to investigate changes in cerebral effective connectivity associated with anomia treatment in two individuals with aphasia. Both patients demonstrated considerable benefits from the anomia treatment. From a clinical point of view, the most successful treatment is the one that results in improvement not only for the items used in therapy, but also for untrained items. The phonological cueing treatment for anomia remediation that was adopted in the present study yielded immediate, item-specific improvements of picture naming, as well as delayed generalization effects to untrained material in both participants.

The rate of improvement following treatment was clearly faster for trained items than for untreated stimuli. Moreover, the effects of training were still present six months post-treatment. This first result - persistent naming improvement after training - is in agreement with several investigations reporting that treatments for word-finding impairments produce clear long-lasting effects on the treated items, while generalization to untreated items, when obtained, is often less robust (e.g., Nickels & Best, 1996).

The second result - delayed naming improvement on undrilled items - might be considered as a consequence of spontaneous recovery. Actually, such an explanation is unlikely in the present study, since both participants were in chronic stage and their naming performances were clearly stable before therapy, as measured over three behavioural probes (baseline probes # 1 through # 3) on the Snodgrass and Vanderwart picture. The cause of the generalization effect appearing only six months post-training remains unclear. It may be speculated that the patients adopted an auto-cueing strategy learnt during the training period.

From a neurobiological standpoint, effective connectivity analysis clearly offers an additional perspective to the investigation of the brain underpinnings of functional recovery in aphasia with respect to traditional methodological approaches to functional imaging, allowing the observation of patterns of functional linkage, rather than the activity of isolated cortical areas. In the present study, effective connectivity analysis revealed participant-specific training- and time-dependent modulations of path-strengths. Differences in age, aetiology of brain damage and lesion size and site might explain the different patterns of effective connectivity observed in the two participants. For this reason, the two cases will be discussed separately.

In the case of S.A., training-dependent modifications of connection-strengths were shown between bilateral inferior frontal areas and the supramarginal portion of the left IPL for the naming of trained items. Conversely, a large pattern of connectivity among regions, mainly in the right hemisphere, was observed for the naming of untrained items. These involved the right IFG, insula, MTG, and IPL. The role of the right hemisphere in aphasia recovery is controversial. Right hemisphere recruitment, associated with aphasia recovery, has been reported, in particular in the homologues of Broca's and Wernicke's areas (Calvert et al., 2000; Crosson et al., 2005; Fernandez et al., 2004). However, the increased activation of right homologous areas, rather than representing a compensatory take-over, might reflect a maladaptive functional reorganization, responsible for the word-finding impairment itself. In fact, the inhibition of some such areas of activation (specifically right, posterior, inferior pars triangularis Broca’s area) with rTMS resulted in improved picture naming in four patients with chronic nonfluent aphasia (Naeser et al., 2005). Results with S.A. seem to support this view, since the mostly right-sided connectivity pattern was associated with the less effective untrained picture naming, as opposed to the more efficient naming of trained material, associated to left hemispheric changes. Nevertheless, time-dependent modifications in coupling among regions were observed for naming untrained items, concomitant with the late increase in the rate of change of improvement for untreated items in picture naming. Specifically, these involved a delayed enhancement of connectivity between Broca's area pars triangularis and the left supramarginal gyrus, which parallels path-strength modulations observed in trained picture naming. The role of Broca’s area in phonological processing is well-known (Demonet et al., 2005). The preservation of Broca's area in S.A. may have allowed an enhancement of the impact of phonological training. The SMG portion of the left IPL represents another crucial component of the phonological loop of Baddeley's verbal working memory model. It has been suggested to be involved in phonological storage (Paulesu, Frith, & Frackowiak, 1993), as well as in lexical processing (Baddeley & Hitch, 1974). It is thus possible that this participant adopted training-induced phonological compensatory strategies for successful lexical retrieval (see Leger et al., 2002, and Vitali et al., 2007 for a similar interpretation). Interestingly, the changes over time in the pattern of connectivity associated with untrained picture naming, which at the end partially overlapped with the pattern associated with trained picture naming, might indicate that S.A. gradually learned to apply the same phonological strategies to improve the naming of untreated items.

