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Dynamics of language reorganization after stroke

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Previous functional imaging studies of chronic stroke patients with aphasia suggest that recovery of language occurs in a pre-existing, bilateral network with an upregulation of undamaged areas and a recruitment of perilesional tissue and homologue right language areas. The present study aimed at identifying the dynamics of reorganization in the language system by repeated functional MRI (fMRI) examinations with parallel language testing from the acute to the chronic stage. We examined 14 patients with aphasia due to an infarction of the left middle cerebral artery territory and an age-matched control group with an auditory comprehension task in an event-related design. Control subjects were scanned once, whereas patients were scanned repeatedly at three consecutive dates. All patients recovered clinically as shown by a set of aphasia tests. In the acute phase [mean: 1.8 days post-stroke (dps)], patients' group analysis showed little early activation of non-infarcted left-hemispheric language structures, while in the subacute phase (mean: 12.1 dps) a large increase of activation in the bilateral language network with peak activation in the right Broca-homologue (BHo) was observed. A direct comparison of both examinations revealed the strongest increase of activation in the right BHo and supplementary motor area (SMA). These upregulated areas also showed the strongest correlation between *improved* language function and *increased* activation (r_{BHo} = 0.88, r_{SMA} = 0.92). In the chronic phase (mean: 321 dps), a normalization of activation with a re-shift of peak activation to left-hemispheric language areas was observed, associated with further language improvement. The data suggest that brain reorganization during language recovery proceeds in three phases: a strongly reduced activation of remaining left language areas in the acute phase is followed by an upregulation with recruitment of homologue language zones, which correlates with language improvement. Thereafter, a normalization of activation is observed, possibly reflecting consolidation in the language system.

Keywords: stroke; aphasia; recovery of function; functional MRI; longitudinal studies

Abbreviations: AAT = Aachen Aphasia Test; AABT = Aachen Aphasia Bedside Test; C = controls; CETI = Communicative Effectiveness Index; fMRI = functional magnetic resonance imaging; IFG = inferior frontal gyrus; LRS = Language Recovery Score; MCA = middle cerebral artery; SMA = supplementary motor area; SPS = spontaneous speech; TT = Token Test

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Introduction

Language is organized in a temporofrontal network (Wise, 2003; Hickok and Poeppel, 2004), which varies continuously across individuals from a left, to a bilateral to a (rarely) right dominant representation (Knecht *et al.*, 2002). This network organization may enable the brain to compensate for loss of function after aphasic stroke. Functional imaging studies of the past 10 years shed light on the patterns of reorganization in the language system after stroke. Summarizing these studies with very heterogeneous designs, methods, patients and deficits, language recovery is assumed to occur in a pre-existing temporofrontal network by an upregulation of the remaining, undamaged network. This includes a recruitment of perilesional tissue (Warburton *et al.*, 1999) as well as an involvement of homologue language areas (Weiller *et al.*, 1995; Musso *et al.*, 1999; Rosen *et al.*, 2000; Leff *et al.*, 2002; Sharp *et al.*, 2004; Crinion and Price, 2005). These studies are based on examinations in the chronic stage after stroke with more or less recovered language function; thus the observed activation describes the reorganized language network rather than the process of reorganization. Except for single-subject

studies (Leger *et al.*, 2002; Fernandez *et al.*, 2004), only few studies performed (two) repeated measurements in a patient cohort to correlate language improvement with changes of activation. In a PET study, Heiss *et al.* (1999) examined aphasic patients with frontal, temporal and subcortical lesions 2 and again 8 weeks after the stroke and concluded that efficient recovery of language function is dependent on a preserved left temporal cortex. However, activation patterns were not correlated with language recovery. Cardebat *et al.* (2003) scanned patients with different lesions of the left middle cerebral artery (MCA) territory 2 and 11 months after the stroke performing a word-generation task. They found positive as well as negative correlations between improvement of performance and task-related activation in a number of perisylvian and frontal areas bilaterally without compiling a systematic pattern of language reorganization. Using the same experimental setting in a subgroup of patients with subcortical aphasia, de Boissezon *et al.* (2005) found that an improvement of performance is correlated only with an increase of activation in the temporal lobe bilaterally. Thus, it is still a matter of debate whether increasing or decreasing activation of different left and right-hemisphere language areas in distinct phases after stroke can be attributed to improvement of language function. There is evidence from the motor system that 'overactivation' in the subacute stage after stroke (Marshall *et al.*, 2000; Calautti *et al.*, 2001) is followed by a gradual normalization of activation patterns (Ward *et al.*, 2003). We speculate that this concept of reorganization after stroke can be generalized to the language system.

