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Brain and Language 85 (2003) 357–368
Brain and Language
www.elsevier.com/locate/b&l

A fMRI study of word retrieval in aphasia

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Accepted 10 September 2002

Abstract

The neural mechanisms underlying recovery of cognitive functions are incompletely understood. Aim of this study was to assess, using functional magnetic resonance (fMRI), the pattern of brain activity during covert word retrieval to letter and semantic cues in five aphasic patients after stroke, in order to assess the modifications of brain function which may be related to recovery. Four out of five patients had undergone language recovery, according to standard testing, after at least 6 months of rehabilitation. The cerebral activation of each patient was evaluated and compared with the activation pattern of normal controls studied with the same fMRI paradigm. In the patients, the pattern of brain activation was influenced by the site and extent of the lesion, by the degree of recovery of language, as reflected by task performance outside the scanner, and by task requirements. In the case of word retrieval to letter cues, a good performance was directly related to the activation in Broca's area, or in the right-sided homologue. On the other hand, in the case of semantic fluency, the relationship between performance level and activation was less clear-cut, because of extensive recruitment of frontal areas in patients with defective performance. These findings suggest that the performance in letter fluency is dependent on the integrity of the left inferior frontal cortex, with the participation of the homologous right hemispheric region when the left inferior frontal cortex is entirely of partially damaged. Semantic fluency, which engages the distributed network of semantic memory, is also associated with more extensive patterns of cerebral activation, which however appear to reflect retrieval effort rather than retrieval success.

Keywords: Recovery; Aphasia; fMRI; Verbal fluency

1. Introduction

The neurological mechanisms responsible for the recovery of aphasia due to acute vascular damage of the language-dominant hemisphere are largely unknown. In the early phase after a stroke, the functional impairment of brain networks not directly affected by the lesion (diaschisis), both in perilesional and contralateral brain areas, might contribute to the global severity of language impairment (Perani, Vallar, Cappa, Messa, & Fazio, 1987; Vallar et al., 1988). The recovery of these "distant effects" has been suggested to play a role in the "early," partial recuperation stage, which takes place in many aphasic patients, in the weeks and months immediately following the stroke (Cappa et al., 1997).

Although recovery may be observed also many years after a stroke, the following stages of aphasia are usually characterised by a slower recovery rate, which has been suggested to be related to functional re-organisation. The hypothesis of a "take-over" of function by homotopic areas in the right hemisphere as the mechanism underlying aphasia recovery goes back to the last century (Gowers, 1895). On the basis of the results of positron emission tomography activation studies (Weiller et al., 1995), a functional re-organisation, involving

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0093-934X/03/$ - see front matter © 2003 Elsevier Science (USA). All rights reserved.
doi:10.1016/S0093-934X(02)00561-8

in particular the regions homotopic to the language areas in the contralateral hemisphere, has been suggested to be responsible for long-term recovery. However, other recent neuroimaging investigations have reported more complex patterns of activation in recovered patients. In particular, several studies have indicated that the reactivation of ipsilateral, perilesional areas is often associated with good recovery (Belin et al., 1996; Cao, Vikingstad, George, Johnson, & Welch, 1999; Heiss, Kessler, Thiel, Ghaemi, & Karbe, 1999; Hund-Georgiadis, Lex, Morris, & von Cramon, 2000; Rosen et al., 2000; Warburton, Price, Swinburn, & Wise, 1999). Besides performance level, another crucial determinant to be considered to interpret the pattern of activation in aphasia is the type of task. As suggested by Gold and Kertesz (2000), it is plausible that tasks, which are known to involve the right hemisphere in normal controls, may be associated with more extensive right-sided activation in aphasics. These typically include semantic comprehension tasks, rather than speech production and word generation. Even within relatively simple tasks, modifications of the linguistic requirements may change the cognitive strategy and result in different pattern of cerebral reorganisation.

In the present study, we took advantage of the well-known difference in word retrieval to letter and to semantic cues. Different component processes are involved in the two tasks. In particular, letter fluency has been suggested to place greater demand on "frontal" strategic processes, while semantic fluency is more dependent from semantic memory, in which the temporal lobe plays a crucial role. There is both behavioral (Martin, Wiggs, Lalonde, & Mack, 1994) and imaging (Mummery, Patterson, Hodges, & Wise, 1996; Paulesu et al., 1997) evidence to support this claim. The two tasks can thus be considered as "probes" for two partially independent networks, involving different brain regions, which may have different potential for reorganisation. Here, we report the anatomo-functional correlates of cued lexical retrieval in five aphasic patients, who showed different degrees of recovery in the late stage of stroke after rehabilitation therapy. The patterns of brain activation were assessed with functional Magnetic Resonance (fMRI) during verbal fluency tasks.

2. Methods

The experimental protocol was approved by the local hospital Ethics Committee, and all the subjects signed the informed consent.

2.1. Normal controls

The pattern of brain activation observed in six normal volunteers during the same tasks has been reported in another paper (Paulesu et al., 1997). For the present study, we studied four additional right-handed male volunteers. All subjects had no history of neurological or psychiatric disorders. Right-handedness was verified using the Edinburgh Inventory (Oldfield, 1971).

2.2. Aphasic patients

Subjects were selected from a large pool of outpatients attending the Language Rehabilitation clinics of Brescia and Milano. They all read and signed an informed consent to the study protocol, which was approved by the local ethical committee. We considered patients in the chronic phase after stroke (time interval range: 10 months–6 years), who had been submitted to an intensive language rehabilitation program for a minimum of six months. In order to be included, the patients had to provide evidence of being able to perform the fluency tests by producing a minimum of four correct responses in at least one of the tests. Patient (4) who was severely aphasic and not able to perform the fluency tasks, was included in the protocol for comparison with the recovered patients. No attempt was made to standardise the therapeutic protocol followed by the patients, which consisted in general of a language stimulation program supplemented, when appropriate, by a cognitive (model-driven) approach: however, they all had attended regularly therapy for a minimum of three weekly sessions.

