



Contribution of the left and right inferior frontal gyrus in recovery from aphasia. A functional MRI study in stroke patients with preserved hemodynamic responsiveness

Casper A.M.M. van Oers^{a,d,*}, Matthijs Vink^b, Martine J.E. van Zandvoort^e, H. Bart van der Worp^a, Edward H.F. de Haan^{e,f}, L. Jaap Kappelle^a, Nick F. Ramsey^c, Rick M. Dijkhuizen^d

^a Department of Neurology, Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, Utrecht, the Netherlands

^b Department of Psychiatry, Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, Utrecht, the Netherlands

^c Department of Neurosurgery, Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, Utrecht, the Netherlands

^d Department of Medical Imaging, Image Sciences Institute, University Medical Center Utrecht, Utrecht, the Netherlands

^e Department of Psychonomy, Helmholtz Institute, Utrecht University, Utrecht, the Netherlands

^f Faculty of Social and Behavioural Sciences, University of Amsterdam, Amsterdam, the Netherlands

ARTICLE INFO

Article history:

Received 22 May 2009

Revised 23 July 2009

Accepted 27 August 2009

Available online 4 September 2009

ABSTRACT

The relative contribution of dominant and non-dominant language networks to recovery from aphasia is a matter of debate. We assessed with functional magnetic resonance imaging (fMRI) to what extent the left and right hemispheres are associated with recovery from aphasia after stroke. fMRI with three language tasks was performed in 13 aphasic stroke patients and in 13 healthy subjects. Severity of aphasia was examined within 2 months after stroke and after at least 1 year. Recovery of naming ability and scores on the Token Test were correlated with data from fMRI in the chronic phase. A breath-hold paradigm was used to investigate hemodynamic responsiveness.

Overall language performance in the chronic phase correlated with higher relative activation of left compared to right perisylvian areas. Recovery of naming ability was positively correlated with activation in the left inferior frontal gyrus (IFG) for semantic decision and verb generation. Recovery on the Token Test was positively correlated with activation in both left and right IFG during semantic decision and verb generation. Hemodynamic response to the breath-hold task was similar in patients and controls.

Our study suggests that in the chronic stage after stroke left IFG activity is associated with improvement of picture naming and sentence comprehension, whereas activity in the right IFG may reflect up-regulation of non-linguistic cognitive processing. Altered hemodynamic responsiveness seems an unlikely confounder in the interpretations of fMRI results.

© 2009 Elsevier Inc. All rights reserved.

Introduction

Recovery of language function after stroke is variable and prediction of outcome in individual patients is difficult (Pedersen et al., 1995). Understanding the mechanisms that play a role in the recovery of language function may aid to predict outcome and potentially reveal targets for new therapeutic approaches.

In more than 90% of right-handed healthy people, the left hemisphere is dominant for language (Springer et al., 1999). After ischemic damage to the left hemispheric language network, enhanced activation of perilesional left hemispheric areas as well as activation of right hemispheric areas have been observed (Crosson et al., 2007;

Heiss and Thiel, 2006; Price and Crinion, 2005). Several neuroimaging studies assessing recovery from aphasia after brain injury have shown robust correlations between language function and activation in left hemispheric language areas (Breier et al., 2004; Cao et al., 1999; Crinion and Price, 2005; Heiss and Thiel, 2006; Meinzer et al., 2008), suggesting that preservation or restoration of the left hemispheric language network is important for recovery of aphasia. The functional relevance of activation of homologous right hemispheric language areas in stroke patients is more ambiguous.

Patients who regained language function after left hemispheric damage have been shown to relapse after subsequent right hemispheric damage (Basso et al., 1989; Gowers, 1887). Furthermore, loss of language function has been observed when the right, but not the left, hemisphere was anesthetized during Wada testing in aphasic patients (Kinsbourne, 1971).

However, earlier imaging studies have not found a direct relation between right hemispheric activation and functional recovery

* Corresponding author. Department of Neurology, University Medical Center Utrecht, Room C03.236, Heidelberglaan 100, P.O. Box 3584 CX, Utrecht, the Netherlands. Fax: +31 30 2542100.

E-mail address: c.a.m.vanoers@umcutrecht.nl (C.A.M.M. van Oers).

(Crosson et al., 2007; Heiss and Thiel, 2006; Price and Crinion, 2005). Enhanced activation of the right hemisphere can be observed within 2 weeks after stroke and may return to control levels after 1 year, whereas left hemispheric activity increases gradually over months to years (Saur et al., 2006), suggesting the temporary early increase of right hemispheric activation does not reflect a functionally relevant gradual reorganization process. Some studies have suggested that early activation of right hemispheric areas reflects changes in transcallosal inhibition and may even be maladaptive (Rosen et al., 2000). For example, activation of primarily right frontal areas has been observed in aphasic patients with left frontal lesions (Blank et al., 2003; Peck et al., 2004; Rosen et al., 2000; Xu et al., 2004), whereas significant right temporo-parietal activation occurred in patients with left temporo-parietal lesions (Abo et al., 2004; Fernandez et al., 2004).

Today, the question is not *if* the right hemisphere can contribute to language recovery, but under which circumstances, when, and to what extent. Increased activity in the right hemisphere is more frequently observed in patients with large ischemic lesions and poor recovery, while patients with small lesions display better outcome in association with recruitment of primarily left language areas (Crosson et al., 2007). Increases in activation in the right IFG from the acute to the subacute phase, but not from the subacute to the chronic phase, have been shown to be associated with improvement of language performance (Saur et al., 2006). Furthermore, transcranial magnetic stimulation (TMS) of the right IFG can hamper speech in aphasic patients in the subacute phase, while having no effect in some of these patients during follow-up in the chronic phase (Winhuisen et al., 2007). This suggests a temporary contribution of the right IFG in the early phase post-stroke, which is absent or more modest at chronic stages, when recruitment of perilesional left hemispheric areas becomes predominant. The association between the extent of the lesion, time after stroke and the severity of aphasia, in relation to the involvement of the right language network to recovery from aphasia, however, remains largely unclear.

Assessment of neural correlates of language recovery may be effectively conducted by combined structural and functional MRI, which allows concurrent measurement of structural damage and functional activation responses, respectively. It is, however, important to keep in mind that functional MRI (fMRI) does not directly measure neuronal activity but uses a vascular signal to probe neural processes. Aphasic stroke patients have been shown to exhibit changes in the hemodynamic response during the performance of a language task (Bonakdarpour et al., 2007). This could have implications for the

interpretation of fMRI results. Therefore, it is helpful to assess cerebrovascular reactivity in stroke patients who take part in an fMRI study. A breath-hold task provides a simple and effective means to evaluate functional status of the vasculature (Thomason et al., 2005).

To elucidate the contribution of left and right brain areas in language recovery, we conducted fMRI during execution of three different language paradigms in patients with aphasia of mixed severity in the chronic stage after stroke, and correlated brain activation with (i) severity of aphasia in the chronic stage (>1 year), (ii) changes in language performance (i.e., picture naming and auditory sentence comprehension) between the subacute (1 month) and chronic (>1 year) phases of stroke, and (iii) size and location of the lesion. Furthermore, a breath-hold paradigm was included to evaluate hemodynamic responsiveness.