The aim of our study was to investigate brain reorganization during language recovery with functional MRI (fMRI) throughout all phases after stroke. We postulated that by scanning patients repeatedly from the acute to the chronic stage and by performing detailed language assessments parallel to fMRI scanning, we would be able to identify the neural correlates underlying language recovery. Specifically, we expected (i) different overall patterns of language activation for the different phases after stroke; (ii) significant changes of activation patterns between examinations; and (iii) differential courses of activation over time within distinct left and right hemispheric language areas. To obtain further evidence for the functional relevance of activation patterns, we computed (iv) the correlation between language performance and task-related activation in the different phases of recovery as well as (v) the correlation between *changes* of activation and *improvement* of language function during the recovery process.

Methods

Subjects

Patients were recruited from the stroke unit of the Department of Neurology, University Medical Centre, Hamburg-Eppendorf. During a time period of 22 months (May 2003–February 2005), 198 patients with aphasia were screened for inclusion into the study. Inclusion criteria consisted of (i) embolic first-ever stroke of the left MCA territory; (ii) evidence of aphasia in the Aachen Aphasia Bedside Test (AABT) or in cases of less severe impairment in the Aachen Aphasia Test (AAT); and (iii) native language German. Exclusion criteria were (i) age $\geq$ 70 years; (ii) hearing deficits; (iii) inability to perform the language-task owing to severity of aphasia (see language paradigm for details); (iv) inability to tolerate a 20 min fMRI examination owing to reduced general health status; and (v) pronounced small vessel disease. Inclusion was selective because of the fact that patients had to understand the task and be able to cooperate during the 20 min fMRI session in the first days after stroke.

The age-matched control group was recruited from the volunteer database at the functional imaging laboratory NeuroImage Nord, Hamburg. Controls reported no history of neurological illness or psychiatric history and were not taking regular medication. Full written consent was obtained from all subjects. In cases of severe aphasia and/or paralysis of the right hand, detailed information was given to relatives of the patient and full written consent was completed at the time of follow-up examination. The study was approved by the local Ethics Committee.

Behavioural evaluation

It is almost impossible to use a single standardized aphasia test throughout the entire course of aphasia recovery; therefore, our aphasia test battery, which was administered at each time of MRI scanning, consisted of tests for both acute and chronic aphasia: (i) the AABT (Biniek *et al.*, 1992); (ii) the subtests repetition, written language, naming and auditory and reading comprehension of the AAT (Huber *et al.*, 1984); (iii) the Token Test (TT) subtest of the AAT; (iv) an analysis of spontaneous speech (SPS); and (v) the Communicative Effectiveness Index (CETI; Lomas *et al.*, 1989). Scores within each of these five assessments were summarized, respectively. In compiling the scores, the TT score was converted such that high scores reflected correct performance, by subtracting the obtained error score from the maximum error score possible for the TT. For an analysis of SPS, we recorded a semi-standardized interview, which was analysed according to the AAT criteria of communicative abilities, articulation and prosody, automated speech, semantic, phonemic and syntactic structure. Task performance in the scanner contributed as a separate language score (*see* language paradigm for details). Thus, there was a set of six language measures for each patient at each examination. These scores were normalized to a range of 0–1 ($score_{nor}$) and averaged into a composite score labelled the 'overall language recovery score' {$LRS = [AABT_{nor} + AAT\ (\text{without TT and } SPS_{nor}) + TT_{nor} + SPS_{nor} + CETI_{nor} + Task_{nor}]/6$} with a resulting range between 0 and 1. The LRS was taken to be a reasonable univariate index of overall level of language performance at any given time for later correlation with activation patterns (*see* imaging analysis).