These criteria resulted in the inclusion of five patients: four were right-handed male subjects (age range 45–69), with left hemispheric ischemic lesions, while one was a right-handed male with no history of familial sinistrality who had become aphasic after a right hemispheric lesion (crossed aphasia).

The clinical features, lesion sites, time of fMRI examination and neurolinguistic data are summarised in Tables 1 and 2.

Brief clinical summaries follow:

Case 1 (full recovery): Forty-six year-old, right handed male, medical doctor (general practitioner) with unremarkable medical history was admitted to the hospital with a sudden onset of mild right-sided weakness and language disturbances. The CT scan showed an infarction in the left temporoparietal cortex. Immediately referred for neuropsychological evaluation, he showed a normal performance on Raven's Coloured Progressive Matrices (RCPM); no evidence of apraxia, and a fluent aphasia with impaired auditory comprehension. An intensive rehabilitation program was started. The patient recovered very quickly, and after one month was not aphasic on standard testing (see Table 1). He decided to quit the rehabilitation program, and to go back to work. At reassessment after 1 year he complained of mild residual difficulties with written language, but was working full time on a very busy schedule.

Table 1
Clinical data

	Age	Years of school	Aphasia at onset (after stroke)	Study time	Follow up	MRI examination
Case 1	46	23	Fluent aphasia	1 year	Complete recovery	LH ischemia: STG, IPL
Case 2	69	5	Anomic aphasia	1 year	Anomic aphasia	LH ischemia: IFG, F/P wm
Case 3	65	8	Wernicke aphasia	10 months	Anomic aphasia	LH ischemia: Tpole,STG,MTG
Case 4	56	23	Global aphasia	2 years	Non-fluent aphasia	LH ischemia: P/O junction (extensive lesion)
Case 5[a]	45	5	Wernicke aphasia	9 months	Anomic aphasia	RH ischemia: IFG, F/Pwm

LH, Left hemisphere; RH, right hemisphere; IFG, inferior frontal gyrus; STG, superior temporal gyrus; MTG, middle temporal gyrus; IPL, inferior parietal lobule; F/P wm: fronto/parietal white matter; Tpole, temporal pole; P/O, parieto/occipital.

[a] Crossed aphasia.

Table 2
Neurolinguistic data

	Token test			Repetition			Written language			Naming			Comprehension		
	I	II	s	I	II	s	I	II	s	I	II	s	I	II	s
Case 1	55	63	+	44	56	+	42	68	+	44	74	+	63	77	–
Case 2	58	63	+	56	61	–	50	59	+	53	59	+	52	56	–
Case 3	43	62	+	51	61	+	59	65	+	48	71	+	47	70	+

A repeated evaluation with the same task (Aachener Aphasie Test) is available only for three patients. Patients FM (II exam) and GB (I and II exam) were evaluated with a different test (Milan Standard Language Examination), thus preventing a quantitative comparison according to the method of Huber, 1983. The scores are standardised (T units) and compared with the Tau statistic. The overall profiles were significantly different in all three cases.

Case 2 (full recovery): Sixty-nine year-old right-handed male, with 5 years of education. He suffered of a sudden onset of right-sided weakness and language disturbances (fluent aphasia). The CT showed a left frontoparietal ischemia. Evaluated in the same month, he had normal performances on RCPM and apraxia tests; the clinical picture was typical of Wernicke's aphasia. He was submitted to language rehabilitation for 8 months; at re-evaluation he was considered to be fully recovered.

Case 3 (good recovery in mild anomic aphasia): Sixty-five year-old right-handed male with 8 years of education, with a history of treated hypertension and chronic ischemic heart disease. He was admitted to the hospital for a sudden onset of weakness of the right arm and language disturbances. The CT showed a left temporal ischemia. The evaluation in the same month showed normal performance on RCPM, Weigl's test and apraxia tests; the aphasic picture was diagnosed as Wernicke's aphasia. He was submitted to rehabilitation for 10 months; a re-evaluation showed a picture of mild anomic aphasia.

Case 4 (severe Wernicke's aphasia, poor recovery): Sixty-one year-old right-handed male, medical doctor, academic, with a history of treated hypertension and one episode of transient ischemic attack (in treatment with ASA). He had sudden loss of consciousness; admitted to the hospital in coma, the CT showed a large parieto-occipital haematoma, which was surgically evacuated. The patient showed a gradual recovery in Intensive Care: after one month, he could produce short sentences, often in English rather than in Italian. There was a severe right hemiparesis. Language rehabilitation was started when the patient was discharged to a Rehabilitation facility. A language examination showed a clinical picture of severe Wernicke's aphasia and severe ideomotor apraxia. The patient has been intensively rehabilitated with limited success; a follow-up re-evaluation showed an improvement in naming and comprehension. Further testing has indicated a relatively stable aphasic picture.

Case 5 (full recovery, crossed aphasia): Forty-five year-old right-handed male with 5 years of education and a medical history of treated hypertension. He had sudden onset of mild left-sided weakness and language disturbances. The CT scan showed a small ischemic area in the right frontoparietal region. He was evaluated after one month: the performance on RCPM and apraxia tests was normal. The diagnosis was of mild Wernicke's aphasia. The patient was submitted to language rehabilitation for two months: in a follow up evaluation, he was considered non-aphasic on standard testing.