Materials and methods

Subjects

A total of 13 stroke patients took part in this study. Characteristics of the patients are listed in Table 1. Patients were included if they (i) had a first-ever ischemic stroke in the territory of the left middle cerebral artery (MCA); (ii) had aphasia assessed within the first two months after stroke with both the Token Test (de Renzi and Vignolo, 1962) and the Dutch version of the Aachen Aphasia Test (Graetz et al., 1992) or the Boston Naming Task (Kaplan et al., 1978); (iii) had a score <3 on the modified Rankin scale (van Swieten et al., 1988), moderate disability, but were able to walk without assistance; (iv) were right-handed; (v) could be followed up after at least 1 year after inclusion; and (vi) had Dutch as their native language. Patients were excluded from the study if they had (i) a history of other neurological or psychiatric diseases; (ii) an inability to perform at least two of the three fMRI language paradigms due to severe aphasia or other disturbances of cognition or sensory function; (iii) an inability to enter the MRI scanner because of non-MRI compatible prostheses; and (iv) an inability to visit the hospital because of reduced mobility. Patients were either selected from a database with 185 stroke patients ($n=6$) who had been assessed with a battery of neuropsychological tests (Nys et al., 2005), or from a group of aphasic stroke patients that had been referred to rehabilitation center “de Hoogstraat” ($n=7$). Characteristics of the patients (mean age 53 ± 14 years; four males) are listed in Table 1. Severity and subtyping of the aphasia (Broca's, Wernicke's, etc.) is conducted according to the Aachen Aphasia Test.

Table 1
Patient characteristics.

Patient	Sex	Age (years)	Time to test 1 (days) ^a	Time to test 2 and MRI (years) ^b	Aphasia profile at MRI ^c	AAT overall	Spontaneous speech (max. 30)	Inverse token (max. 50)	Repeating (max. 150)	Written language (max. 90)	Naming (max. 120)	Comprehension (max. 120)	Δ -naming	Δ -Token Test
1	F	49	49	4.5	Broca III	-122	22	0	42	1	0	84	0.0	0.0
2	F	50	11	1.5	Anomic I	57	25	33	140	89	113	114	12.5	22.0
3	F	36	31	1.3	Anomic II	51	24	35	134	83	114	111	2.6	5.0
4	F	34	27	3.8	Anomic II	21	25	31	106	63	109	101	11.3	18.0
5	M	55	30	4.7	0	55	24	39	144	84	112	102	7.4	24.0
6	M	52	38	1.4	Broca III	-135	13	4	22	3	1	66	0.1	4.0
7	F	65	8	4.2	Wernicke I	-3	27	20	110	35	97	84	4.9	20.0
8	M	74	47	3.2	Broca III	-45	16	39	53	64	48	107	5.7	5.0
9	F	67	5	4.2	Anomic II	43	23	29	128	82	109	109	17.7	29.0
10	M	70	53	1.9	Anomic II	39	23	37	125	85	107	91	-0.5	1.0
11	F	53	6	4.0	0	60	29	45	138	88	117	113	18.0	28.0
12	F	29	18	2.9	0	61	28	45	147	90	112	105	3.0	13.0
13	F	57	56	1.3	Broca III	-83	10	5	92	6	16	77	0.7	5.0

Language performance scores, at time to test 2, are expressed in arbitrary units (maximum scores between parentheses). AAT overall: overall performance on the Aachen Aphasia Test; Δ -naming: recovery of naming (difference in Z scores); Δ -Token Test: recovery on the Token Test, between first and second language tests.

^a Time from stroke to language testing in the subacute phase.

^b Time from stroke to language testing and MRI in the chronic phase.

^c I = mild; II = moderate; III = severe; 0 = no aphasia.

The severity is based on reference scores of a Dutch group of aphasia patients that was used to develop and test the Dutch version of the Aachen Aphasia Test.

At the time of MRI, the aphasia of three patients had completely recovered. The other patients had anomia ($n=5$), Broca's aphasia ($n=4$), or Wernicke's aphasia ($n=1$) (Table 1). Thirteen age-matched volunteers (mean age 54 ± 16 years; four males) without neurological or psychiatric illnesses were recruited as controls. Written consent was obtained from all subjects. The study was approved by the local Medical Ethical Review Board.

Language testing

At time-point 1, in the first 2 months (26 ± 18 days) after stroke, all patients underwent the Token Test, which is a part of the Aachen Aphasia Test. In addition, the severity of aphasia was assessed with the complete Aachen Aphasia Test ($n=8$) or Boston Naming Task ($n=4$), or both ($n=1$).

At time-point 2, 1 day before the MRI session (1.3–4.7 years post-stroke) the Aachen Aphasia Test, Boston Naming Task, and Token Test were again conducted in all patients. The score on the Token Test was subtracted from its maximum score of 50 to ensure that higher scores reflected better performance, similar to the scores on the other subtests of the Aachen Aphasia Test and the Boston Naming Task.

In order to create a single measure reflecting overall language performance in the chronic phase, with within group differences being most important, a principle component analysis was performed on scores of all subtests of the Aachen Aphasia Test using MATLAB (The Mathworks Inc.) (Schaechter et al., 2006; Ward et al., 2003). The first principle component, which accounts for the largest variability within the data, was taken as the composite language performance score.

Recovery of language function from the subacute to the chronic phase was measured from differences in confrontation picture naming (Boston Naming Task or naming subtask of the Aachen Aphasia Test) performance and Token Test scores. To combine the scores on the different naming tests into a single score reflecting change in naming performance over time, the scores on the Boston Naming Task and naming subtest of the Aachen Aphasia Test were normalized to scores from a Dutch control population of aphasia patients (Graetz et al., 1992; van Loon-Vervorm et al., 1996), and converted into Z scores. For each patient, the difference between the subacute and chronic stage Z scores was calculated as a measure of recovery. In addition, for all patients, recovery on the Token Test was measured by subtracting the score at time-point 2 from the score at time-point 1. The Token Test scores were not normalized before subtraction.

MRI

Language paradigms

In order to assess different aspects of the language system we used three different fMRI language paradigms. Tasks that require verbal fluency or semantic decision predominantly activate Broca's area (left IFG) (Bookheimer, 2002; Poldrack et al., 1999). Since particular interest was paid to the IFG and the tasks had to be easy enough for aphasia patients we used the following tasks, all visually presented in a blocked design: (i) picture word matching; (ii) semantic decision; and (iii) verb generation (D'Arcy et al., 2007; Ramsey et al., 2001; Wise et al., 1991). The semantic decision and picture word matching tasks both require a decision based on semantics.

The picture word matching task consisted of trials (six blocks of 28 s) of a simultaneously presented picture (Snodgrass and Vanderwart, 1980) and a word, of which the subjects were asked whether these matched. Subjects responded by pressing a left (correct) or right (incorrect) button with the left (non-paretic) hand. To control for non-language processing, such as activation of

the motor system, task blocks were interleaved with a control condition where subjects were asked to press the left or right button when an arrow pointing left or right was presented (six blocks of 28 s). In addition, six blocks (28 s each) were added in which subjects had to fixate on a centrally presented stimulus.

In the semantic decision task, subjects had to judge whether a noun in the middle of the screen referred to an animal. These task blocks (6×28 s) were alternated with the same control condition and blocks with a fixation cross as in the picture word matching task.

