

Early Aphasia Rehabilitation Is Associated With Functional Reactivation of the Left Inferior Frontal Gyrus

A Pilot Study

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Background and Purpose—Early poststroke aphasia rehabilitation effects and their functional MRI (fMRI) correlates were investigated in a pilot, controlled longitudinal study.

Methods—Twelve patients with mild/moderate aphasia (8 Broca, 3 anomic, and 1 Wernicke) were randomly assigned to daily language rehabilitation for 2 weeks (starting 2.2 [mean] days poststroke) or no rehabilitation. The Aachen Aphasia Test and fMRI recorded during an auditory comprehension task were performed at 3 time intervals: mean 2.2 (T1), 16.2 (T2), and 190 (T3) days poststroke.

Results—Groups did not differ in terms of age, education, aphasia severity, lesions volume, baseline fMRI activations, and in task performance during fMRI across examinations. Rehabilitated patients significantly improved in naming and written language tasks ($P < 0.05$) compared with no rehabilitation group both at T2 and T3. Functional activity at T1 was reduced in language-related cortical areas (right and left inferior frontal gyrus and middle temporal gyrus, right inferior parietal lobule and superior temporal gyrus) in patients compared with controls. T2 and T3 follow-ups revealed a cortical activation increase, with significantly greater activation in the left hemisphere areas in rehabilitated patients at T2 and T3, and a time \times treatment effect at T2 in the left inferior Broca area after rehabilitation. Left inferior frontal gyrus activation at T2 significantly correlated with naming improvement.

Conclusions—Early poststroke aphasia treatment is useful, has durable effects, and may lead to early enhanced recruitment of brain areas, particularly the left inferior frontal gyrus, which persists in the chronic phase. (*Stroke*. 2014;45:545-552.)

Key Words: aphasia ■ language therapy ■ magnetic resonance imaging, functional ■ neuroimaging ■ rehabilitation outcome

An important issue for language rehabilitation after stroke is the relationship between the effects of therapeutic interventions and the functional changes observed in brain language-related areas. Most studies focused on the spontaneous recovery of language,¹⁻⁷ but only a few, often single case descriptions, focused on patients submitted to language rehabilitation.⁸⁻¹³ All of these were conducted on chronic patients.

The rate of complete spontaneous (ie, without language therapy) aphasia recovery poststroke has been estimated at $\approx 33\%$ in the first month, 43% after 4 months, and 50% 12 months later.¹⁴ However, the concept of spontaneous recovery of language may not be appropriate (as human beings are extensively exposed to language). The term language therapy commonly relates to formal interventions provided by speech therapists aimed at improving different language abilities with specific exercises.

Evidence supports the use of language rehabilitation in stroke, particularly if intensively administered for short courses in chronic aphasics.^{15,16} In a pilot study, Godecke et al¹⁷ found that daily aphasia therapy in early stroke, that is, mean 3 days poststroke (dps), resulted in improved communication outcomes in moderate to severe aphasia.

Brain plasticity induced by language training has not been extensively investigated to date. Several studies, conducted in chronic patients, suggested that functional correlates of aphasia recovery could be either the activation of predominantly left hemisphere (LH) language-related areas¹⁸⁻²² or of the homologous right hemisphere (RH) areas,^{2,23-25} but often the authors do not clarify whether patients were formally treated and to what extent, or not. Saur et al⁴ suggest that in the postacute stages of recovery (2 weeks poststroke), the LH areas would be reduced in activation, whereas after months

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they would increase their activation, reflecting the language improvement. Patients examined in the study were reportedly submitted to language therapy, but details on its duration and type were not provided.

A maladaptive role of the RH language-related areas in aphasia recovery has also been hypothesized; Breier et al¹¹ and Heiss and Thiel²⁶ suggested that the RH could be implicated when large LH lesions are present or when aphasia recovery is incomplete. Finally, brain modulation with transcranial direct current stimulation or transcranial magnetic stimulation also supports this hypothesis, because anodal inhibition over the RH has been reported to improve naming in chronic aphasics.^{6,27} The recruitment of RH may reflect maladaptive functional reorganization, brought about by the presence of the lesion itself, or a transcallosal disinhibition, unrelated to the level of recovery.

Furthermore, some studies clearly addressing the functional correlates of language rehabilitation, particularly anomia, performed on chronic patients found LH,¹⁰ bilateral,^{9,28} or RH²⁹ activation. It is worth noting that functional MRI (fMRI) studies using different tasks^{8,19,20,24,30,31} also found variable activation patterns within the language-related areas (see Thompson and den Ouden³¹ for a review), suggesting that the whole network could be consistently activated by different language modalities.

In conclusion, language improvement was consistently found to be associated with modifications at a neural level, but the effect of rehabilitation on brain plasticity, particularly in the acute phase, is unclear and the way in which training modulates functional recovery remains to be determined.

Therefore, the aim of the present pilot study was double-fold. First, we aimed to replicate previous findings on the efficacy of early poststroke aphasia rehabilitation in people with moderate to severe aphasia¹⁷ on a group of patients with mild/moderate aphasia. We predicted that daily language rehabilitation leads to the improvement of communicative outcomes. Second, we aimed to investigate the functional correlates of language rehabilitation. We predicted that language therapy should be able to address brain plasticity,³² promoting an early shift from RH to LH language-related areas in rehabilitated patients. Hence, early recruitment of LH perilesional areas would be the correlate of language improvement in early treated patients.

Material and Methods

Patients

Inclusion criteria were: (1) first ever acute stroke in the territory of the middle cerebral artery; (2) aphasia with mildly impaired oral comprehension, that is, comprehension sufficient to perform a screening task of the fMRI paradigm; (3) native Italian speakers; (4) right-handedness³³; (5) absence of previous history of other neurological or psychiatric diseases; (6) absence of general contraindications to MRI; (7) age <80 years; (8) absence of hearing deficits. Twelve first-ever-stroke patients participated, with 6 randomly assigned to Rehab group and 6 to NRehab group. A random number generator was used to randomize participants. The study was conducted in accordance with the Helsinki Declaration and was approved by the Spedali Civili of Brescia institutional board. Informed oral consent was obtained from each patient and written informed consent by the closest relative. See the online-only Data Supplement for additional information.