2.3. Experimental design

Blood oxygenation level measurements were collected in frames of consecutive T2* weighted fMRI multislice scans. Three complete frames (A,B,C) were acquired for each patient/normal control. In each frame, a total of 6 task epochs were acquired, each lasting 30 s (corresponding to 10 T2* scans), according to the following task design:

(A) Rest–VF-Ph1–Rest–VF-Ph2–Rest–VF-Ph3;

(B) Rest–VF-Animals1–Rest–VF-Animals2–Rest–VF-Animals3;

(C) Rest–VF-Tools1–Rest–VF-Tools2–Rest–VF-Tools3;

where:

- Rest: Subjects were instructed to empty their mind and to avoid inner speech.
- VF-Ph (phonemic verbal fluency): Subjects were given a letter of the alphabet (either 'c' or 'f' or 'p') immediately before the onset of each task session, and were instructed to list covertly (without articulation) as many common nouns that begin with that letter as possible.
- Animals/Tools (semantic verbal fluency): Subjects were instructed to generate covertly as many common nouns as possible belonging to the 'animal' or to the 'tool' category.

Instructions were recalled by the examiner at the beginning of each task epoch, by saying aloud a fixed cue (i.e., letters 'c,' 'f,' 'p' for task VF-Ph; 'animals' and 'tools' for task Animals/Tools).

Subjects were trained in the different tasks before positioning on the magnet cradle. After total scan acquisition, subjects were asked to perform again the fluency task for the three letters and the two categories (30 s for each condition). The mean number of words produced for, respectively, the phonemic and semantic fluency, as well as category consistency, were thus monitored immediately after scanning. These were: in case 1, 9 for phonemic fluency and 10 for semantic fluency; in case 2, 9 and 12; in case 3, 3 and 6; in case 4, 1 and 0; in case 5, 10 and 12.

2.4. Scanning procedures

MRI scans were performed on a 1.5 T General Electric Signa Horizon System (GE, Milwaukee, WI, USA), equipped with Echo-speed gradient coils and amplifier hardware, using standard quadrature head-coil. Scout spin-echo sagittal scans (TE = 20 ms, TR = 500 ms, FOV = 240×240 mm, matrix 256×192) were acquired to visualise the anterior and posterior commissures on a midline sagittal section and to facilitate data acquisition roughly along the bicommissural plane. Prior to fMRI data collection, a structural spin-echo data set matched to the fMRI images (TE = 20 ms, TR = 600 ms) was acquired in order to facilitate subsequent stereotactic normalisation with SPM software of the MRI images. Field homogeneity was adjusted by means of "global shimming" for each subject.

The acquisition of the functional images with gradient-echo echo planar sequence (TE = 60 ms, TR = 3000 ms) occurred by using 8 slices volumes (FOV 280×210 mm, matrix 96×64); the volume matrix was then resample to $128 \times 128 \times 8$ resulting in a final voxel size of $2.19 \times 2.19 \times 6$ mm. The acquisition of three separate scan sessions allowed some rest between tasks, control of head position plus reinforcement and re-instruction for the task.

2.5. Data analysis

After image reconstruction, raw-data visualisation and pre-processing was performed with ANALYZE-5 (BRU, Mayo Foundation, Rochester, MN, USA). All subsequent data analysis was performed in MATLAB 4.2 (Math Works, Natick, MA, USA) using Statistical Parametric Mapping software (SPM-96, Wellcome Department of Cognitive Neurology, London, UK).

The data from normal subjects were analysed as a group, using the simple main effects analysis reported in a previous paper (Paulesu et al., 1997). For the patient data, we performed data analysis on a single subject basis, because of the different anatomical locations of brain lesions.

fMRI scans were subdivided into three groups according to the three experimental conditions (phonemic fluency, semantic fluency for animals and for tools), and their corresponding rests and then each group was realigned separately; all scans were then normalised into the standard stereotactic space implemented in the SPM-96 software, to allow inter-subject data averaging and comparison across tasks. Stereotactic normalisation was first performed for the spin-echo high-resolution structural MRI volume, which was in the same space as the fMRI. The normalisation parameters identified for this structural volume were then applied to the fMRI data by SPM-96. At this stage the data matrix was interpolated to produce voxel dimensions of $2 \times 2 \times 4$ mm. After stereotactic normalisation, the common stereotactic space for patients covered planes from −12 to +36 mm, according to the bicommisural plane (see Paulesu et al., 1997 for details on data of normal controls). All the stereotactically normalised scans were smoothed through a Gaussian filter of $10 \times 10 \times 10$ mm to reduce anatomical differences among subjects and to improve signal to noise ratio. High-pass filtering was used to remove artefactual contribution to fMRI signal such as physiological noise from cardiac and respiratory cycles. Global differences in fMRI signal were co-varied out for all voxels.

For statistical comparison, we used the implementation of the general linear model for fMRI data (Friston et al., 1995) for SPM-96. The experiment was treated as a 3×2 factorial design (factors: types of fluency; task: fluency or rest). Simple main effects of the phonemic and semantic fluency in comparison with their time-matched resting scans were calculated. These comparisons produced images of those brain areas significantly more active in one task with respect to the other one. Comparisons of means were made for all voxels by using the t statistic, thus generating statistical parametric maps of the t values SPM $\{t\}$, which were, transformed to Z distribution maps. A Bonferroni corrected threshold at $p < .001$ was applied to the statistical maps.

The SPM results for each patient were descriptively compared to the results of the group study in normals engaged in the same paradigm.