During the verb generation task, subjects were instructed to think of a verb associated with a presented noun (for example, coffee-to drink). Task blocks (8×30 s) were alternated with visual presentation of a fixation cross in the middle of the screen (8×30 s).

During a training session 1 day before the MRI examination and again directly before scanning, subjects practiced all tasks with different stimuli. During the scanning session, subjects once more were given a few practice trials before each fMRI run. To match task difficulty between subjects, interstimulus intervals within blocks of the language tasks were individually calibrated by multiplying the mean reaction time during the practice session with 1.8. In a pilot study this turned out to ensure performance accuracy above 80% (data not shown).

Breath-hold paradigm

For the breath-hold paradigm, subjects were visually cued to hold their breath for 20 s after normal inspiration by showing them a number counting down to zero. Breath-hold blocks (3×20 s) were alternated with rest blocks with a fixation cross in the middle of the screen (4×30 s). A belt around the abdomen registered respiration.

Data acquisition

MRI was performed on a Philips Achieva 3T scanner. A T_1 -weighted scan (repetition time (TR)/echo time (TE) = 9.9/4.6 ms, flip angle = 8° , acquired voxel size = $1.0 \times 1.0 \times 1.0$ mm³, reconstructed voxel size = $0.88 \times 0.88 \times 1.0$ mm³, field-of-view (FOV) = $224 \times 168 \times 160$ mm³, transverse orientation) was used for anatomical localization. A FLAIR scan using an eight-element head coil equipped for parallel imaging (SENSE) (TR/TE/inversion time (TI) = 11000/125/2800 ms, acquired voxel size = $0.65 \times 0.94 \times 4.0$ mm³, reconstructed voxel size = $0.45 \times 0.45 \times 4.0$ mm³, FOV = $230 \times 183 \times 129$ mm³, transverse orientation) was used for visualizing the lesion. For functional imaging a 3D PRESTO-SENSE sequence (TE/TR = 32.4/21.75 ms, scan duration 500 ms, flip angle = 10° , FOV = $256 \times 192 \times 160$ mm³, voxel size = 4.0 mm³ isotropic, sagittal orientation) was used (Neggert et al., 2008). The first 10 scans of each functional run were discarded to allow for signal saturation. The picture word matching and semantic decision sessions consisted of 1008 scans, the verb generation session of 1020 scans, and the breath-hold session of 360 scans.

Data analysis

Data were analyzed using SPM2 (Wellcome Department of Imaging neuroscience; <http://www.fil.ion.ucl.ac.uk/spm/>). Functional images were realigned and co-registered with the anatomical and FLAIR images. A manually drawn outline of the hyperintense lesion on the FLAIR image was used for calculating lesion volume and was masked out during subsequent normalization of the patients' images to the Montreal Neurological Institute template (Brett et al., 2001). Normalized functional images were smoothed with an 8-mm Gaussian filter.

Language paradigms

First, for each subject, and for each task separately, a general linear model (GLM) analysis was performed to obtain average brain responses (i.e., b values) associated with language processing. To correct for drifts in the signal, a high-pass filter was applied to the data

with a cut-off frequency of 0.006 Hz for the semantic decision task and picture word matching task, and a cut-off frequency of 0.008 Hz for the verb generation task.

Second, regions-of-interest (ROIs) in the left hemisphere and their right hemispheric homologues were created using the Wake Forest University Pick Atlas (Maldjian et al., 2003) and consisted of (i) the inferior frontal gyrus (IFG), representing the anterior language region, (ii) posterior language region consisting of the angular, supramarginal, and entire superior and middle temporal gyri, and (iii) combined anterior and posterior language regions (combined language areas). The inferior temporal gyrus was not included because of substantial magnetic susceptibility-induced signal loss in this area (data not shown). For each patient the relative amount of ischemic damage in each ROI was calculated by dividing the volume of lesioned tissue within the ROI by the total ROI volume.

Third, for each subject, the number of activated voxels (i.e., showing activation above a threshold of $p < 0.05$, Family Wise Error corrected) was counted in each ROI to obtain the degree of activation for each ROI. Since no significant activation was observed in the lesion, the lesion area was not masked out for this analysis. The laterality index was calculated for each pair (left and right) of ROIs using: $\text{laterality index} = (L - R) / (L + R)$, where L is the number of activated voxels in the left ROI and R is the number of voxels in the right ROI. The laterality index reflects the degree of activation in a left hemispheric ROI in relation to its contralateral counterpart.

Breath-hold paradigm

For analysis of the breath-hold data, the signal intensity time-course over 360 scans was averaged for all voxels in right combined language areas after filtering with a high-pass filter with a cut-off frequency of 0.008 Hz. First, to assess differences between the healthy hemisphere of patients and controls the time-course of individual patients was correlated with the average time-course of all control subjects. As a reference, the time-courses of the individual control subjects were correlated with the average time-course of the control group using the jack-knife approach. Second, to detect intra-individual differences between the left and right hemisphere, a GLM analysis was performed analogous to the analysis of the language fMRI sessions, using the individual average time-course in right homologous language areas as the regressor-of-interest.

The number of significantly responsive voxels ($p < 0.001$, uncorrected) in unlesioned left and right language areas were calculated for all stroke and control subjects. In contrast to the language paradigm, the breath-hold paradigm resulted in significantly responsive voxels inside the lesion area. Therefore, the lesion was masked out for ROI analysis of the breath-hold data for adequate comparison with the language fMRI data. The number of responsive voxels in each ROI was divided by the total number of voxels in the unlesioned part of the ROI.

Statistics

All values are expressed as mean \pm SD. A $p < 0.05$ was considered statistically significant. A binomial test was used to test whether the subjects' performance scores during the execution of language paradigms were above chance level. Group activation maps for the language paradigms were created with a one-sample t -test ($p < 0.001$, uncorrected). To test for differences in the amount of activation in the combined language area between the different tasks for both groups, a multivariate test was performed. Between-group differences in the number of activated voxels in each ROI were evaluated by two-sample t -testing.

Performance in the chronic phase, lesion size and fMRI activation

To assess the relation between language performance in the chronic phase and language related activation within the patient

group, online performance on the picture word matching and semantic decision task during scanning and performance on the verb generation task right before scanning, were correlated with the number of activated voxels (for both hemispheres) and laterality indices in the ROIs. Furthermore, overall language performance in the chronic stage was correlated with the number of activated voxels (for both hemispheres) and laterality indices in the ROIs. Lesion size was correlated with overall language performance. The number of activated voxels in right hemispheric ROIs was correlated with lesion volume and with the percentage of damage in their left hemispheric counterparts. Correlations were tested with a Pearson's correlation test.

Recovery of language and fMRI activation

The difference between the Token Test score and naming Z score at time-points 2 and 1 within the patient group was tested with a paired t -test. Recovery of naming and on the Token Test was correlated with the number of activated voxels (for both hemispheres) and laterality indices in the ROIs. Recovery of these language modalities was also correlated with lesion size with use of Pearson's correlation test.

Breath-hold response

We calculated Pearson's correlation coefficients between percentages of responsive voxels during language tasks and the breath-hold paradigm in the combined language area to evaluate whether the degree of activation was directly linked to the level of cerebrovascular reactivity. Two-sample t -tests were used for the comparisons of the numbers of activated voxels, laterality indices and percentages of responsive voxels during breath-hold, between patients and controls.