Methods

All patients had a CT scan and a NIHSS (National Institute of Health Stroke Scale) evaluation performed in the first 24 hours poststroke.

Details of lesion volume analysis are available in the online-only Data Supplement.

Patients who entered the study were assessed 3 times, both with neuropsychological evaluation and with fMRI. Examinations were conducted ≈ 2 dps (T1: mean [SD], 2.2 [1.3] dps), 2 weeks post-stroke (T2: 16.2 ± 1.3 dps), and 6 months later (T3: 190 ± 25.5 dps). Neuropsychological assessment and fMRI were separated by ≤ 24 hours. Ten sex- and age-matched healthy subjects were also examined with the same fMRI paradigm only once.

Neuropsychological Evaluation

The Aachen Aphasia Test (AAT)³⁴ was used in all 3 examinations, given the moderate severity language impairment of our patients and the high test–retest reliability of the AAT. The test includes subtests of repetition, naming, reading, writing, oral, and written comprehension; a 50-item version of the Token test; and a semiquantitative scoring of several aspects of spontaneous speech (communicative ability, articulation and prosody, automatic speech, semantic, phonemic, and syntactic structure). Neuropsychological assessment was performed by a blinded speech therapist. We separately considered oral and written comprehension in the AAT comprehension subtest to better understand the behavioral data. The number of correct responses was used for all the subtests, except for spontaneous speech, which was scored with a mean of each spontaneous speech aspect's score.

Severity (based on the Italian AAT version) and subtyping of patients' aphasia was also obtained, according to the AAT procedure.

Aphasia Treatment

For each treated patient, language therapy started 2 dps after the first evaluation and lasted until the subsequent examination, ≈ 2 weeks post-stroke. Treatment consisted of a 1-hour session per day, for 5 days per week. After T2, no patient was further rehabilitated. Given the low severity of their aphasia and the low impact of the disorder on their everyday activities, this was not considered an ethical violation. For details on rehabilitation, see the online-only Data Supplement. NRehab patients did not undergo any language rehabilitation, as was the clinical practice of our hospital in the acute phase of stroke. However, they were all exposed to the natural speech environment of people they were visited, and this could be considered an unstructured language therapy.

fMRI Examination

fMRI Paradigm

An oral comprehension task was used in an event-related fMRI experiment at T1, T2, and T3, similar to the task used in Saur et al.⁴ This task was chosen because comprehension is thought to be the earliest linguistic-improving ability poststroke and because of the well-studied functional correlates of the comprehension task in the poststroke acute phase. Details of fMRI paradigm are available in the online-only Data Supplement.

Image Analysis

Details of fMRI acquisition and preprocessing are available in the online-only Data Supplement. For each subject, analysis was performed by pooling correct and incorrect predictors (intelligible sentences) versus reverse speech and noise [1 1 -1 -1], and relative contrast maps were calculated with a confidence level ≤ 0.001 .

First of all, within-group analysis was performed, using a general linear model approach with statistical threshold of 0.001 (uncorrected), considering contrasts in each examination (T1, T2, T3) for both controls and patients. To understand the difference in activation between Rehab and NRehab, a between-group comparison was performed for each examination (T1Rehab>T1NRehab, T2Rehab>T2NRehab, T3Rehab>T3NRehab), considering significant effects at $P < 0.001$. A cluster size threshold of 160 mm³ was used. Moreover, to study the longitudinal effect of rehabilitation on brain activations, a within-group analysis of contrasts between examinations (T2>T1 and T3>T2) was performed as well for both Rehab and NRehab groups (error level <0.005; uncorrected).

Finally, as postrehabilitation differences were expected to be found, a region of interest (ROI) selection was carried out to perform a single ROI statistical analysis. To perform ROI selection, controls' and patients' activation at all examinations (Rehab and NRehab at T1, T2, and T3) were pooled. ROIs were defined based on the resulting whole group activation: bilateral inferior frontal gyrus (IFG) and bilateral superior temporal gyrus (STG). A 2-way ANOVA on ROI activations using Group (2 levels: Rehab and NRehab) as a between-factor and Time (3 levels: T1, T2, and T3) as a within-factor was performed for each ROI, with a confidence level of 0.05.

Results

Sociodemographical and Clinical Features

Rehab patients included 2 women and 4 men, whereas NRehab patients included 3 women and 3 men. Age, education (years of schooling), and NIHSS were not statistically different between the groups. At baseline, the patients showed Broca aphasia in 8 cases, anomic aphasia in 3, and mild Wernicke aphasia in 1 case. Lesions mainly involved areas in the left frontal lobe: insula, thalamus, internal and external capsula, and the parietotemporal junction. Neither thrombolytic nor clonidine, antipsychotic, or antiepileptic drugs were administered to the included patients. No differences in lesion volume were detected between the 2 groups. The Broca area was damaged by the lesion in 3 patients both in the Rehab and in the NRehab groups. All the included patients completed the study, except 1 participant in the NRehab group who died after T2 because of a cardiac arrest (for details about sociodemographic features, see Table I in the online-only Data Supplement; for details of lesion volume analysis, see Figure I and the Results section in the online-only Data Supplement).