3. Results

3.1. Normal subjects

Tables 3 and 4 report the results of the simple main effects of the phonemic and semantic verbal fluency tasks compared to the time-matched rest condition. For normal controls the pattern of activation was comparable to the one reported in the previous paper (see

Table 3
Phonemic fluency vs rest: activation foci

Area	Normals	Case 1	Case 2	Case 3	Case 4	Case 5[a]
L IFG (44–45)	−56,22,16/8.0 −44,26,20/7.1	−52,14,16/7.9 −38,18,8/4.3 −32,20,16/4.1	−58,10,8/6.1	—	—	—
L IFG (47)	−46,24,0/7.6	−42.38.−4/5.0				
L DLPF cortex (6,9,10)	−34,10,40/7.7 −50,16,44/7.4 −32,38,32/5.3 −52,38,8/5.7	—	—	—	—	—
L basal ganglia	−20,8,0/6.4 −20,14,12/6.4 −10,2,12/5.6	—	—	—	—	—
L thalamus	−6.−10,4/6.0 −16,6,16/5.9	—	—	—	—	—
L IPL (40)	−42,−28,52/6.4 −44,−30,40/4.6	—	—	—	—	—
L STG (22)	—	—	−58,−8.8/4.1	—	—	—
L MTG (21)	—	—	−38,−60,−4/4.8	—	—	—
L cuneus (18)	—	—	−4,−84,12/4.9	—	—	—
L ligual (18)	—	—	−14,−70,−0/4.4	—	—	—
R IFG (44–6)	—	—	—	—	—	54,10,16/4.3
R IFG (45—46)	40,30,8/5.9	—	40,32,12/4.4 46,38,16/4.1	—	—	—
R IFG (47)	58,22,0/5.0	—	40,36,−4/5.4	—	—	—
R DLF (46–9)	—	—	—	—	—	54,16,32/4.1 56,30,36/3.9
R DLF(9–10)	—	—	50,51,12/4.4	—	—	—
R thalamus	20,−6,12/7.1	—	—	—	—	—
R STG (22)	—	—	64,−30,12/4.2	—	—	—
R MTG (21)	—	—	38,−56,0/4.9	—	—	—
R Tpole (22–38)	—	—	66,8,4/4.9	—	—	—
R cuneus (18)	—	—	14,−82,12/5.8 30,−72,8/6.1	—	—	6,−86,0/4.4
L/R retrosplenial cortex	−8,−76,8/4.6 2,−66,4/4.0	—	−4,−48,12/4.1	—	—	—
L/R pre-SMA (6)	0,14,56/6.8 2,24,44/6.6	—	—	—	—	—

Numbers refer to stereotactic coordinates x, y, z and Z scores; numbers in parentheses refer to Brodmann areas.
[a] Crossed aphasia.

Table 4
Semantic fluency vs rest: activation foci

Area	Normals	Case 1	Case 2	Case 3	Case 4	Case 5[a]
L DLF cortex (46,9)	−34,26,32/8.4 −46,32,28/7.0 −44,36,16/6.4 −40,50,16/7.4	−34,46,20/5.8	—	—	—	—
L IFG (45,46)	−26,38,4/7.2 −40,26,4/5.5	−38,24,4/3.8	−34,38,8/4.9 −34,42,0/5.6	—	—	—
L IFG (44–45)	—	−52,14,16/6.6	—	—	−48,12,12/5.0	—
L IFG (47)	—	−44,40,0/4.3	−58,12,4/5.2	—	—	—
L SFG (10)	—	—	−32.60.−4/5.7 −36.52.−1 2/5.1	—	—	—
L DLF (10)	—	—	–	−20,62,16/4.5 −24,60,8/3.8	—	—
L MTG (21)	−44,−48,0/6.5 −50,−44,0/7.4	—	—	—	—	—
L IPL (40/19)	−26,−52,44/6.6 −30,−44,48/7.4	—	—	—	—	—
L cuneus (18)	—	—	−30,−78,8,5.3 −20,−80,4/6.6	—	—	—
L lingual(18)	—	—	−18,58,0/5.5	—	—	—
L thalamus	—	—	—	—	−14,−18,12/5.0 −6,−16,8/5.1	—
R IFG (45,46)	46,36,8/5.1 38,32,4/4.3	—	—	—	—	—
R IFG (44–45)	—	54,14,12/5.6	—	—	44,24,12/6.2 48,28,4/6.2 42,20,20/6.0 60,18,12/4.3	54,10,16/6.4
R IFG (47–45)	—	—	42,36,−4/6.6 50,48,0/6.6	—	—	40,22,0/5.7 58.16.−4/4.1
R DLF (46–9)	—	—	—	—	44,40,24/3.5	54,18,36/5.4 56,26,36/4.7
R SFG(10)	—	—	32,58,−4/6.5	12,64,20/4.5 14,58,4/5.6	—	—
R thalamus	—	—	—	—	12,−20,8/4.6	—
L/R Medial FG (10)	—	—	—	−8,54,−8/5.4 0,62,0/5.2 6,66,4/5.1	—	—
L/R retrosplenial cortex	−20,−66,8/6.0 −4.−68.20/5.3	−2,−54,8/4.2	—	—	—	—
L/R cuneus (18)	−2,−86,8/7.7 16,−78,8/7.6 −10.−90,12/6.5	—	—	—	—	6.−86.0/5.7
L/R thalamus	−4,−8,12/7.3	—	—	—	—	—

Numbers refer to stereotactic coordinates *x*, *y*, *z* and *Z* scores; numbers in parenthesis refer to Brodmann areas.
[a] Crossed aphasia.

Paulesu et al., 1997). In particular, we found a selective activation of the left frontal operculum (Ba 44) during phonemic fluency and a larger activation of the retrosplenial cortex in the semantic fluency.

More in detail, during *phonemic fluency* compared to the rest condition, in the left hemisphere there were activation foci in the inferior frontal gyrus (Ba 44,45,47), and dorsolateral frontal (Ba 9,6) cortex, the inferior parietal lobule (Ba 40), the basal ganglia and thalamus; in the right hemisphere, only the inferior frontal cortex (Ba 45,46) and the thalamus were activated; the retrosplenial cortex was activated bilaterally as well as the pre-SMA (Ba 6). During *semantic fluency* compared to the rest condition, in the left hemisphere there were activations in the triangular division of the Broca's area (Ba 45), but not in the opercular (Ba 44), in the dorsolateral frontal cortex (Ba 46,9), the middle temporal gyrus (Ba 21) and the occipito-parietal junction (Ba 40/19). A large area of activation was found in the retrosplenial cortex and cuneus (Ba 18) (see Tables 3 and 4, Fig. 1a).