Results

Subjects

The locations of the patients' chronic infarcts are shown in Fig. 1. The lesion size and location, and degree of damage in the left language ROIs are shown in Table 2. Three patients were not able to perform the verb generation task. Semantic decision results were excluded from the analysis for one patient who did not perform above chance level. The other tasks were successfully executed by these patients and included for further analysis. All other subjects performed well above chance level on all fMRI language paradigms. Performance accuracy (%; controls vs. patients) for picture word matching, semantic decision and verb generation were 93 ± 8 vs. 88 ± 10 , 91 ± 4 vs. 80 ± 15 and 97 ± 4 vs. 79 ± 17 , respectively.

Activation pattern

For both groups, average activation maps showed activation in the inferior, middle, and medial superior frontal gyri, middle temporal gyrus, supramarginal gyrus, the angular gyrus, posterior part of the inferior temporal gyrus, basal ganglia, fusiform gyrus, posterior occipital lobe, and cerebellum on both sides (Fig. 2). The different language tasks activated largely similar areas. The number of activated voxels in left language areas (patients vs. controls) for verb generation, picture word matching and semantic decision were 407 ± 156 vs. 590 ± 180 , 165 ± 152 vs. 240 ± 162 , and 152 ± 118 vs. 287 ± 164 , respectively. These numbers were significantly larger for verb generation than for picture word matching and semantic decision for both patients and controls ($F 22.3$, $p < 0.001$). The number of activated voxels and laterality indices in ROIs for patients and controls are shown in Table 3. As a result of the lesion, the number of activated voxels in the left IFG was significantly lower in patients than in controls for all language tasks. The laterality index in the combined language areas was lower in patients than controls.

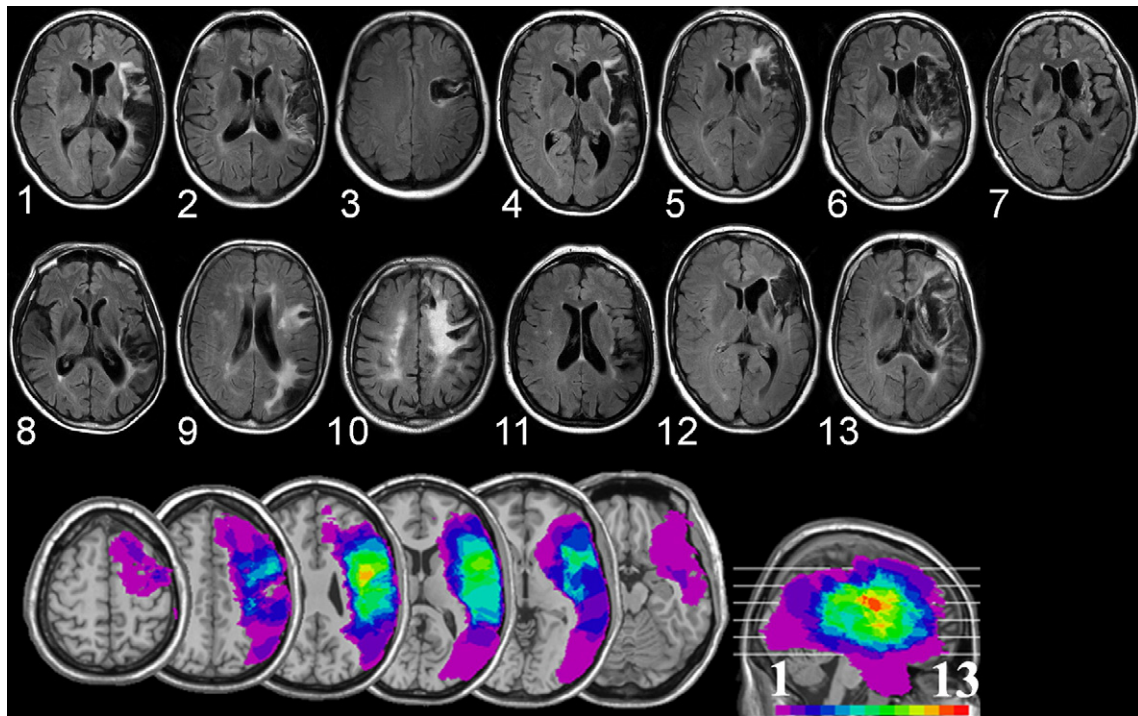


Fig. 1. FLAIR MR images of axial brain slice with maximum ischemic damage for each patient (1–13), and distribution of all patients' lesion areas on a brain template. Color-coding reflects number of patients (1–13) with local lesion overlap.

Performance in the chronic phase, lesion size and fMRI activation

Within the patient group, activation in left or right hemispheric ROIs or laterality indices were not correlated with online performance on the fMRI tasks. Overall language performance was positively correlated with the laterality index for semantic decision ($r=0.60$, $p=0.039$) and we detected a trend for picture word matching ($r=0.51$, $p=0.078$). The overall language performance at the time of MRI was inversely correlated with lesion volume ($r=-0.64$, $p=0.018$). The number of activated voxels in right hemispheric ROIs was not related to either lesion volume or percentage of damage in the left hemispheric counterparts of the ROIs.

Recovery of language and fMRI activation

From the subacute to the chronic phase, patients' performance on the Token Test and on naming improved significantly from 14.5 ± 14.3

to 27.9 ± 15.6 ($p=0.001$) and from -10.2 ± 5.9 to -3.8 ± 6.2 ($p=0.004$), respectively (see Table 1).

Recovery of naming ability was positively correlated with the number of activated voxels in the left IFG for semantic decision ($r=0.76$, $p=0.004$) and verb generation ($r=0.71$, $p=0.021$). Recovery on the Token Test was positively correlated with the number of activated voxels in both left and right IFG during semantic decision ($r=0.77$, $p=0.004$ (left); $r=0.64$, $p=0.024$ (right)) and verb generation ($r=0.64$, $p=0.047$ (left); $r=0.73$, $p=0.017$ (right)). Change of naming and change on the Token Test were not correlated with lesion volume.

Breath-hold response

The average time-courses of BOLD signal intensity changes in right language areas in controls and patients during the breath-hold paradigm are shown in Figs. 3A and B, respectively. The area with significant BOLD responsiveness ($p<0.001$, uncorrected) for a control subject and a patient are shown in Figs. 3C and D, respectively. One control subject was discarded, as she did not hold her breath during the second task block. Grey matter was widely responsive in both controls and patients. There was markedly reduced responsiveness in the infarcted area. The correlation coefficient between the average signal intensity time-courses in right language areas in individual healthy controls and the average time-course in all other controls was 0.61 ± 0.10 (range: 0.47–0.75). For patients, the correlation coefficient with the average time-course in controls was 0.44 ± 0.32 (range: -0.30–0.78). The difference between patients and controls did not reach significance ($p=0.13$). For four patients with correlation coefficients more than 2 standard deviations lower than the mean in healthy controls, it was questionable whether they had fully held their breath. Since three of them exhibited above average activation during the language paradigms, it is unlikely that their cerebrovascular reactivity was substantially impaired. The other patient showed sparse language-related activation. However, exclusion of this patient from the fMRI analyses did not substantially change the results (data not shown).