Aphasia Evolution Results

Because the neuropsychological data were not all normally distributed at Shapiro–Wilk test, the data were analyzed by means of nonparametric Mann–Whitney *U*-tests, with Bonferroni correction. AAT subtest scores for Rehab and NRehab groups at T1, T2, and T3 are reported in Table II in the online-only Data Supplement. At T1 evaluation, groups were not statistically different in all AAT subtests, whereas at T2, Rehab patients obtained a statistically higher score in both naming and written language subtests compared with NRehab patients (mean

naming: 110/120, 80/120; *P*=0.01; mean written language: 84.5/90, 48.7/90; *P*=0.02). Although all the patients examined singularly or as separate groups improved in all AAT scores at T2, the remaining AAT subtests were not statistically different between groups. The same was observed at T3 (mean naming: 113/120, 98/120; *P*=0.004; mean written language: 85.5/90, 71/90; *P*=0.03), confirming a significantly better performance of Rehab patients compared with NRehab patients in written language and naming tests. During the clinical interview at T2, Rehab patients and their relatives appeared satisfied about the improvement in language functions.

fMRI Results

Task performance analysis did not reveal differences between groups across examinations (see the online-only Data Supplement). In control subjects, the analysis revealed strong bilateral activation of several brain language-related areas: left and right IFG, anterior part of left and right STG, left inferior parietal lobule (IPL) and precuneus, left supplementary motor area in the medial frontal gyrus, and left middle temporal gyrus. Two days after the stroke, all Rehab and NRehab aphasic patients, as a group, showed a markedly reduced cortical activation both in the RH and in the LH compared with controls. In particular, clusters of activation were found in left and right IFG, left and right middle temporal gyrus, right IPL, and right STG (Table 1 and Figure 1). Based on activations of controls and patients, we selected the following ROIs: bilateral IFG, left middle temporal gyrus, right STG, and left IPL.

Group analysis at T2 follow-up showed different patterns of activation in Rehab and NRehab groups. Rehab patients activated left and right IFG, left and right STG, left IPL/supramarginal gyrus, and left supplementary motor area, whereas in NRehab patients, the main activated area at T2 was only the right IFG. The remaining language-related areas, except left IPL/supramarginal gyrus, showed less cortical activation. At 6-month follow-up (T3), an increase in both hemispheres' cortical activations was similarly seen in both groups, mainly localized in LH, particularly the left and right IFG, left STG, left and right IPL/supramarginal gyrus, and left supplementary motor area (Figure 2 and Table 2). This pattern was confirmed by the between-group comparison. At T1, no difference between Rehab and NRehab groups was found, as was expected,

Table 1. Baseline Brain Activation During Functional MRI Comprehension Task in Control Group and Patients

Control Group					Patients at Acute Phase (T1)				
Coordinates	Side	Area	BA	T	Coordinates	Side	Area	BA	t
-48 20 13	L	IFG	45, 47	13.27	-43 19 1	L	IFG	47	5.00
-58 -50 18	L	STG/AnG	39	5.83	-46 13 15	L	IFG	44	4.57
-55 -62 6	L	MTG	37	5.93	-48 -71 17	L	MTG	39, 22	4.62
	L	IPL	40	5.06	-57 -47 32	L	IPL	40	4.95
-34 -65 39	L	Precuneus	39	6.32	-1 0 58	L	SMA	6	6.51
-2 4 48	L	SMA	6	10.54	60 -34 40	R	IPL	40	5.42
47 16 -3	R	IFG	45	8.77	47 23 -6	R	IFG	47	4.66
62 -16 6	R	STG	22	6.13	46 -53 27	R	STG	39	5.09
					47 -56 9	R	MTG	39, 22	4.5

P<0.001; uncorrected. AnG indicates angular gyrus; BA, broadman area; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; L, left, MTG, middle temporal gyrus; R, right; SMA, supplementary motor area; and STG, superior temporal gyrus.

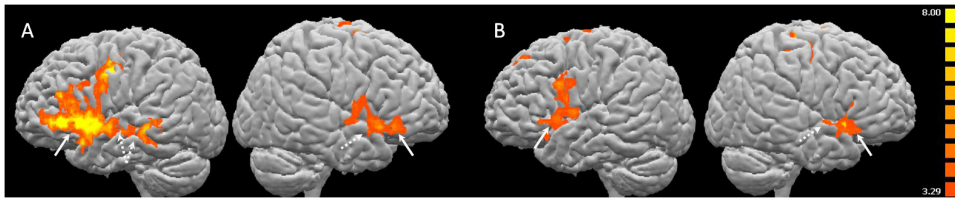


Figure 1. Baseline brain activation during functional MRI (fMRI) comprehension task in control group and patients. **A**, Brain activation in left and right hemisphere during the fMRI comprehension task in control group. **B**, Brain activation in left and right hemisphere

during the fMRI comprehension task in patients (both Rehab and NRehab) at acute phase (T1). Activations in language-related areas of inferior frontal gyrus, mainly in the operculum (white arrow), in superior and middle temporal gyrus (dotted line). Statistical significance level, $P < 0.001$; uncorrected.

whereas at T2, left IFG revealed to be predominantly activated by Rehab patients followed, at 6 months poststroke, by a similar recruitment of areas predominantly located in the LH, again with a higher recruitment observed in Rehab patients compared with NRehab patients (Figure 2 and Table 2). The opposite NRehab>Rehab contrast showed no areas with increased activation in the NRehab versus the Rehab group.

Within-group changes in brain activation over time ($T2 > T1$ and $T3 > T2$) are visualized in Figure 3 and reported in Table 3. After a 2-week course of language rehabilitation, an increased activation was found in left IFG (Broca area) and in STG in Rehab patients, whereas NRehab group showed change in activation of right IFG and left IPL. The 6-month follow-up (no language rehabilitation condition for both groups) change in activation was similarly present in LH Broca area, STG, and IPL in both groups. To summarize, left IFG was predominantly recruited 2 weeks after the stroke only in patients submitted to language rehabilitation, whereas after 6 months, all the patients had a prevalent recruitment of brain language-related areas located in the LH.

These results were subsequently confirmed using ANOVA: a treatment \times time interaction was found in the left IFG at T2 only ($F = 10.2$; $P = 0.009$), with significantly higher activation in the Rehab group as revealed by post hoc test ($P < 0.05$). No significant difference was found between groups at T1 and T3, neither in other ROIs, indicating left IFG as the crucial site of different brain activation between groups, at T2 only.

Analysis of Correlations

To further corroborate the previous results, a correlation between functional changes after rehabilitation in ROIs and naming and written language changes ($T2 > T1$) was performed. A significant correlation was found between functional imaging changes in the left IFG ($T2 > T1$) only and improvement in naming ($r = 0.957$; $P < 0.003$) in Rehab, and changes in the right

IFG only and improvement in naming ($r = 0.821$; $P < 0.015$) in NRehab. See Figure 3 for details.