3.2. Patients

As for normal controls, we consider only the activated foci at a high statistical threshold ($p < .001$, Bonferroni corrected). This makes a descriptive com-

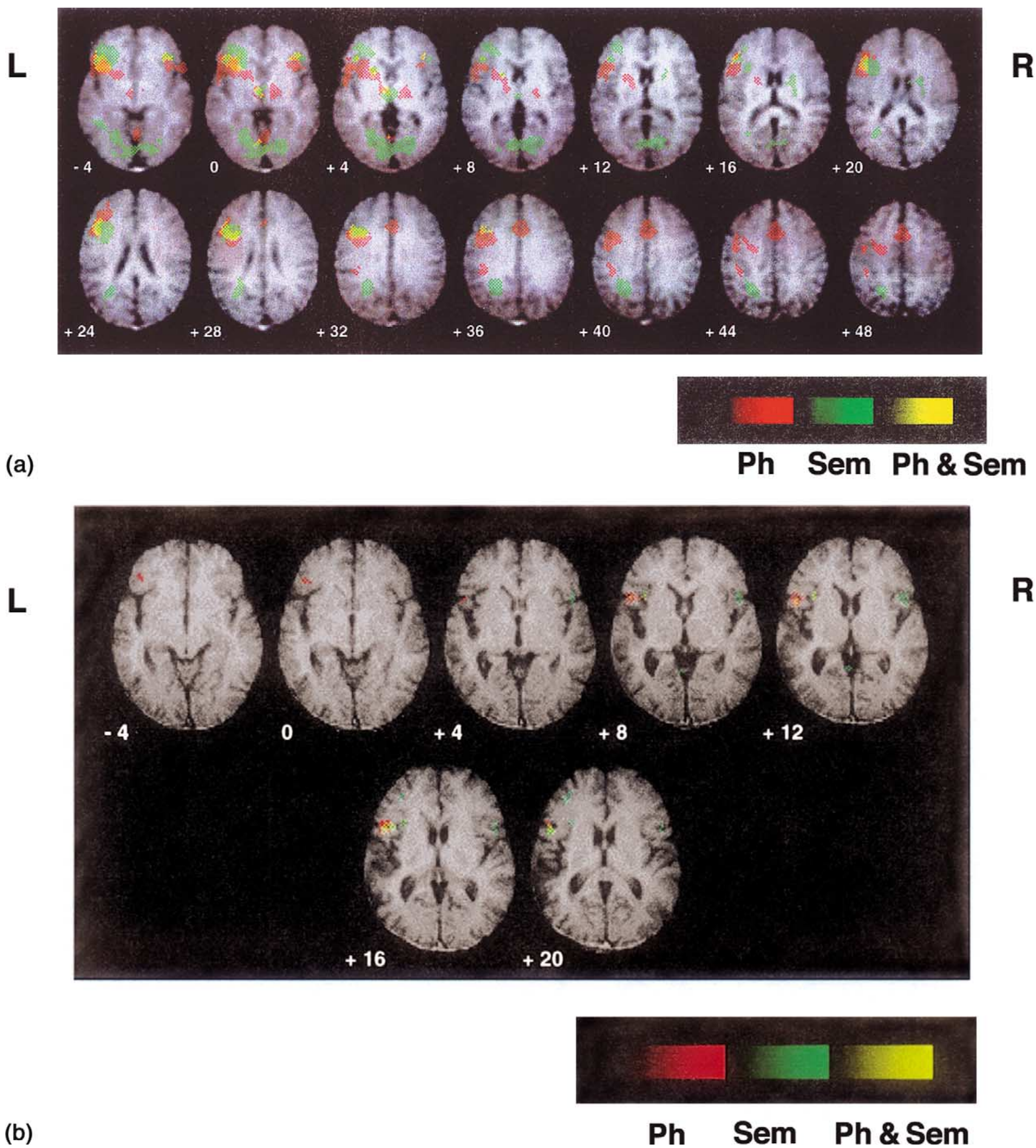
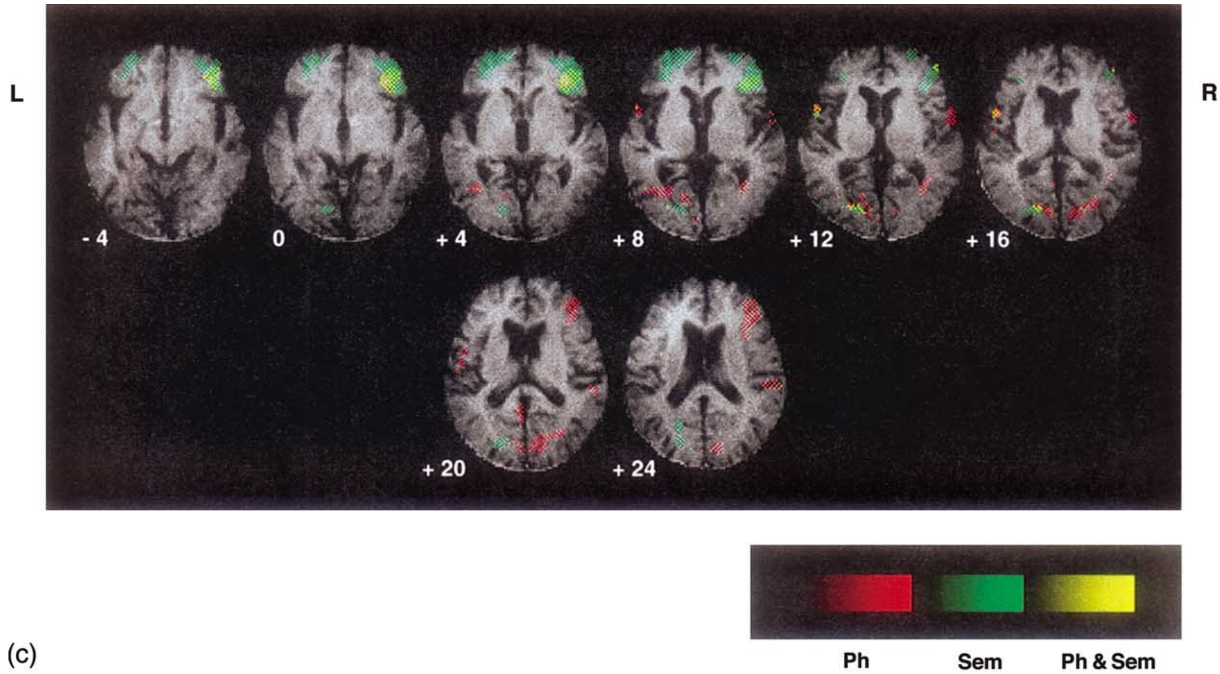
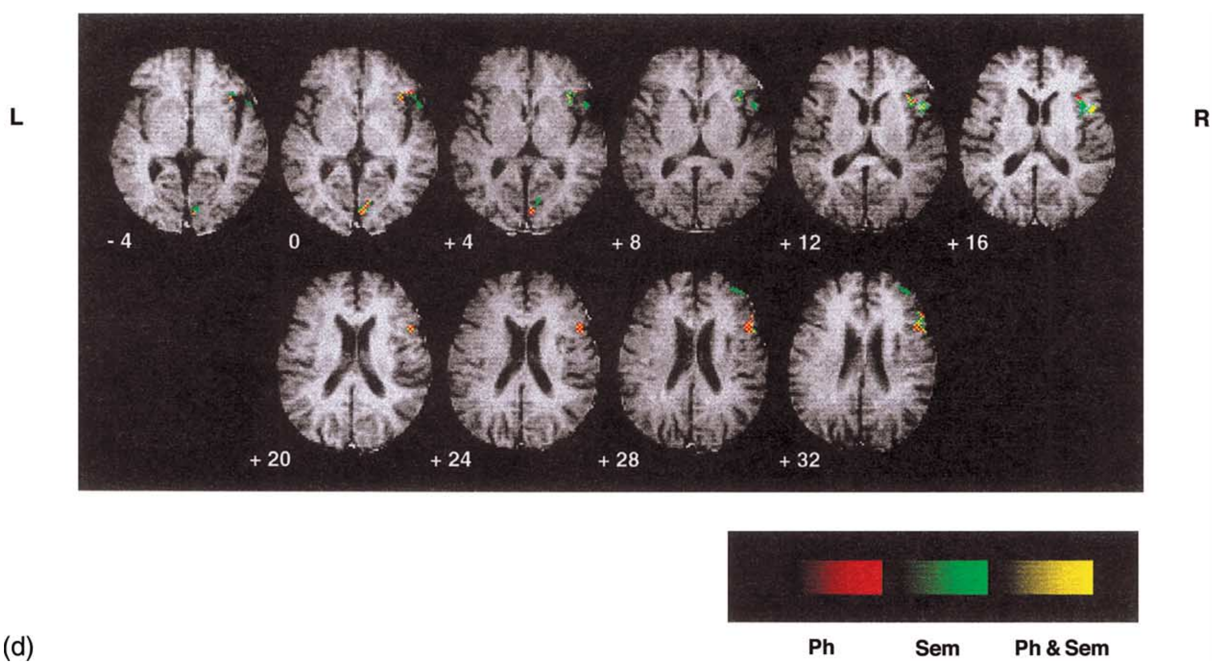