Table 2

Lesion site, size and degree of damage to left language ROIs.

Patient	Site of lesion in left hemisphere	Lesion volume (cm ³)	Damage to IFG (%)	Damage to posterior language region (%)
1	Frontal, temporal, parietal	104.2	37	74
2	Frontal, parietal	49.6	54	8
3	Frontal	41.0	25	0
4	Frontal, parietal	69.3	50	31
5	Frontal	48.2	59	0
6	Frontal, temporal, striatocapsular	87.3	63	28
7	Striatocapsular	6.0	0	0
8	Temporal, parietal	49.3	0	28
9	Frontal, temporal, parietal	75.0	12	33
10	Frontal	49.8	2	2
11	Parietal	10.4	0	5
12	Frontal	41.6	65	0
13	Frontal, temporal, striatocapsular	167.3	93	55

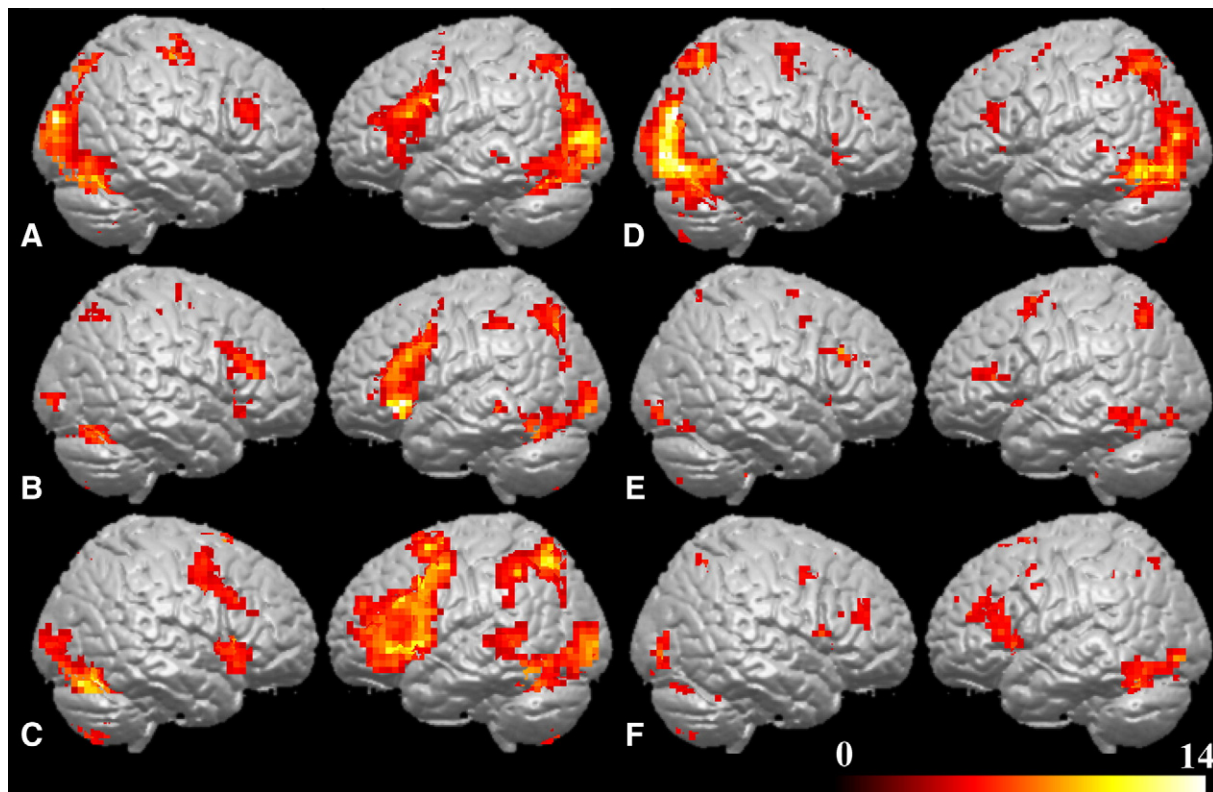


Fig. 2. Group activation maps ($p < 0.001$, uncorrected) for controls (A, B, C) and patients (D, E, F) during picture word matching (A, D), semantic decision (B, E), and verb generation (C, F). Color-coding reflects t -values.

Percentage of activation during language tasks and percentage of responsiveness during breath-hold was not correlated in the combined language areas. Percentage of responsive voxels in the unlesioned part of left and right language areas combined in controls (left: $76.4 \pm 9.2\%$; right: $72.3 \pm 5.7\%$; laterality index: 0.03 ± 0.05) was not different from patients (left: $68.3 \pm 24.6\%$; right: $77.5 \pm 8.2\%$; laterality index: -0.10 ± 0.22).

Discussion

In the present study, better overall language performance more than 1 year after ischemic stroke was associated with higher relative activation of the left compared to the right hemisphere. Language recovery from the subacute phase to the chronic phase after stroke was associated with left IFG activity in the chronic phase. Both left and right IFG activation in the chronic phase were correlated with improvement of sentence comprehension (Token Test). A breath-

hold paradigm demonstrated that the majority of chronic patients had adequate hemodynamic responsiveness in left and right language regions.

In the patient and control group, all three language tasks induced activation in language areas that are commonly activated across a range of comparable language tasks in controls (Ramsey et al., 2001). Activated volumes were larger in the verb generation paradigm than in the other tasks. This is at least partly explained by the stronger baseline task for the picture word matching and semantic decision tasks, while verb generation was contrasted with a fixation cross. Moreover, a smaller constraint in response options during verb generation as compared to the other tasks results in increased activation of the left IFG through a higher demand on selection between competitive alternatives (Schnur et al., 2009).

Activation responses in chronic stroke patients were detected in the same left hemispheric areas as in controls, although to a lesser extent due to the ischemic lesion. The amount of activity in right hemispheric

Table 3
Language-related activation in patients and controls.

Task	ROI	Controls			Patients		
		Left ^a	Right ^a	LI ^b	Left ^a	Right ^a	LI ^b
Picture word matching	IFG	172 ± 29	80 ± 21	0.47 ± 0.08	87 ± 21*	78 ± 20	-0.02 ± 0.15*
	Posterior language areas	67 ± 19	24 ± 8	0.48 ± 0.12	78 ± 27	66 ± 26	0.19 ± 0.16
	Combined language areas			0.47 ± 0.08			0.12 ± 0.12*
Semantic decision	IFG	200 ± 24	84 ± 22	0.43 ± 0.07	85 ± 22*	57 ± 11	0.12 ± 0.16*
	Posterior language areas	87 ± 25	41 ± 13	0.38 ± 0.14	67 ± 15	61 ± 15	0.10 ± 0.12
	Combined language areas			0.43 ± 0.06			0.12 ± 0.13*
Verb generation	IFG	371 ± 25	147 ± 24	0.47 ± 0.06	225 ± 43*	156 ± 32	0.16 ± 0.13*
	Posterior language areas	220 ± 38	106 ± 33	0.41 ± 0.08	182 ± 34	145 ± 43	0.27 ± 0.13
	Combined language areas			0.44 ± 0.06	225 ± 43*		0.27 ± 0.13*

^a Number of activated voxels.

^b Laterality index.