Discussion

Two main results arise from this pilot study: first, the clinical efficacy of aphasia rehabilitation has been well demonstrated in acute poststroke patients; second, the possible functional correlate of this treatment-related language improvement is supposed to be the left IFG early activation during the process of aphasia recovery.

Rehabilitation was found to improve naming abilities as well as writing and reading aloud in aphasic patients. The lack of significant difference in comprehension and repetition may, in our opinion, be because of the milder deficits presented by some of the patients, possibly inducing a ceiling effect. The language improvement of Rehab patients, which was evident after 15 days, persists 6 months after stroke. The present results are in line with Godecke et al's¹⁷ findings and may have relevant clinical implications. Although the results need to be confirmed on larger samples of patients harboring aphasic syndromes of diverse severity, they seem to support early daily rehabilitation program of aphasic stroke patients as a valuable intervention. The results also provide at least partial answers to clinicians in deciding whether to wait for spontaneous improvement to occur or provide intensive early aphasia treatment. On the contrary, the present findings are not in line with the negative results of the ACT Now Study,³⁵ in which communication therapy and unstructured social contact were compared in the first 4 months after stroke. This latter study seems to rule out any added benefit of communication therapy. However, important methodological difference could explain the different results: contrary to the present study, the ACT Now Study was not focused on the first-ever-LH-stroke patients, but also included patients with dysarthria, and critical

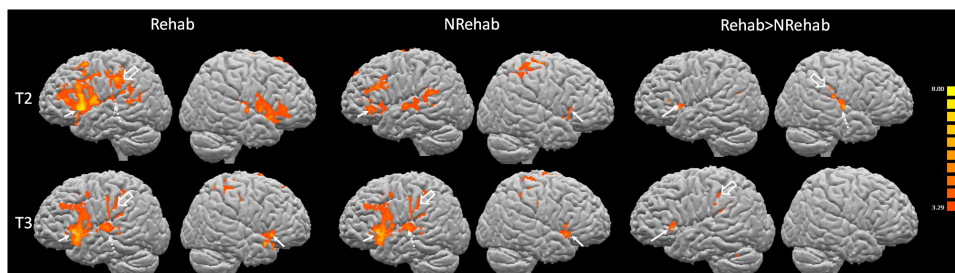


Figure 2. T2 and T3 brain activation during functional MRI (fMRI) tasks. T2 (upper line) and T3 (lower line) activation in Rehab and NRehab patients, and Rehab>NRehab in left hemisphere (left) and right hemisphere (right) at T2 and T3. Activation shown in the inferior frontal gyrus (white arrow), superior temporal gyrus (dotted arrow), inferior parietal lobule, and angular gyrus (open arrow). Statistical significance level, $P < 0.001$; uncorrected.

Table 2. Clusters of Activation in Rehab and NRehab Patients at T1, T2, and T3 Examinations

	Rehab					NRehab					Rehab>NRehab				
	Coordinates	Side	Area	BA	t	Coordinates	Side	Area	BA	t	Coordinates	Side	Area	BA	t
T1	-45 20 1	L	IFG	45, 37	3.91	-51 29 1	L	IFG	47	3.77	Nothing				
	-60 -46 28	L	IPL	40	3.65	-57 -25 28	L	IPL	40	2.94					
	-56 -59 0	L	MTG	22	3.42	-60 -40 4	L	MTG	22	3.22					
	50 23 -3	R	IFG	47	4.22	-18 11 67	L	SMA	6	3.89					
	48 -38 55	R	IPL	40	3.92	48 17 4	R	IFG	45	3.95					
	3 7 64	R	SMA	6	4.15	51 -34 53	R	IFG	40	2.83					
					18 5 70	R	SMA	6	4.30						
T2	-48 20 10	L	IFG	45, 47	6.68	-48 21 0	L	IFG	47	4.80	-52 16 3	L	IFG	44, 45	7.35
	-54 -58 21	L	STG/AnG	39	3.52	-37 -56 32	L	STG/AnG	39	4.05	-49 28 9	L	IPL	40	7.18
						-48 29 24	L	MFG	46	4.10	-55 -62 28	L	STG	39	6.37
	-57 -42 29	L	IPL/SmG	40	4.22	-2 6 52	L	SMA	6	5.26	-1 20 56	L	SMA	6	5.53
	-56 -32 6	L	STG	22	5.20										
	-3 -13 52	L	SMA	6	6.50										
	46 20 5	R	IFG	45	4.21	48 20 10	R	IFG	45	5.67	61 -29 30	R	IPL	40	6.80
	59 -38 13	R	STG	22	5.73						54 4 13	R	IFG	44, 46	4.57
40 -43 38	R	SmG	40	4.40											
T3	-46 19 9	L	IFG	45, 46	7.24	-49 19 9	L	IFG	45, 44	8.72	-49 -35 36	L	IPL	40	5.42
	-54 -56 14	L	STG	39	5.28	-58 -41 6	L	STG	22	7.72	-52 25 9	L	IFG	45	6.10
	-50 -30 33	L	IPL	40	6.70	-57 -39 22	L	IPL	40	6.13	-34 25 0	L	IFG	47	6.10
	-2 0 54	L	SMA	6	6.36	-1 0 58	L	SMA	6	7.20					
	47 25 5	R	IFG	45, 44	6.62	42 19 6	R	IFG	45	6.76	50 24 4*	R	IFG	45	4.64
	63 -29 22	R	IPL/SmG	40	5.65	46 -54 38	R	IPL/SmG	40	4.80	63 -37 25*	R	IPL	40	3.73

Between-group analysis in acute (T1), subacute (T2), and chronic (T3) stage after stroke. $P < 0.001$; $P < 0.005$. AnG indicates angular gyrus; BA, broadman area; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; L, left; MFG, middle frontal gyrus; MTG, middle temporal gyrus; R, right; SMA, supplementar motor area; SmG: supramarginal gyrus; STG, superior temporal gyrus; and t, Student *t*.