Fig. 1. Axial MRI slices with superimposed foci of activation for phonemic (red), semantic (green) verbal fluency and areas of common activations for both tasks (yellow), (a) normal control group; (b) case 1; (c) case 2; (d) case 5 (patients with good recovery). See Tables 3 and 4 for stereotactic coordinates of activation foci.



(c)



(d)

Fig. 1. (*continued*)

parison between patients' activations and activations in the normal controls possible.

Case 1: In this patient, who had enjoyed a fast and complete recovery of language abilities, and whose left frontal cortex was spared by the lesion, the activations associated with both fluency tasks were mostly left hemispheric and comparable to those observed in normal controls.

Case 2: Had also a good recovery. However, his left inferior frontal gyrus was partially involved by the lesion. The spared components of the inferior frontal gyrus were activated during phonemic task. In this case, there was a larger degree of right hemispheric activation, in particular for phonemic fluency, in the frontal and temporal cortex.

Case 3: Had only an incomplete recovery, associated with a relatively large temporal lesion. The lack of significant activations for phonemic fluency appears to be in agreement with his poor performance, while bilateral frontal activation in the case of semantic fluency was associated with an intermediate level of performance.

Case 4: Had the most severe aphasia, and the least satisfactory recovery, notwithstanding prolonged language rehabilitation. He had a severely impaired performance in the fluency tasks and no significant activations were found for the phonemic fluency task. Nevertheless, activations were observed bilaterally in the thalamus and in the frontal regions (very extensive on the right) during semantic fluency. It is noteworthy that the patient made great effort and reported "to see vivid images of animals and tools" during the latter task.

The crossed aphasic (*case 5*). who had an almost complete language recovery, showed activation foci comparable to the normal subjects, but only in the right hemisphere. This is the first in vivo evidence of selective activation of the right hemisphere during language-related tasks in a patient who recovered from crossed aphasia.