* $p < 0.05$, patients vs. controls.

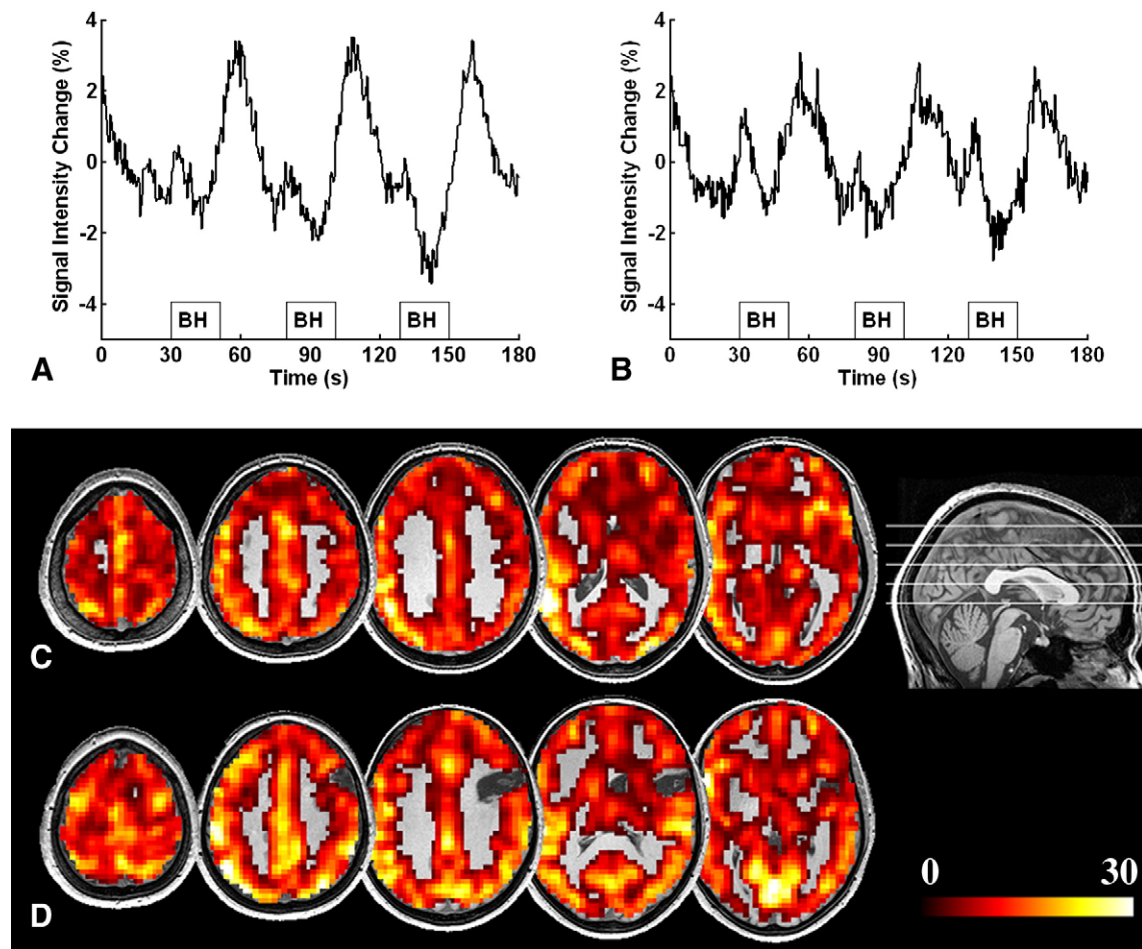


Fig. 3. Response during breath-hold paradigm. Average change in signal intensity in right language areas over time in controls (A) and patients (B). BH: breath-hold block. Standard deviations for time-points (mean; range) for controls: 0.48; 0.20–1.0, and patients: 0.59; 0.18–1.26. Map of responsiveness ($p < 0.001$, uncorrected) in a control (C) and patient (D) superimposed on subject's anatomical scan. Color-coding reflects t -values.

areas was largely similar to that in controls. This corresponds with previous studies that showed normalization of right hemispheric activity in right perisylvian language areas after 2 weeks post-stroke (Heiss et al., 1999; Saur et al., 2006).

Previous neuroimaging studies in stroke patients have underlined the importance of restitution or restoration of the pre-morbid language network in the dominant left hemisphere for recovery from aphasia (Crosson et al., 2007; Heiss and Thiel, 2006; Price and Crinion, 2005). In line with these findings, we found that a better overall score on the Aachen Aphasia Test in the chronic phase was correlated with a higher relative contribution of left compared to right perisylvian areas during certain fMRI language tasks.

In our study, improvement on the Token Test was positively correlated with activation in both the left and right IFG during semantic decision and verb generation. By contrast, recovery of naming was only associated with activity in the left IFG. The left IFG is a crucial area for various linguistic processes such as lexical-semantics, phonology and syntax. It is therefore not surprising that the left IFG is involved in recovery of many subcomponents of language, such as sentence comprehension and picture naming. Our data suggest that the right IFG contributes more during auditory sentence comprehension than during picture naming.

Picture naming requires integration of the visual, phonological, semantic and motor systems, while auditory sentence comprehension involves auditory, phonological, semantic, syntactic and motor processing. Since the patients did not exhibit hearing or visual impairments in

the subacute or chronic phase, reorganization of these primary sensory brain systems are not suggestive to play a role in the observed dissociation.

Right IFG may be especially involved in making inferences when processing load increases (Shears et al., 2008). Indeed, the right IFG has been shown to be activated when processing load of various linguistic tasks increases (Kaan and Swaab, 2002), besides playing a role in oddball detection (Huettel and McCarthy, 2004) and inhibition (Vink et al., 2005). In our study, each of the words comprising the stimulus sentences in the Token Test have to be kept in working memory before a correct motor program can be initiated to solve the trial. The demand on working memory and executive processing during the Token Test would therefore be higher than for picture naming. The increase of right IFG activation with increased task difficulty and learning of new or forgotten words in healthy controls as well as patients (Raboyeau et al., 2008) points toward an indirect contribution of the right IFG to linguistic processing in terms of working memory or executive control (Rosen et al., 2000).

The incorporation of contralesional (right) homologues into the language network may be more prominent in case of extensive damage. In our study, the infarction varied substantially in extent and location. Yet, the IFG was most consistently affected (10 out of 13 patients). However, we did not find a significant correlation between lesion volume or damage in the language areas in the dominant hemisphere (i.e., left IFG and posterior language area) and activation in the non-dominant hemispheric counterparts.