*Uncorrected.

time window for rehabilitation was not considered in the first 2 weeks poststroke.

The second main finding of the present study was that patients submitted to early intensive (2 weeks) poststroke rehabilitation showed a different recruitment of language-related cortical areas compared with the no treatment group, particularly involving the LH. Although all patients showed a dramatic decrease in cortical activations compared with controls 2 dps, Rehab patients showed larger predominantly left-sided areas at the second examination, particularly the left Broca area, compared with NRehab patients, correlating with language behavioral improvement. A further increase in activation in LH at 6-month (T3 to T2) follow-up (when both groups were not submitted to language rehabilitation), with a persistently higher activation in Rehab patients, was also found. In our opinion, the intensive aphasia training protocol seems to promote the early shifting of activation to the LH in the first 2 weeks poststroke, as observed in our patients submitted to early aphasia therapy. On the other hand, NRehab group showed a pattern of activation which is similar to the one found in the Saur et al (2006) patient group, ie, a reduced activation in the L language area in the acute phase, followed by a recruitment of homologue language zone in subacute phase and by a normalization of activation in chronic phase. Importantly, we could reasonably rule out the practice effect of task on fMRI results.

In fact, we did not find differences over time in fMRI task performance, especially between T1 and T2, and if practice had influenced the findings, we would have expected decreased activation between T1 and T2,³⁶ which is the opposite of what we actually found.

These findings suggest that a possible correlate of early language poststroke rehabilitation could be the earlier recruitment of the LH, namely the left Broca area, whereas the correlate of spontaneous, and possibly less efficient, language recovery in NRehab patients could be the activation of right IFG, which we found to be related with language improvement in NRehab only.

Our results support Saur et al⁴⁷'s hypothesis of a different temporal dynamics in LH and RH activation after stroke, but most importantly, they point to a specific correlation between early language training and early recruitment of the left Broca area. The frequency of left IFG involvement in the ischemic lesion was identical in the 2 groups, so the possibility that the results may be driven by a sparing of the area seems unlikely. The fall in activation of many language-related areas not involved in the lesion at T1, and their subsequent activation over time, may be otherwise ascribed to their early functional suppression because of diaschysis and the eventual reduction of the ischemic penumbra, associated with a specific exercise-induced brain plasticity. It may be speculated that the more the

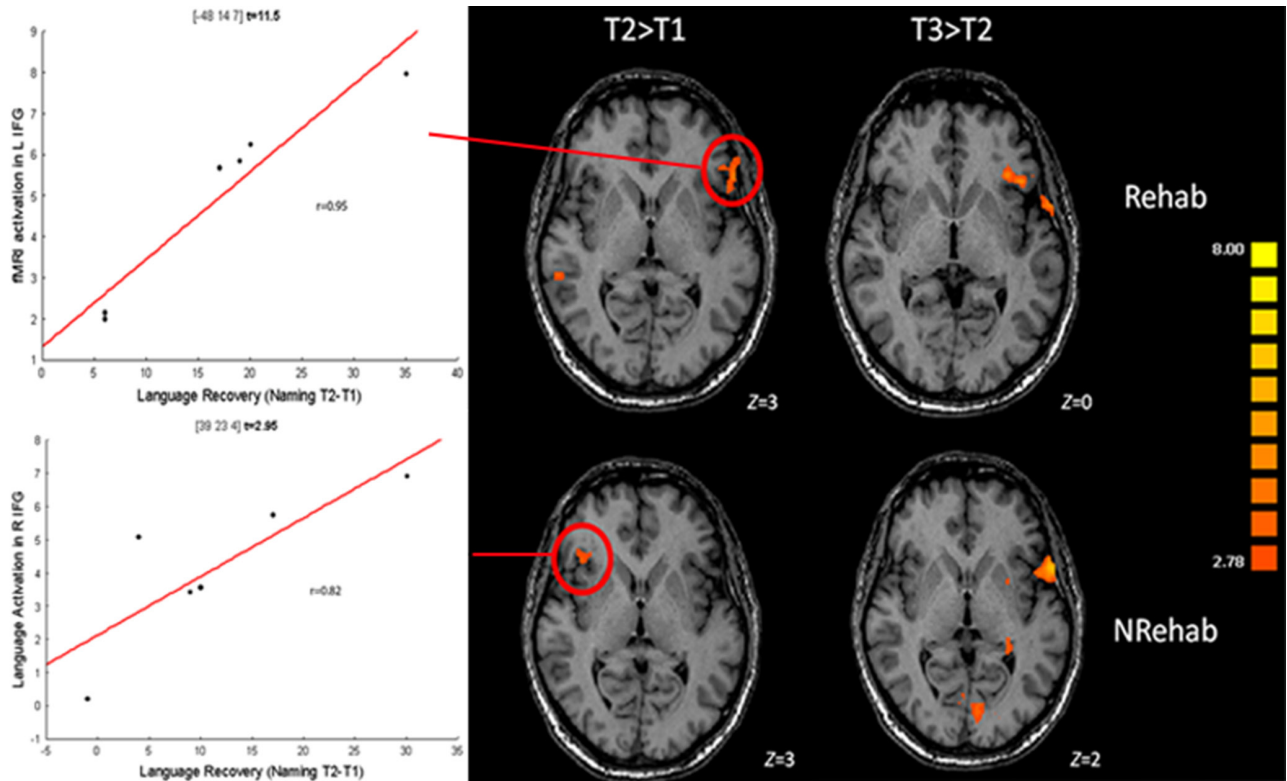


Figure 3. Brain activation changes over time and correlations with clinical data. The functional MRI contrast show changes in activation at different follow-ups in Rehab (upper line) and NRehab (lower line) patients. In the scatter plots (left column) are shown the results of correlation analysis between T2>T1 activation of the inferior frontal gyrus (IFG; left [L] IFG for Rehab and of right [R] IFG for NRehab; y axis) and naming ability improvement (T2>T1; x axis). T3>T2 activation of the L IFG and T2>T1 activation of the R and L superior temporal gyrus for both groups do not correlate with clinical performance. Statistical significance level, $P < 0.005$; uncorrected.

naming abilities after language training, the higher and earlier would be the recruitment of the left Broca area, possibly causing persistent effects after 6 months.