Study design and fMRI language paradigm

Study design

Patients were first scanned 0–4 days post-stroke (dps) (Ex1, mean: 1.8 dps) and again ~2 weeks later before discharge or transfer to a rehabilitation facility (Ex2, mean: 12.1 dps). A follow-up examination in the chronic stage was carried out ~4–12 months post-stroke (Ex3, mean: 321 dps). Control subjects were scanned once.

fMRI paradigm

The paradigm consisted of an auditory comprehension task based on modified stimuli from a previously published study (Baumgaertner *et al.*, 2002). To create simple and highly predictable language input, sentences followed a regular pattern (i.e. a person was doing a typical job). All sentences were presented in a correct version (e.g. 'The pilot *flies* the plane') and in a version containing a semantic violation (e.g. 'The pilot *eats* the plane'). The same set of stimuli played in reverse served as control condition for the intelligible sentences. Thus, in an event-related design we presented 46 correct, 46 violated and 92 reversed sentences, which were assigned to six sessions. Order of sentences within a session was pseudo-randomized, with pairs of violated and correct sentences never occurring in the same session. Order of sessions was randomized across patients. The duration of the stimuli ranged from 1730 to 2720 ms and the interstimulus interval varied between 3000 and 6000 ms. That rate of stimulus presentation turned out to be feasible for the aphasic patients. The sentences were spoken by a female voice and recorded with the commercial software Cool Edit 2000 (http://www.mp3converter.com/cool_edit_2000.htm) with a sampling rate of 16-kHz and 16-bit resolution. Reversed speech was generated using the same software.

Task and stimulus presentation

During pre-test, it turned out that it was too difficult for patients with aphasia to use two different buttons (i.e. one for correct and one for 'false' sentences). Therefore, we reduced the task to pressing a button whenever a mistake was detected. Reversed sentences thus had to be categorized as false. The criterion for inclusion in the study was reached when a patient was able to distinguish between intelligible and reversed speech beyond chance in a training session. Stimuli were presented by the software Presentation (http://nbs.neuro-bs.com). Stimulus presentation was binaural with MR compatible headphones with the volume set at the same level for all participants, which had been tested before to be comfortable despite the scanner noise. The beginning of each session was indicated by a short announcement via headphones. During scanning, subjects wore a mask covering their eyes.

Data acquisition

fMRI was performed on a 3T Siemens TRIO system (Siemens, Erlangen, Germany). A total of 115 fMRI scans per session with 32 contiguous axial slices covering the whole brain (3 mm thickness, 1 mm gap) was acquired using a gradient echo echoplanar imaging (EPI) T_2*-sensitive sequence [repetition time (TR) = 1.83 s, echo time (TE) = 25 ms, flip angel = 70°, matrix = 64 × 64, field of view = 192 × 192 mm]. The first five volumes were discarded to allow for T_1 equilibration effects. Diffusion-weighted imaging for infarct detection in the acute stage was performed on a 1.5 T Siemens Symphony system using a spin-echo echoplanar imaging sequence (TR = 4800 ms, TE = 105.2 ms, slice thickness = 6 mm with 0.6-mm gap, field of view = 240 × 240 mm, matrix = 256 × 256). Twenty isotropic reconstructions with a *b*-value of 1000 s/mm were used to delineate infarct masks for subsequent normalization (*see* below).

Image analysis

Imaging data were analysed using Statistical Parametric Mapping (SPM2; Wellcome Department of Imaging Neuroscience; http://www.fil.ion.ucl.ac.uk/spm/; Friston, 1994; Worsley, 1995) implemented in MATLAB 6.5 (Mathworks, Natick, MA, USA).

Preprocessing

All slices were corrected for different acquisition times of signals by shifting the signal measured in each slice relative to the acquisition of the middle slice (slice timing). All volumes were then spatially realigned to the first volume in order to correct for movement. For control subjects, resulting volumes were then normalized to a standard echoplanar image template based on the Montreal Neurological Institute (MNI) reference brain, and re-sampled to 3 × 3 × 3 mm voxels (Friston *et al.*, 1995). This normalization process may result in incorrect normalization in brains with lesions. In order to take this into account for the stroke patients, a mask of the lesion was created on the base of the co-registered diffusion-weighted stroke MRI sequences (DWI). These DWI sequences revealed the early infarct with high contrast and maximal extension and were therefore suitable for delineating the infarction with a customized SPM-based tool. This mask was then incorporated into the normalization step for all patients (Brett *et al.*, 2001). All normalized images were then smoothed using a 9 mm isotropic isotropic Gaussian kernel to account for intersubject differences.