Breath-hold

BOLD fMRI measures a hemodynamic response of the brain that is related to neuronal activity (Logothetis et al., 2001). In patient studies the assumption that vascular reactivity is unaltered and that differences in the measured BOLD MR signal response therefore directly reflect differences in neuronal activity is not unequivocal. In patients with stroke, altered cerebrovascular reactivity may distort hemodynamic activation responses (Krainik et al., 2005; Rossini et al., 2004). In stroke patients with aphasia this may result in an increase in time-to-peak of the hemodynamic response in left perisylvian areas (Bonakdarpour et al., 2007). Assessment of vascular reactivity could aid in distinguishing between altered neuronal processing and altered hemodynamic responsiveness as an explanation for changes in fMRI responses in cerebrovascular disease patients. We applied a 20-s breath-hold paradigm that has been shown to be a practical approach to test cerebrovascular reactivity non-invasively (Thomason et al., 2005). The temporal pattern of BOLD signal intensity changes during the breath-hold paradigm in healthy controls in our study corresponded with that described previously: (1) an initial small increase in signal reflecting chest expansion and decreased intra-thoracic pressure, reduced vascular resistance and increase of blood inflow of blood to the brain; (2) a decrease of the signal due to lowering heart rate and decreasing cerebral perfusion as a result of autonomic regulation by baroreceptors; (3) a signal increase due to increase in cerebral blood flow following rise in arterial CO₂ pressure; (4) return to baseline signal following normalization of physiological parameters (Thomason et al., 2005).

In our study, the time-course of the BOLD MR signal during a breath-hold paradigm was largely similar in structurally intact right and left language areas in all subjects that performed the paradigm adequately, except for one patient. The observed differences in language-related fMRI activation can therefore not be explained by altered cerebrovascular reactivity. Nevertheless, assessment of hemodynamic responsiveness may well provide important information for fMRI studies in stroke patients, particularly at earlier stages when reactivity may be impaired (Saur et al., 2006).

Limitations and future directions

In order to make inferences about the contribution of the observed activation to specific subcomponents of language, the tests used for the behavioral assessment and the tasks used during the fMRI examination should ideally be matched. Nevertheless, in our study activation of left and right hemispheric ROIs was not significantly correlated with performance of the online fMRI tasks. The fMRI tasks had been designed to be easy enough for dysphasic patients to perform. Although three patients were unable to conduct the verb generation and one was unable to conduct the semantic decision task, many patients reached accuracy higher than 90% (7 out of 13 for picture word matching, 6 out of 12 for semantic decision and 4 out of 10 for verb generation). This ceiling effect may have masked a possible correlation.

The language tasks in this study were not designed to activate Wernicke's area to a large extent. Therefore, no conclusions can be drawn from the absence of evidence of involvement of the posterior language area in recovery from aphasia in the chronic phase.

Unfortunately, fMRI was not conducted in the earlier phases after stroke in the current study. Future studies with a longitudinal design, with a close match between the tasks used for neuroimaging and behavioral assessment, can help to further elucidate the contribution of different brain areas and particularly the right IFG in relation to behavioral recovery.

Conclusions

Our study confirms that restoration of left hemispheric language areas, including the IFG, the superior and middle temporal gyri, and

the angular and supramarginal gyri is associated with good language performance more than 1 year after ischemic stroke. Left IFG activity was associated with improvement of linguistic functions such as object naming and sentence comprehension, while the right IFG may contribute through non-linguistic processing related to increased demand of working memory or executive control reflecting task difficulty or learning. The majority of patients showed a similar hemodynamic responsiveness to a breath-hold paradigm in structurally intact language areas compared to healthy controls, making altered cerebrovascular reactivity an unlikely confounder in the interpretations of our fMRI results in chronic stroke patients.

Acknowledgments

This study was sponsored by the Netherlands Heart Foundation, grant 2003B196. Dr. Dijkhuizen was financially supported by a fellowship of the Royal Netherlands Academy of Arts and Sciences.

References

- Abo, M., Senoo, A., Watanabe, S., Miyano, S., Doseki, K., Sasaki, N., Kobayashi, K., Kikuchi, Y., Yonemoto, K., 2004. Language-related brain function during word repetition in post-stroke aphasics. *Neuroreport* 15, 1891–1894.
- Basso, A., Gardelli, M., Grassi, M.P., Mariotti, M., 1989. The role of the right hemisphere in recovery from aphasia. Two case studies. *Cortex* 25, 555–566.
- Blank, S.C., Bird, H., Turkheimer, F., Wise, R.J., 2003. Speech production after stroke: the role of the right pars opercularis. *Ann. Neurol.* 54, 310–320.
- Bonakdarpour, B., Parrish, T.B., Thompson, C.K., 2007. Hemodynamic response function in patients with stroke-induced aphasia: implications for fMRI data analysis. *Neuroimage* 36, 322–331.
- Bookheimer, S., 2002. Functional MRI of language: new approaches to understanding the cortical organization of semantic processing. *Annu. Rev. Neurosci.* 25, 151–188.
- Breier, J.I., Castillo, E.M., Boake, C., Billingsley, R., Maher, L., Francisco, G., Papanicolaou, A.C., 2004. Spatiotemporal patterns of language-specific brain activity in patients with chronic aphasia after stroke using magnetoencephalography. *Neuroimage* 23, 1308–1316.
- Brett, M., Leff, A.P., Rorden, C., Ashburner, J., 2001. Spatial normalization of brain images with focal lesions using cost function masking. *Neuroimage* 14, 486–500.
- Cao, Y., Vikingstad, E.M., George, K.P., Johnson, A.F., Welch, K.M., 1999. Cortical language activation in stroke patients recovering from aphasia with functional MRI. *Stroke* 30, 2331–2340.
- Crinion, J., Price, C.J., 2005. Right anterior superior temporal activation predicts auditory sentence comprehension following aphasic stroke. *Brain* 128, 2858–2871.
- Crosson, B., McGregor, K., Gopinath, K.S., Conway, T.W., Benjamin, M., Chang, Y.L., Moore, A.B., Raymer, A.M., Briggs, R.W., Sherod, M.G., Wierenga, C.E., White, K.D., 2007. Functional MRI of language in aphasia: a review of the literature and the methodological challenges. *Neuropsychol. Rev.* 17, 157–177.
- D'Arcy, R.C., Bolster, R.B., Ryner, L., Mazerolle, E.L., Grant, J., Song, X., 2007. A site directed fMRI approach for evaluating functional status in the anterolateral temporal lobes. *Neurosci. Res.* 57, 120–128.
- de Renzi, E., Vignolo, L.A., 1962. The Token Test: a sensitive test to detect receptive disturbances in aphasics. *Brain* 85, 665–678.
- Fernandez, B., Cardebat, D., Demonet, J.F., Joseph, P.A., Mazaux, J.M., Barat, M., Allard, M., 2004. Functional MRI follow-up study of language processes in healthy subjects and during recovery in a case of aphasia. *Stroke* 35, 2171–2176.
- Gowers, W.R., 1887. Lectures on the diagnosis of diseases of the brain. Churchill, London.
- Graetz, P., De Bleser, R., Willmes, K., 1992. Akense Afasietest, Nederlandse versie. Swets & Zeitlinger, Lisse.
- Heiss, W.D., Thiel, A., 2006. A proposed regional hierarchy in recovery of post-stroke aphasia. *Brain Lang.* 98, 118–123.
- Heiss, W.D., Kessler, J., Thiel, A., Ghaemi, M., Karbe, H., 1999. Differential capacity of left and right hemispheric areas for compensation of poststroke aphasia. *Ann. Neurol.* 45, 430–438.
- Huettel, S.A., McCarthy, G., 2004. What is odd in the oddball task? Prefrontal cortex is activated by dynamic changes in response strategy. *Neuropsychologia* 42, 379–386.
- Kaan, E., Swaab, T.Y., 2002. The brain circuitry of syntactic comprehension. *Trends Cogn. Sci.* 6, 350–356.
- Kaplan, E., Goodglass, H., Weintraub, S., 1978. The Boston Naming Test. Lea & Febiger, Philadelphia.
- Kinsbourne, M., 1971. The minor cerebral hemisphere as a source of aphasic speech. *Arch. Neurol.* 25, 302–306.
- Krainik, A., Hund-Georgiadis, M., Zysset, S., von Cramon, D.Y., 2005. Regional impairment of cerebrovascular reactivity and BOLD signal in adults after stroke. *Stroke* 36, 1146–1152.
- Logothetis, N.K., Pauls, J., Augath, M., Trinath, T., Oeltermann, A., 2001. Neurophysiological investigation of the basis of the fMRI signal. *Nature* 412, 150–157.
- Maldjian, J.A., Laurienti, P.J., Kraft, R.A., Burdette, J.H., 2003. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage* 19, 1233–1239.