The hypothesis of an incomplete aphasia amelioration sustained mainly by the right-sided language-related areas, particularly by the right IFG (right Broca homologue) and, conversely, a better outcome related to activation in left perilesional areas,

has been sustained by many authors,^{7,11,30,37,38} if not all,³⁹ when examining chronic aphasics. Only in some patients, right IFG activation would be essential for residual language function; however, its compensatory potential would be less effective than in patients who recover left IFG function.

Our results support the role of left IFG activation in acute poststroke patients submitted to language rehabilitation and

Table 3. Within-Group Analysis at Baseline and Follow-Ups (Change in Activation T2>T1 and T3>T2)

	Rehab					NRehab				
	Coordinates	Side	Area	BA	t	Coordinates	Side	Area	BA	t
T2>T1	-48 14 7	L	IFG	44	4.63	-45 -49 28	L	IPL	40	3.60
	54 -34 10	R	STG	22	4.58	39 23 4	R	IFG	45	3.45
T3>T2	-37 24 3	L	IFG	45	5.02	-50 35 10	L	IFG	44	6.67
	-34 26 1			47		-44 29 0			46	
						-46 11 9			47	
	-55 14 -2	L	STG	22	5.21	-58 -53 9	L	STG	22	5.06
	-39 -31 36	L	IPL	40	5.18					
						-64 -49 -5	L	MTG	21	4.66
						-47 -72 20	L	AnG	39	5.03
						-62 -22 15	L	SmG	40	4.35
	33 29 1	R	IFG	45-47	4.65	47 17 11	R	IFG	45	4.91
					47 -55 37	R	IPL	40	3.88	

$P < 0.005$; uncorrected. AnG indicates angular gyrus; BA, broadman area; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; L, left; MTG, middle temporal gyrus; R, right; SmG, supramarginal gyrus; STG, superior temporal gyrus; and t, Student *t*.

point to the potential role of right IFG as the neural substrate for aphasia spontaneous recovery.

The activation of left IFG has also been described as a reflection of a therapy-induced improvement of naming^{8,12} in chronic aphasics, whereas right IFG has been described to be activated both by healthy subjects who were taught to name objects in a foreign language⁴⁰ and in aphasics with left IFG lesions.⁴¹ Our study suggests a possible dichotomy between LH and RH IFG activation, respectively, in early rehabilitated and spontaneously recovered aphasics. The differential activation of left IFG reported in patients who received rehabilitation seems to specifically reflect an effect of language therapy in the first 2 weeks poststroke.

Neural correlates of the training-induced neuropsychological improvement have been reported to be different in relation to the linguistic task used,^{42,43} as well as in relation to the training used both in aphasia¹² and in other nonstroke-induced neuropsychological symptoms, that is, the executive functions and information processing training in multiple sclerosis.⁴⁴

This pilot study, however, has several limitations. First, the study used a small number of patients with relatively low severity of aphasia, probably because of the small lesion size. This small sample size reflects on the difficulty in including homogeneous acute stroke aphasics in an fMRI study. Second, we did not use a control therapy, because the daily social interaction of patients in the stroke unit could, in our opinion, be considered an unstructured language treatment. Third, the inclusion of patients with moderate/mild baseline impairment may have induced a ceiling effect that prevented a higher improvement in their performance over time. Fourth, data were not corrected for multiple comparisons because of the small sample size, causing the statistical power to be low. Finally, we found improved output language tests in our patients, which we tended to associate with brain activation induced by a comprehension task. On this point, we argue that, in conjunction with several studies,³¹ the same language-related areas have been activated by different tasks (either comprehension or naming). Hence, it is not unlikely that different language tasks activate the same language-related areas. Further studies with different fMRI language tasks, larger samples including patients with more severe aphasia, and using ecological scales on communicative abilities will be useful.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL:

Early aphasia rehabilitation is associated with functional reactivation of the left inferior frontal gyrus: a pilot study

Mattioli F, Ambrosi C, Mascaro L, Scarpazza C, Pasquali P, Frugoni M, Magoni M, Biagi L, Gasparotti R.

Supplemental Methods:

Patients: Patients were recruited from the Stroke Unit of Spedali Civili of Brescia (Italy) during a 24 month period from January 2008 to December 2009. 85 patients with aphasia were screened for the study. The reasons for exclusion were the following: no native Italian speakers (n=6); age > 80 (n=19); previous diagnosis of dementia or psychiatric disorders (n=8); stroke in the territory other of the MCA (n=21); severe aphasia with severe comprehension impairment (n=7); pacemaker carriers (n=6); claustrophobia (n=2); severe obesity, i.e. impossibility to put the patient in the MRI scanner (n=1) and deafness (n=4). A total of 12 stroke patients were included.

Lesions analysis: For each patients, lesion extent and location were documented by using the T1 Diffusion Weighted (DW) scan. Lesions were manually traced by a neurologist expert in image analysis on the MRI template scan from the Montreal Neurological Institute provided with the MRICron software (Rorden and Brett, 2000; free available at <http://www.mricron.com/mricron>). This scan is normalized to Talairach space and it is a widely used template for normalization in functional brain imaging (e.g. Moretti et al. 2009). The original DW MRI of each patients was always available during the tracement, and anatomical landmarks were used to better define the boundaries of each lesions. After superimposing individual brain lesions onto the standard Ch2 brain template, MRICron automatically calculated the total brain lesion volume (in cc). The individual lesion volume are reported in table S1.