Statistical analysis

Statistical analysis was performed in two stages. In the first stage ('first level'), we used a repeated-measures single-subject fixed effects model comprising all follow-up fMRIs. Correct sentences, sentences with a semantic violation and both types played in reverse were modelled as four separate conditions. Movement parameters derived from the realignment procedure were included as covariates of no interest. The sentence onsets and the sentence durations were modelled as delta functions convolved with a canonical haemodynamic response function as implemented in SPM2. Voxel-wise regression coefficients for all conditions were estimated using least squares within SPM2 (Friston *et al.*, 1994), and statistical parametric maps of the *t*-statistic (SPM{*t*}) from each condition were generated. At this stage, we computed the contrast of each of the experimental conditions against rest, resulting in four separate contrast images for each follow-up and for each patient.

The first experimental question related to whether activation shows distinct patterns in controls (C) and patients for the different examinations (Ex1–Ex3). This question was addressed in a second-stage analysis ('second level'), for which the contrast images of the four conditions for controls and patients at each examination were entered into an ANOVA (analysis of variance) model including a correction for non-sphericity. Because we were interested in language-specific activation, we contrasted intelligible speech (correct and violated sentences) with reversed speech (e.g. contrast vector = [1 1 –1 –1]). To contrast patterns at different phases, we also looked for an interaction of time of testing with language conditions (e.g. contrast vector = [–1 –1 1 1 1 1 –1 –1]). The identical analysis was performed for the comparison of the patient group at each examination with the control group.

To quantify the course of language activation over time within distinct language areas, we computed parameter estimates for the language effect (intelligible speech > reversed speech) in the peak voxel of each activated area. This was done by extracting the data

from the respective contrast images of each subject. We performed repeated-measures ANOVAs using the SPSS 13.0 software to test for significant changes over time within each area. Data were corrected for non-sphericity using the Greenhouse–Geisser correction. In areas with significant changes over time, *post hoc* paired *t*-tests were carried out. For comparisons of patients with controls we used two-sample *t*-tests separately for each examination.

The second experimental question related to whether (i) the *degree* of language impairment at the different phases (Ex1, Ex2 and Ex3) and (ii) the *improvement* of language function at the subsequent examination (Ex2/Ex1, Ex3/Ex2 and Ex3/Ex1) were correlated with task-specific activation. These questions were addressed in six separate simple regression analyses at the second level, each consisting of one behavioural score and one contrast image for each patient. For (i), contrast images consisted of the language contrast [1 1 –1 –1] calculated in the fixed effects model at the first level for each subject at each examination. The LRSs of each examination (LRS_{Ex1}, LRS_{Ex2}, LRS_{Ex3}) were then correlated with language-specific activation, and correlation coefficients were calculated for significant voxels. For (ii), contrast images consisted of the interaction contrast (e.g. [–1 –1 1 1 1 1 –1 –1]). The improvement of language function was calculated by dividing later LRSs by earlier LRSs, resulting in improvement scores for each patient ($LRS_{Ex2/Ex1}$; $LRS_{Ex3/Ex2}$; $LRS_{Ex3/Ex1}$). The improvement in LRSs were then correlated with changes of language-specific activation (Ex2 versus Ex1; Ex3 versus Ex2; Ex3 versus Ex1). Again, correlation coefficients were calculated for significant voxels.

Statistical inference

For the language activation in controls and aphasic patients at different phases, we report regions that showed significant effects at $P < 0.05$ *corrected* for multiple comparisons across the whole brain; for comparisons of patients at different phases, for comparisons of patients with controls and for the correlation analyses, the statistical threshold was lowered to $P < 0.001$ *uncorrected* for multiple comparisons across the whole brain. The changes of language activation over time for distinct areas were tested at an overall type-I error level of 0.05. One-factor repeated-measures ANOVAs were carried out at a type-I error level of 0.05/number of regions considered, and the Bonferroni–Holm procedure (Holm, 1979) was applied to the multiple paired *t*-tests for comparison of pairs of phases post-onset separately for the different regions considered.