In conclusion, in the patients with good recovery (1, 2, and 5) the activation foci involved prevalently the perilesional or undamaged regions in the language dominant hemisphere. However, activations of the right homologue hemispheric structures were also found: this was particularly evident in the patient with a lesion involving the inferior frontal gyrus (Case 2). In the two patients with, respectively, incomplete (Case 3) or poor (Case 4) recovery, an impaired performance in the phonemic fluency task was associated with the lack of significant activations; on the other hand, there was an extensive activation during semantic fluency, which extended beyond Broca's area in the dorsolateral prefrontal cortex, in particular on the right side.

4. Discussion

In agreement with previous findings (Poline, Vandenberghe, Holmes, Friston, & Frackowiak, 1996), in normal subjects phonemic and semantic fluency were associated with prevalent left prefrontal cortex activation. Some areas of task-specific activation were also present. In particular, the opercular portion of Broca's area (Ba 44) and the basal ganglia and thalamus were engaged by phonemic fluency, whereas the left middle temporal gyrus (Ba 21) and the retrosplenial cortex/cuneus were activated by semantic fluency. These data confirm our previous fMRI finding of an anatomo-functional dissociation in the systems for word retrieval by phonemic and semantic cues in normal subjects (Paulesu et al., 1997). The opercular division of Broca's area corresponds to the region previously indicated as the main anatomical counterpart of the rehearsal system of verbal working memory (Paulesu, Frith, & Frackowiak, 1993), and may be committed to lexical retrieval through a phonemic/articulatory route. This hypothesis about the opercular portion of the IFG is confirmed by several other PET activation studies in normals (Fiez, 1997).

On the other hand, during semantic fluency there was a discrete activation of Ba 46, which suggests that this area subserves a different linguistic function. Selective activations of the more anterior portion of IFG (Ba 45,46) have been associated with semantic encoding (Demb et al., 1995); the same areas are activated by tasks which are not explicitly verbal, such as object identification (Perani et al., 1995), or the observation of meaningful actions and grasping of real objects (Decety et al., 1997; Rizzolatti, Fadiga, Gallese, & Fogassi, 1996), suggesting a central role in semantic processing. A large number of neuroimaging studies, using a range of different tasks, have implicated the left inferior frontal gyrus (IFG) in the retrieval of semantic knowledge (Martin, Haxby, Lalonde, Wiggs, & Ungerleider, 1995; Perani et al., 1995; Petersen, Fox, Posner, Mintun, & Raichle, 1988; Vandenberghe, Price, Wise, Josephs, & Frackowiak, 1996). Activation in similar locations, including Ba 9 and 10, have been observed in association with working memory tasks (Owen, 1997; Petrides, Alivisatos, Meyer, & Evans, 1993), in particular with verbal working memory (Smith, Jonides, Marshuetz, & Koeppe, 1998). This may suggest an association with some aspects of working memory, specific to both the fluency task. One of these aspects may be the fact that during a fluency task, words generated one-by-one must be held "in mind," in order to avoid their repetition (since the subjects of fluency studies are usually invited not to repeat the words generated). An alternative interpretation is supported by a recent investigation (Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997), which argued that it is not the retrieval of semantic knowledge per se that is associated with left IFG activation, but rather the need to select some relevant feature of semantic knowledge from a set of competing alternatives.

A left middle temporal region was also activated in the semantic fluency task: a similar focus of activation has been reported by others (Mummery et al., 1996). The retrosplenial cortex/cuneus regions were also found to be engaged both in phonemic and semantic fluencies. These regions are involved in tasks requiring mental imagery (Kosslyn, Thompson, & Alpert, 1997), and it may be suggested that a "visualisation" strategy can be also engaged while retrieving words for fluency tasks.

It is noteworthy that an involvement of homotopic right frontal areas was present also in normal subjects. This finding is compatible with other studies of word generation (Poline et al., 1996), as well as with the results of language activation studies in general (Frackowiak & Friston, 1994), and indicates that the right hemisphere of the intact brain is involved in normal language function. This idea is of course not new in neuropsychology, and is supported by a large body of evidence coming from different fields of investigation (see, for example, Bogen, 1997, and other papers in the same issue).

These results provide the baseline for the evaluation of the patterns of brain activation in aphasic patients and underline the crucial role of task requirements.

In the case of letter fluency, there was a clear-cut relationship between the presence of activation in the left inferior prefrontal cortex and the level of performance outside the scanner; the latter, not surprisingly, was dependent from the degree of recovery. Indeed, the three patients with good recovery, and a high level of performance in the fluency task (Cases 1, 2, and 5), showed an activation in the inferior frontal gyrus of the language-dominant hemisphere, with an increased contralateral participation in case 2. In patients with subnormal performance (Cases 3 and 4), we did not find significant activations during letter fluency tasks in comparison with rest. It is noteworthy that in both cases the lesion apparently spared the IFG. However, the extensive lesions may have resulted in its disconnection from other parts of the language network.

In the case of semantic fluency, the patients with good recovery showed activation in the IFG in both Ba 44 and 45, i.e., without the dissociation observed in normal controls for the opercular and the triangular components according to the type of fluency. It may be argued that this activation pattern in recovered aphasics reflects the utilisation of an effortful lexical retrieval strategy (Fiez, 1997). Similar activations have been observed in association with paradigms requiring the generation of willed actions (Frith, Friston, Liddle, & Frackowiak, 1991). However, extensive prefrontal activation in the left and right dorsolateral frontal regions, extending beyond Broca's area could be observed in the two patients with poor performance. This could reflect the "mental effort" in trying to achieve lexical retrieval on the basis of semantic cues. It is noteworthy that patient 4, in particular, made great effort during the task and reported "to see vivid images of animals and tools".