Language Rehabilitation: No ethics were violated using the treatment/no treatment randomization, since rehabilitation of aphasia in the acute post stroke phase was not widely accepted as useful at the time of this study. Language rehabilitation was conducted on an in patient basis, mainly focusing on verbal comprehension and lexical retrieval. In each session, after a short and simple dialogue with the patient, covering his mood and status, as well as any relevant episodes occurred during the day, a naming task was usually conducted, where patients had to spontaneously

name items taken from the Snodgrass and Vanderwart (1980) set. In the case of failure, all the facilitations were given. Single word as well as sentence comprehension was also treated with the help of available common objects and objects pictures. A semi structured rehabilitation setting was used, instead of a rigidly predetermined set of tasks identical for all the subjects, due to the clinical condition of the acute phase and the location (the stroke unit) where the rehabilitation was conducted. Generally, a stimulation of the impaired linguistic functions was conducted by the therapist, according to the deficits shown by the AAT.

fMRI paradigm: Patients listened to a recorded voice pronouncing semantically correct sentences, randomly intermixed with semantically violated ones and reversed ones, for the control condition and had to press a button with the right hand only if they heard a semantically correct sentence. The sentences were simple (subject-verb-object, i.e. *the boy eats the apple*, for a semantically correct phrase, or *the boy reads the apple* for a semantically violated; balanced for gender, number) and short (<2500 ms). 28 sentences were used for each run (7 semantically correct, 7 semantically violated and 14 reverse), which was repeated 4 times in each examination. The correct response number was measured for all the patients each time. Presentation was randomized across runs. fMRI examinations were performed on a 1.5 Siemens Avanto (Siemens, Erlangen Germany) equipped with an 8 channel head coil (Invivo-Gainesville), using an integrated audio-video system (eloquence Invivo-Gainesville) connected to an external computer.

An event-related paradigm was generated with EPRIME software (Psychology Software Tools Pittsburgh). Recording and reverse processing was performed with Adobe Audition software (Adobe system incorporated, San Jose', California).

fMRI acquisition and preprocessing: We used cushions to minimize patients head movement inside the scanner. The acquisition protocol consisted of the repetition of 126 BOLD volumes (SE-EPI/ TR=2500ms, TE=50ms, Matrix 64*64, FOV= 224*224 mm, 3.5mm slice thickness) with the following scheme: a volume with a 'bip' (noise) sound to alert the patient of the incoming sentence, a volume with the recorded sentence and 2 or 3 volumes of rest. fMRI acquisition time was about 21'20''. The first 2 volumes were discarded to eliminate T1 effects. After functional scanning, an anatomical image was collected using a magnetized prepared rapid acquisition gradient-echo echo planar imaging (MPRAGE) sequence, (TR/TE 2050/2.56 ms, 256 mm FOV, 256*256 matrix, 144 sagittal slices for an effective resolution of 1.0 mm.

fMRI images were processed with Brain Voyager QX (vs. 1.9- Brain Innovation – Maastricht The Nederland). A pre-processing with high pass filtering for drifts removal and slice scan time correction (cubic spline interpolation) was performed, as well as a 3D motion correction with images spatially realigned to the first volume. Functional data were co registered with the 3D anatomical images, which were normalized to the Talairach space. A mask of the lesion was created on the base of co-registered MRI in order to take into account the possible errors in normalization due to lesions. A correction for the delay of the hemodynamic response was also applied to the boxcar design matrix. A general linear model approach was used for contrast evaluations.

Supplemental Results:

Lesions analysis: Lesion volume in Rehab ($669,04 \pm 438,21 \text{ mm}^3$) and NRehab ($716,92 \pm 581,30 \text{ mm}^3$) patients was not statistically different (two independent sample t-test: $p=0.87$). We performed a correlation analysis between lesions volume and the improvement in naming and written language between T1 and T2 to investigate the possibility that bigger improvement in clinical tests were due to smaller lesion size. Both the correlations were not significant (lesions volume and written language improvement: Spearman $R = 0.23$; $p=0.46$; lesions volume and naming improvement: Spearman $R = 0.40$; $p=0.19$), supporting the assumption that improvement in clinical performance is not driven by lesion size.

fMRI Behavioral results: the percentages of correct answer were analyzed. Mean correct answers at T1 were 0.82 and 0.93 in Rehab and NRehab groups respectively, at T2 were 0.83 and 0.89 and at T3 were 0.81 and 0.83. Since the data of both groups at each time were normally distributed (T1: $W=0.9$, $p=0.19$ at Shapiro Wilk test; T2: $W=0.92$, $p=0.29$; T3: $W=0.91$, $p=0.26$), a repeated measure ANOVA was conducted on percentage of correct answer, using Group (two level) as between subjects variable, and Time (three level) as within subjects variable. The results revealed no significant results (main effect of Group: $F[1,10]=1,51$, $p=0,24$; main effect of Time: $F[2,20]=1,97$, $p=0,16$; Group x Time Interaction: $F[2,20]=1,35$, $p=0,28$).

Supplementary Table I: Clinical Characteristics of patients

Patients	Age (years)	Sex	Education (years)	Type of Aphasia	Fluency	Site of lesion (Left MCA territory)	Lesion volume (mm ³)	fMRI examinations (days post-stroke)			Initial NIHSS
								T1	T2	T3	
<i>Rehabilitated</i>											
RL	70	M	17	Anomic	Fluent	Precentral gyrus + MFG + IFG	1254,44	2	15	192	5
VA	79	M	8	Broca	NonFlu	MFG + IFG	160,96	0	15	259	4
VGL	69	M	8	Broca	NonFlu	External and internal capsulae, CR, MFG	244,92	2	18	162	5
PM	75	F	5	Broca	NonFlu	Precentral gyrus + STG	1088,53	3	17	203	4
FAR	63	F	5	Anomic	Fluent	IFG + MFG	612,30	3	16	193	3
LR	37	M	8	Anomic	Fluent	Insula + MTG + STG	653,12	3	17	183	4
MEAN	65,5		8,5				669,04	2,1	16,3	198	4,16
SD	15		4,4				438,21	1,6	1,2	32,5	0,75
<i>Non Rehabilitated</i>											
PL	72	F	3	Broca	NonFlu	Insula + External capsula	149,53	1	15	213	4
GR	59	F	5	Broca	NonFlu	IFG + Insula	44,09	2	16	181	4
RF	63	F	5	Broca	NonFlu	IFG + STG	612,30	4	14	+	6
MC	46	M	8	Broca	NonFlu	IFG + insula +	816,40	3	17	187	4
BU	76	M	10	Broca	NonFlu	insula + parietotemporal cortex	1583,13	2	18	170	4
VB	60	M	5	Mild Wernicke	Fluent	Parietotemporal cortex + insula	1096,08	2	17	163	4
MEAN	62,6		6				716,92	2,3	16,1	182	4,3
SD	11		2,5				581,30	1,0	1,4	19,2	0,81
Significance	0,48		0,69				0,87	0,93	0,92	0,42	0,94