In the case of G.R., training-dependent modifications of connection-strengths were reported between the IPL bilaterally, the right MTG, and the right homologue of Broca's area for the naming of trained items. Conversely, untrained picture naming enhanced connectivity between the left MTG and the left IPL. In contrast to S.A., G.R. presented training-dependent changes in effective connectivity for untrained picture naming exclusively in the left dominant hemisphere. This could be explained by the fact that participant G.R. was already much better at picture naming before therapy than S.A., as indicated by his performance in the three pre-training behavioural probes (baseline probes # 1 through # 3). The better naming performance of G.R. may indicate the engagement of preserved left-perilesional tissue. However, the fact that only two brain regions were shown to be associated with untrained picture naming may be a consequence of a methodological limitation of the SEM technique. Since the researcher has to predetermine the potentially linked areas, this could bias observation away from unexpected results. Nevertheless, the extension of G.R.'s lesion limited the number of possible ROIs included in the model. On the other hand, the substantial involvement of the right hemisphere – with the exception of the left IPL - in picture naming following phonological training (as shown in

Fig. 3A) deserves particular consideration, as it appears to be in contrast with the assumption that this rehabilitation approach would be more suitable for tapping into the left hemisphere's phonological processing abilities. In this particular case, however, the size of the participant's lesion – which spared only limited cortex in the left hemisphere – may have promoted the contribution from the right hemisphere towards therapy-induced naming recovery. A study by Catani et al. (Catani, Jones, & ffytche, 2005) revealed extensive white matter connections from the IPL to the ventrolateral prefrontal cortex and to the temporal lobe in the left hemisphere. The authors refer to the IPL as "Geschwind's territory", arguing that it plays an important role in a parallel processing language network of the left hemisphere. Because G.R.'s large left hemisphere lesion included essential portions of this area, it is possible that the right hemisphere homologues of this language network would be recruited. As already mentioned, however, several studies suggested that the increased right hemisphere activity associated with speech production in recovered aphasics may be maladaptive rather than facilitatory (Blank, Bird, Turkheimer, & Wise, 2003; Fernandez et al., 2004; Naeser et al., 2004; Rosen et al., 2000). Thus, the role of the right hemisphere in G.R.'s recovery should be interpreted with caution, as increased left-perilesional cortical connectivity was also observed as a result of the treatment. As in the case of S.A., time-dependent modifications in coupling between regions were observed for naming untrained items, concomitant with the late improvement for untreated items in picture naming. These changes were very similar to those associated with phonological training, and involved an enhancement of connectivity among the IPL and the MTG bilaterally, and the Broca's area right homologue. This finding suggests that training and generalization effects share similar cortical patterns of functional integration, supporting the hypothesis that G.R. might have adopted training-induced lexical retrieval strategies to improve untrained picture naming.

In conclusion, the results from SEM provide the first evidence for the existence of a selective pattern of functional integration related to improved picture naming following phonological training. Our connectivity results provide evidence supporting the hypothesis that the cerebral reorganization underpinning anomia treatment depends on lesion location and extension (Crosson et al., 2007). In fact, the training modulated the connections among perilesional areas when the lesion was smaller (S.A.), and among the right homologues when the lesion was more extensive (G.R.).

Moreover, this study contributes to the characterization in terms of effective connectivity of the positive impact of learning transfer to untrained material. The present findings seem to support the notion that the generalization of the impact of a systematic training for anomia to untrained items relies upon neuronal correlates which are similar to those associated with item-specific training-induced improvement. This is consistent with the idea that both training and generalization reflect the adoption of comparable cognitive strategies for the compensation of lexical retrieval impairments. Although the patients benefit of a generalization of the training only after six months raises the question of a possible role of spontaneous recovery, we consider this hypothesis unlikely for G.R. In fact, the experimental training took place four years after the stroke. Spontaneous recovery of anomia is uncommon after such a long interval from the vascular event. Furthermore, during this period no spontaneous anomia improvements were reported in medical records. On the other hand, the hypothesis of a spontaneous anomia recovery can not be completely excluded for S.A, because of his younger age, the onset time of the accident (12 months before the study) and its traumatic aetiology. However, the fact that in both patients the recovery of untrained items relies upon the same pattern of connection of trained items makes the explanation of the effect of generalization of the training more likely.