The present results underscore the complexity of the interpretation of the results of imaging studies of recovery. The hypothesis that the undamaged contralateral hemisphere may have an important role in the development of compensatory mechanisms (Cappa & Vallar, 1992) stems from the observation of the difference in long-term prognosis between conditions associated with bi-hemispheric damage, such as amnesia, and those which follow to unilateral lesions, as aphasia. The hypothesis of a take-over of the linguistic functions of the language-dominant left hemisphere by the contralateral hemisphere, originally proposed by Gowers (1895) was attributed to the 'unmasking' of pre-existing, functionally committed areas, which are normally inhibited by the contralateral "dominant" hemisphere (Moscovitch, 1977). Weiller et al. (1995) coworkers reported a PET investigation of a group of partially recovered patients with Wernicke's aphasia. The patients' cerebral perfusion was measured at rest and during nonword repetition and verb generation. The main result of their study was that, in comparison to control subjects, the patient group had a more extensive recruitment of frontal and temporal right hemispheric regions, homotopic to the language areas of the left hemisphere. The verb generation task is certainly very demanding, also for normal subjects, and calls for an extensive activation of the right hemisphere also in many right-handed subjects (Frackowiak, 1997; Poline et al., 1996). Furthermore, the use of a group analysis in the study of Weiller and coworkers decreases the likelihood to detect activation in perilesional areas, which will necessarily vary in individual subjects because of differences in lesion size and location. There is however some support for the hypothesis of a right-sided functional shift, coming from a longitudinal functional MR study of two patients (Thulborn, Carpenter, & Just, 1999). The first had a transient aphasia due to a stroke involving Broca's area; an increased right-sided activation during the comprehension of written sentences was observed after 76 h and after 6 months. Even more interesting are the findings in the second patient, for whom a pre-stroke functional MR was fortuitously available. These studies document the shift from a left-sided activation of Wernicke's area, to a right-sided activation after the stroke in Wernicke's area itself.

Several other studies, however, have indicated that the idea of a right-sided take over of linguistic function may be too simplistic. An important study by Belin et al. (1996) reported PET activation in patients with chronic non-fluent aphasia, who had shown considerable improvement after the introduction of Melodic Intonation Therapy (MIT). The pattern of brain activation in comparison with rest indicated extensive right-sided involvement during single word repetition. However, in the other active task, which required repetition of words with MIT intonation, the right hemisphere was actually deactivated, and a significant increase was found in the left frontal areas. The authors argue that the right-sided activations might reflect a "maladaptive" functional reorganisation, due to the presence of the left lesion itself, while actual recovery may be associated with the reactivation of left-hemispheric undamaged structures. In a PET study of fluency (verb generation) Warburton et al. (1999) concluded for a crucial role of perilesional areas in the left hemisphere (in particular of the temporal regions), in mediating efficient word retrieval performance in recovered aphasics. Several PET studies by the Koeln group (Heiss et al., 1999; Kessler, Thiel, Karbe, & Heiss, 2000) have shown, using word repetition as the activation task, that, while right hemisphere appears to contribute to the aphasics' performance, a good recovery is associated with the "reactivation" of left temporal areas: of course, this is possible only if they are spared, at least partially, by the lesion. There are also neurophysiological findings suggesting that good recovery is associated with the return to a "normal" left-sided asymmetry (Thomas, Altenmueller, Marckmann, Kahrs, & Dichgans, 1997). An important role of bilateral, rather than right sided, activation is supported by an fMRI study of verb generation and picture naming (Cao et al., 1999), and by a combined PET-fMRI study of patients with damage to the IFG studied during word-stem completion (Rosen et al., 2000). Important insight is becoming available from the investigation of single cases. In general, the latter type of investigation, such as in the present study, moves away from the excessive simplification of the group studies. Given the multiple aspects of language and linguistic processing, and the correlated complexity of its neurological underpinnings, specific questions should be asked about individual recovering patients. In particular, the role of cognitive strategies, allowing different modalities to perform the same task, should be taken into account when attempting to interpret activation data in recovered aphasics (Calvert et al., 2000; Gold & Kertesz, 2000).

In conclusion, the present findings appear to provide further evidence that, at least in the case of effortful lexical search and retrieval tasks, recovery is crucially dependent from the reactivation of the dedicated network of areas, supplemented, in the case of partial damage, by their contralateral homologues. This appears in particular to apply to tasks requiring the access and manipulation of phonological knowledge. The situation may be different in the case of tasks which are amenable to different cognitive strategies, such as semantic memory access. In the latter case, more complex patterns of re-organisation may be observed. In particular, right hemispheric activation, involving areas which are part of the normal, bi-hemispheric language network, may represent the correlate of effortful recruitment of subsidiary processing resources in order to cope with the requirements of the task. This suggestion is in line with some recent imaging reports of a relationship between the extent of right hemispheric activation and "task difficulty" (Just, Carpenter, Keller, Eddy, & Thulborn, 1996). In this case, it is likely that the pattern of cerebral activation may actually reflect "retrieval effort" rather than "retrieval success".

A major limitation of this study is the use of covert verbal responses, which prevents any direct control of the performance of the patients during scanning. The collection of fluency data immediately after the scanning session may be considered only as an approximation to actual performance. It must be underlined that all patients had been repeatedly tested with comparable word fluency tasks before inclusion in the study: therefore, their level of behavioural performance was well known. Future studies should ideally include a longitudinal investigation, and a formal (parametric) correlation between brain activation and task performance. It must be however underlined that a major problem, which makes an "ideal" investigation difficult to perform, is the choice of a task, in which patients in the acute stage could achieve a reasonable level of performance (see Price & Friston, 1999, for a careful discussion of this crucial methodological issue).

Acknowledgments

This study was partially supported by the V European Program for the project Connectivity in language rehabilitation in stroke in Europe (LSDE).

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