- Meinzer, M., Flaisch, T., Breitenstein, C., Wienbruch, C., Elbert, T., Rockstroh, B., 2008. Functional re-recruitment of dysfunctional brain areas predicts language recovery in chronic aphasia. *Neuroimage* 39, 2038–2046.
- Neggers, S.F., Hermans, E.J., Ramsey, N.F., 2008. Enhanced sensitivity with fast three-dimensional blood-oxygen-level-dependent functional MRI: comparison of SENSE-RESTO and 2D-EPI at 3 T. *NMR Biomed.* 21, 663–676.
- Nys, G.M., van Zandvoort, M.J., de Kort, P.L., van der Worp, H.B., Jansen, B.P., Algra, A., de Haan, E.H., Kappelle, L.J., 2005. The prognostic value of domain-specific cognitive abilities in acute first-ever stroke. *Neurology* 64, 821–827.
- Peck, K.K., Moore, A.B., Crosson, B.A., Gaiefsky, M., Gopinath, K.S., White, K., Briggs, R.W., 2004. Functional magnetic resonance imaging before and after aphasia therapy: shifts in hemodynamic time to peak during an overt language task. *Stroke* 35, 554–559.
- Pedersen, P.M., Jorgensen, H.S., Nakayama, H., Raaschou, H.O., Olsen, T.S., 1995. Aphasia in acute stroke: incidence, determinants, and recovery. *Ann. Neurol.* 38, 659–666.
- Poldrack, R.A., Wagner, A.D., Prull, M.W., Desmond, J.E., Glover, G.H., Gabrieli, J.D., 1999. Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex. *Neuroimage* 10, 15–35.
- Price, C.J., Crinion, J., 2005. The latest on functional imaging studies of aphasic stroke. *Curr. Opin. Neurol.* 18, 429–434.
- Raboyeau, G., De Boissezon, X., Marie, N., Balduyck, S., Puel, M., Bezy, C., Demonet, J.F., Cardebat, D., 2008. Right hemisphere activation in recovery from aphasia: lesion effect or function recruitment? *Neurology* 70, 290–298.
- Ramsey, N.F., Sommer, I.E., Rutten, G.J., Kahn, R.S., 2001. Combined analysis of language tasks in fMRI improves assessment of hemispheric dominance for language functions in individual subjects. *Neuroimage* 13, 719–733.
- Rosen, H.J., Petersen, S.E., Linenweber, M.R., Snyder, A.Z., White, D.A., Chapman, L., Dromerick, A.W., Fiez, J.A., Corbetta, M.D., 2000. Neural correlates of recovery from aphasia after damage to left inferior frontal cortex. *Neurology* 55, 1883–1894.
- Rossini, P.M., Altamura, C., Ferretti, A., Vernieri, F., Zappasodi, F., Caulo, M., Pizzella, V., Del Gratta, C., Romani, G.L., Tecchio, F., 2004. Does cerebrovascular disease affect the coupling between neuronal activity and local haemodynamics? *Brain* 127, 99–110.
- Saur, D., Lange, R., Baumgaertner, A., Schraknepper, V., Willmes, K., Rijntjes, M., Weiller, C., 2006. Dynamics of language reorganization after stroke. *Brain* 129, 1371–1384.
- Schaechter, J.D., Moore, C.I., Connell, B.D., Rosen, B.R., Dijkhuizen, R.M., 2006. Structural and functional plasticity in the somatosensory cortex of chronic stroke patients. *Brain* 129, 2722–2733.
- Schnur, T.T., Schwartz, M.F., Kimberg, D.Y., Hirshorn, E., Coslett, H.B., Thompson-Schill, S.L., 2009. Localizing interference during naming: convergent neuroimaging and neuropsychological evidence for the function of Broca's area. *Proc. Natl. Acad. Sci. U. S. A.* 106, 322–327.
- Shears, C., Hawkins, A., Varner, A., Lewis, L., Heatley, J., Twachtman, L., 2008. Knowledge-based inferences across the hemispheres: domain makes a difference. *Neuropsychologia* 46, 2563–2568.
- Snodgrass, J.G., Vanderwart, M., 1980. A standardized set of 260 pictures: norms for name agreement, image agreement, familiarity, and visual complexity. *J. Exp. Psychol. [Hum. Learn.]* 6, 174–215.
- Springer, J.A., Binder, J.R., Hammeke, T.A., Swanson, S.J., Frost, J.A., Bellgowan, P.S., Brewer, C.C., Perry, H.M., Morris, G.L., Mueller, W.M., 1999. Language dominance in neurologically normal and epilepsy subjects: a functional MRI study. *Brain* 122, 2033–2046.
- Thomason, M.E., Burrows, B.E., Gabrieli, J.D., Glover, G.H., 2005. Breath holding reveals differences in fMRI BOLD signal in children and adults. *Neuroimage* 25, 824–837.
- van Loon-Vervoorn, W.A., Heesbeen, I.M.E., Kooij, A.P., Straus, C.J., 1996. De Boston Benoemtaak. Normering voor Nederland.
- van Swieten, J.C., Koudstaal, P.J., Visser, M.C., Schouten, H.J., van Gijn, J., 1988. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 19, 604–607.
- Vink, M., Kahn, R.S., Raemaekers, M., van den, H.M., Boersma, M., Ramsey, N.F., 2005. Function of striatum beyond inhibition and execution of motor responses. *Hum. Brain Mapp.* 25, 336–344.
- Ward, N.S., Brown, M.M., Thompson, A.J., Frackowiak, R.S., 2003. Neural correlates of motor recovery after stroke: a longitudinal fMRI study. *Brain* 126, 2476–2496.
- Winhuisen, L., Thiel, A., Schumacher, B., Kessler, J., Rudolf, J., Haupt, W.F., Heiss, W.D., 2007. The right inferior frontal gyrus and poststroke aphasia: a follow-up investigation. *Stroke* 38, 1286–1292.
- Wise, R., Chollet, F., Hadar, U., Friston, K., Hoffner, E., Frackowiak, R., 1991. Distribution of cortical neural networks involved in word comprehension and word retrieval. *Brain* 114 (Pt. 4), 1803–1817.
- Xu, X.J., Zhang, M.M., Shang, D.S., Wang, Q.D., Luo, B.Y., Weng, X.C., 2004. Cortical language activation in aphasia: a functional MRI study. *Chin Med. J. (Engl.)* 117, 1011–1016.