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Table 1. Demographic and clinical data for the 2 participants in the study.

Patient	Age (in years)	Gender	Education (in years)	Etiology	Lesion site (as defined on MRI)	Months post-onset
S.A.	24	Male	8	Closed head injury	Left prefrontal cortex Left fronto-parieto-occipital white matter	12
G.R.	52	Male	13	Ischemic stroke	Territory of left middle cerebral artery, involving fronto-temporo-parietal areas and extending to the temporo-parieto-occipital junction	48

Table 2. S.A.'s neuropsychological and language assessment nineteen months post-onset.

	SCORE	SEVERITY
Neuropsychological Assessment		
Word Fluency		
Phonological Fluency	4	Pathological
Semantic Fluency	7	Pathological
Non-Verbal Reasoning		
Raven's Progressive Matrices (0-48)	28	Normal
Attention		
Matrix Test (0-60)	22	Pathological
Visuo-Spatial Memory		
Corsi's Test	4	Pathological
Supra-Span Visuo-Spatial Learning (0-30.78)	24.03	Normal
Rey-Osterrieth Complex Figure Test – Delayed recall (0-36)	15.5	Normal
Visuo-SpatialAbilities		
Rey-Osterrieth Complex Figure Test – Copy (0-36)	34	Normal
Calculation		
Written Calculation	13.2	Pathological
Language Assessment		
Aachener Aphasie Test		
Spontaneous Speech (0-5)		
Communicative behaviour	1	
Articulation and prosody	3	
Automatized language	4	
Semantic Structure	3	
Phonologic Structure	4	
Syntactic Structure	2	
Token Test (0-100)	46	Severe
Speech Repetition (0-150)	128	Mild
Written language (0-90)	23	Severe/Moderate
Naming (0-120)	34	Severe
Comprehension (0-120)	83	Moderate/ Mild
Snodgrass & Vanderwart Naming Test		
Naming (0-260)	77 (29.6%)	

Table 3. G.R.'s language assessment 5- and 10-months post-onset.

	5-months post-onset	**10-months post-onset**
Spatial and Temporal Orientation	Impaired	Normal
Oral Production		
Spontaneous language	Stereotyped, limited to yes/No and greetings, perseverations	Stereotyped, perseverations, but slightly improved compared to the first evaluation
Automatized Language	Impaired	Normal (numbers and days of the week)
Repetition	Impaired at the level of sounds, words and sentences	Improved at the level of sounds and words, but still defective at the level of sentences
Naming	Impaired, but sensitive to phonological cueing Perseverations	Impaired, but sensitive to phonological cueing
Picture Description	Impaired	N/A
Reading	Impaired	Impaired (only high-frequency words)
Written Production		
Copy	Normal	Normal
Spontaneous	Impaired	Impaired
Oral Comprehension		
Single Words	Good	Good
Sentences	Impaired	Impaired
Token Test	Impaired	Improved performance, although still impaired
Written Comprehension		
Single Words	Impaired	Impaired
Sentences	Impaired	Impaired
Apraxia		
Bucco-facial	Mild	Absent
Ideomotor	Mild	Absent
Constructional	Absent	Absent
Ideatory	Absent	Absent

Table 4. Number of items correctly named by S.A. in the five experimental probes

Probes	Training items	Control items	Spontaneous items
#1	0/20	0/20	1/18
#2	0/20	0/20	1/18
#3 – 1st fMRI	0/20	0/20	1/18
#4 – 2nd fMRI	15/20*	0/20	3/18
#5 – 3rd fMRI	18/20*	6/20*	7/18*