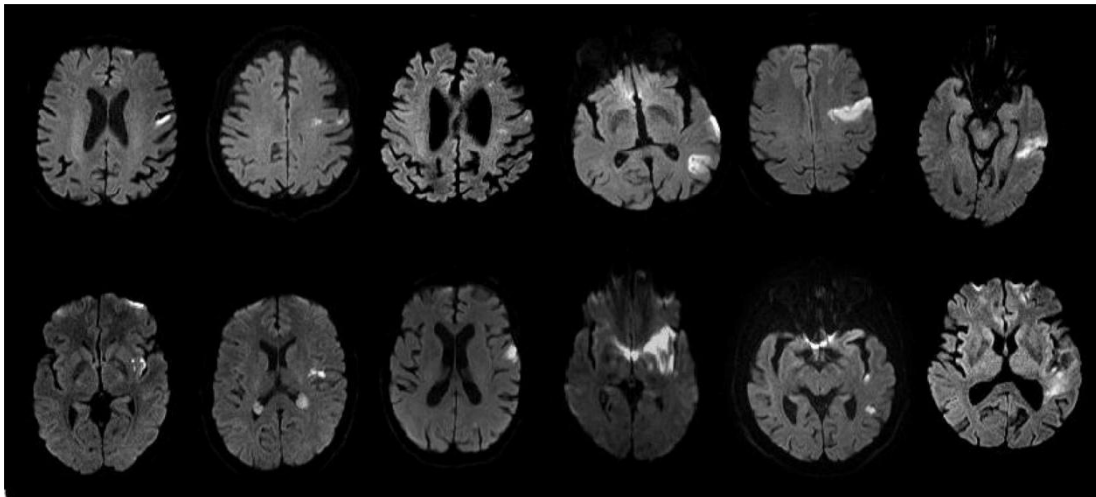
M= male, F= female; NonFlu = non fluent aphasia; MCA = middle cerebral artery , SFG = Superior frontal gyrus, MFG = middle frontal gyrus, IFG = inferior frontal gyrus, CR = corona radiate, STG: superior temporal gyrus, MTG: middle temporal gyrus; NIHSS = National Institute of Health Stroke Scale: no deficit = 0, maximal deficit = 34. Significance = p value at non parametric Mann Whitney U test.

Supplementary Table II: AAT results at the three examinations

	Spontaneous Language (0-5)			Repetition (0-150)			Written Language (0-90)			Naming (0-120)			Oral comprehension (0-60)			Written comprehension (0-60)			Token Test (0-50)		
	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3
<i>Rehabilitated</i>																					
RL	4.1	5	4.8	146	149	150	79	89	90	110	116	113	51	55	53	52	56	53	41	47	48
VA	3.8	4.8	4.1	135	146	140	79	88	89	110	116	110	50	58	56	58	56	57	41	48	46
VGL	3.5	4.3	4.6	125	143	147	74	77	82	96	115	113	48	48	53	49	49	53	45	45	38
PM	1.8	1.8	3.8	117	115	130	61	81	85	63	83	111	44	43	53	41	40	53	20	22	28
FAR	4.6	4.8	4.8	122	141	140	46	84	80	82	117	116	47	51	54	42	56	54	27	35	41
LR	4.1	4.5	4.5	122	140	142	77	88	87	99	116	118	52	53	55	51	58	55	42	48	48
MEAN	3.7	4.2	4.4	128	138	142	69.3	84.5	85.5	93.3	110	113	48.8	51	54	48.8	52.5	54.2	36	40.8	41.5
SD	1.0	1.2	0.4	10.6	12.1	6.9	13.3	4.8	3.9	18.5	13.5	3	2.9	5.3	1.3	6.4	6.9	1.6	10	10.5	7.7
<i>NotRehabilitated</i>																					
PL	3.6	3.8	3.8	133	141	143	36	64	58	94	104	110	52	55	53	47	56	53	24	38	35
GR	4.3	4.3	5	142	140	142	87	86	87	116	115	109	58	56	57	51	58	58	42	42	38
RF	0.5	3.3	+	31	35	+	10	10	+	50	54	+	51	45	+	52	46	+	16	18	+
MC	3.3	4	3.6	128	135	144	21	25	69	57	66	99	33	47	51	35	38	51	10	17	39
BU	3.3	3.8	4.3	111	136	141	73	80	78	77	107	106	45	46	44	43	45	44	35	40	36
VB	2.7	3.3	3.6	22	50	88	0	25	68	14	31	75	36	47	46	24	23	46	2	6	21
MEAN	3.0	3.8	3.8	94.5	106	131	37.8	48.7	71	68	79.5	98	45.7	49.3	50.2	42	45.7	50.4	21.5	26.8	33.8
SD	1.3	0.4	0.6	53.7	49.6	24.4	35.1	32.7	11	35.8	34.1	14.5	10	4.8	5.3	10.8	12.5	5.6	15.2	15.1	7.3
p*	0.2	0.0	0.2	0.48	0.06	0.93	0.13	0.02	0.03	0.17	0.01	0.004	0.93	0.48	0.17	0.39	0.39	0.17	0.09	0.06	0.08
	4	6	4																		

Values denotes row scores obtained from patients. **p* denotes significance at Mann-Whitney U test.

Supplementary Figure I: Patient's MRI lesions.



In the upper line Non Rehabilitated patients' lesions are shown; in the lower line Rehabilitated patients' lesions are shown.

Supplementary References:

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Early Aphasia Rehabilitation Is Associated With Functional Reactivation of the Left Inferior Frontal Gyrus: A Pilot Study

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