* $p<0.05$ vs. Probe #3 (Fisher's Exact Test)

Table 5. Number of items correctly named by G.R. in the five experimental probes

Probes	Training items	Control items	Spontaneous items
#1	0/18	0/18	18/18
#2	0/18	0/18	18/18
#3 – 1st fMRI	0/18	0/18	18/18
#4 – 2nd fMRI	12/18*	3/18	14/18
#5 – 3rd fMRI	14/18*	7/18*	16/18

* $p<0.05$ vs. Probe #3 (Fisher's Exact Test)

Table 6. ROIs identified in the two aphasic participants for the SEM analysis with the x, y, and z coordinates according to the Talairach's stereotaxic space, and the F score for the peak voxel in each region (significant at $p < 0.001$ uncorrected, in the SPM analysis for all effects of interest).

ROIs	S.A.				G.R.			
	x	y	z	F	x	y	z	F
Left inferior frontal gyrus (Ba 45)	-42	22	12	2.45	-	-	-	-
Right inferior frontal gyrus (Ba 45)	42	20	12	2.23	40	24	16	3.63
Left insula	-34	4	0	2.55	-	-	-	-
Right insula	34	4	0	5.31	34	4	0	3.9
Left middle temporal gyrus (Ba 37)	-56	-68	0	1.94	-58	-68	4	4.17
Right middle temporal gyrus (Ba 37)	54	-68	0	5.39	54	-64	4	6.03
Left inferior parietal lobule (Ba 40)	-52	-48	32	3.34	-56	-46	28	2.78
Right inferior parietal lobule (Ba 40)	56	-48	36	2.23	56	-46	28	3.26

Legend for figures

Figure 1. Representative MR anatomic slices showing the brain lesion in S.A. (top) and G.R. (bottom).

Figure 2 and Figure 3. Patients' pattern of effective connectivity with training-dependent modulation of path-strengths for trained (A) and untrained (B) correct picture naming, and time-dependent modulation of path-strengths for untrained correct picture naming (C). For each patient, results are superimposed onto transversal slices of their own T1*weighted normalized brain images. Training- and time-dependent modulations of effective connectivity between regions are illustrated with arrow lines of different colours (red and yellow, respectively). Dotted red lines represent training-dependent modulation of effective connectivity for untrained picture naming. Legend: L = left hemisphere; R = right hemisphere; IFG = inferior frontal gyrus; MTG = middle temporal gyrus; IPL = inferior parietal lobule.

Figure 1.

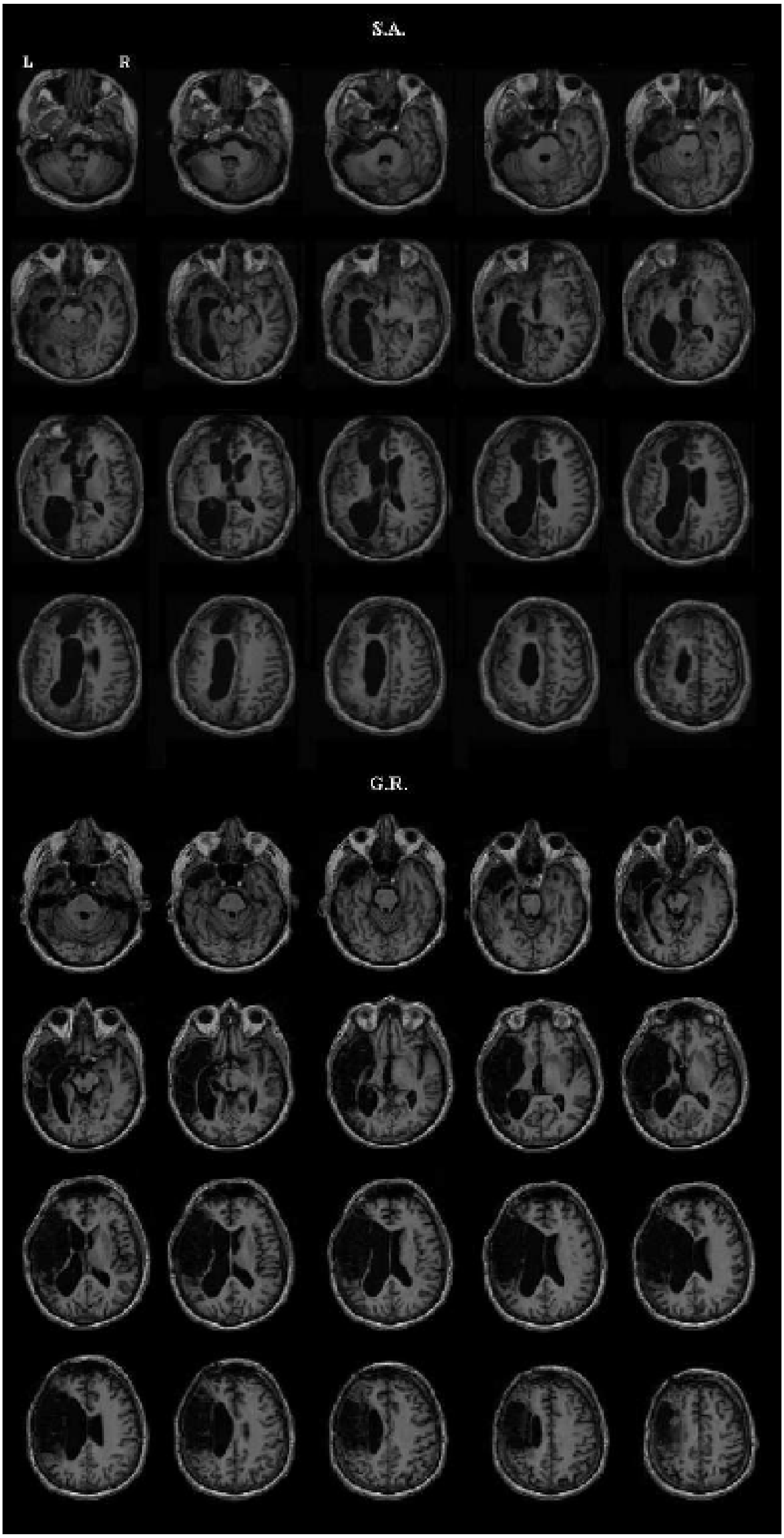


Figure 2

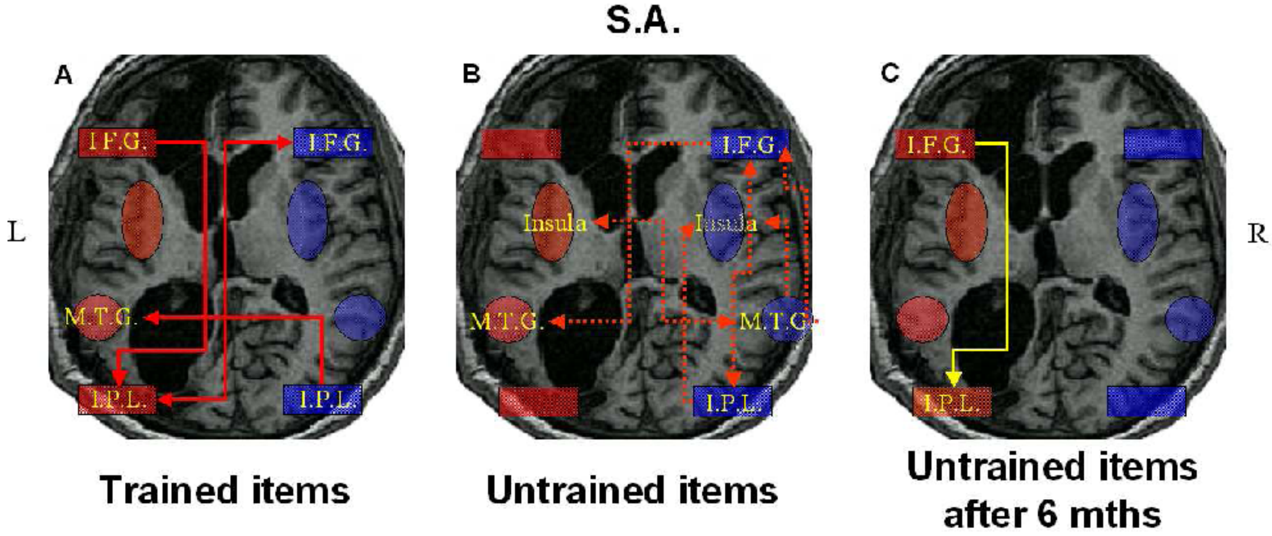
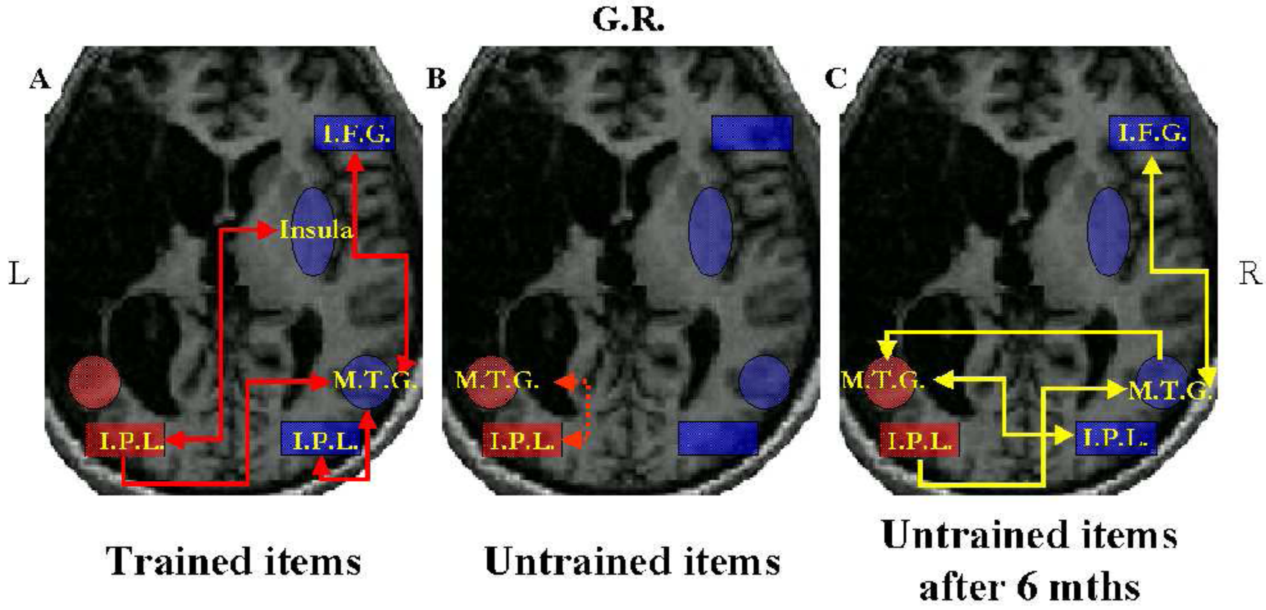

S.A.
A
B
C
L
R
I.F.G.
I.F.G.
M.T.G.
I.P.L.
I.P.L.
I.F.G.
Insula
Insula
M.T.G.
M.T.G.
I.P.L.
I.F.G.
I.P.L.
Trained items
Untrained items
Untrained items after 6 mths

Figure 3


G.R.
A
B
C
L
R
I.F.G.
Insula
M.T.G.
I.P.L.
I.P.L.
M.T.G.
I.P.L.
I.F.G.
M.T.G.
M.T.G.
I.P.L.
I.P.L.
Trained items
Untrained items
Untrained items
after 6 mths