Results

Clinical data

The control group comprised 11 male and three female subjects, aged between 18 and 66 years [mean (SD): 48.6 (13.9) years]. From a total of 198 consecutively screened aphasic stroke patients, 14 met our inclusion criteria and were recruited [range: 16–68 years, mean (SD): 51.9 (14.2), 11 male and three female]. One patient completed the first and second fMRI but dropped out afterwards because of health problems; one patient failed to perform the task in the scanner because he experienced interference with the scanner noise and two patients with fluent aphasia terminated the scanning session early because they could not cope with the test situation. All other patients we screened ($n = 180$) were excluded before scanning. The reasons for exclusion were (i) severity of aphasia (too mild/too severe; $n = 49/11$); (ii) reduced general health status ($n = 20$); (iii) previous infarcts ($n = 11$); (iv) large vessel disease with haemodynamic infarctions ($n = 6$); (v) aetiology (intracerebral haemorrhage, tumour, dementia; $n = 29$); (vi) age and small vessel disease ($n = 20$); (vii) hearing deficits ($n = 3$); (viii) German not the first language ($n = 7$); (ix) neuropsychological impairments other than aphasia ($n = 13$); and (x) other (contraindications for MRI, cooperation, technical problems; $n = 11$).

Patient characteristics are listed in Table 1. The site of cerebral infarction was determined from the diffusion-weighted MRI examination 1–4 days post-stroke. All patients were found to have infarcts of the MCA territory. Four patients had frontal infarcts (two with additional temporoparietal lesion), five patients had temporoparietal infarcts (two with additional subcortical lesion), four had striatocapsular infarcts (two with additional small polytope cortical lesions) and one patient (patient 14) had a frontal and parietal cortical infarction (Table 1 and Fig. 1).

Initial MR angiography and perfusion-weighted imaging revealed MCA-stem occlusion in six patients and MCA-branch occlusion in eight patients. Systemic thrombolysis was performed in nine patients. These nine patients showed complete recanalization in the MRI-follow-up examination at the time of the first fMRI. Four patients were examined by transcranial colour-coded duplex sonography and were found to have equal flows in both MCA before fMRI examination (Table 1). One patient (patient 11) showed persistent MCA occlusion one day after the stroke, and complete re-canalization was demonstrated in the first 7 days post-stroke. Therefore, it remains unclear whether there was a persistent MCA occlusion at the time of the first fMRI examination in this patient.

Behavioural results

Twelve controls and 12 patients were right-handed with a score > 90 in the Edinburgh Handedness test. Both the healthy and the stroke group contained a left-handed person (both with a score of 0) and a converted left-handed person (scores of 35 and 70). All controls were able to perform the task adequately [mean task performance = 98, range = 96–100 (% correct)].

At admission, nine patients presented with non-fluent aphasia and five patients with fluent aphasia. Using the classification criteria of the AAT, at the time of the last fMRI, six patients had completely recovered, four patients showed persistent minimal language impairment and four were still classified as aphasic (three anomic and one global).

Concerning the LRS, patients showed different degrees of language impairment in the acute phase ($LRS_{mean} = 0.44$;

Table 1 Patient characteristics

Patient	Age (years)	Sex	Handedness #	fMRI examinations (days post-stroke)			Initial NIHSS	Site of lesion (L MCA territory)	Vessel occlusion	Thrombolysis (min post-stroke)	Recanalization Day 1
				Ex1	Ex2	Ex3					
01 HA	65	M	35	2.2	15	376	8	Frontal	MCA- branch	100	Complete*
02 RD	58	F	95	1.1	15	397	13	SC	M1	300	Complete*
03 RL	55	M	100	1.8	12	396	17	Frontal + parietal	M1	300	Complete*
04 IK	48	M	100	1.2	8	513	18	SC	M1	120	Complete*
05 PW	65	M	100	0.9	13	457	13	SC + cortical	M1	No	MCA+
06 HS	55	M	100	1.2	12	352	3	Temporal	MCA- branch	No	MCA+
07 MM	37	M	90	1.9	10	295	7	Parietal + SC	MCA- branch	175	Complete*
08 AK	57	M	100	1	10	188	3	Temporal	MCA- branch	180	Complete*
09 TW	16	M	0	1.1	11	224	16	Frontal	MCA- branch	130	Complete*
10 KO	43	M	100	3	9	323	16	Temporoparietal	MCA- trif	100	Complete*
11 BN	39	F	100	4	16	253	21	Temporoparietal + SC	M1	No	Persistent*
12 DR	64	F	100	2.5	13	137	7	SC + cortical	M1	180	Complete*
13 PK	68	M	100	0.3	3	102	7	Frontal + temporal	MCA- branch	No	MCA+
14 LJ	57	M	100	4	15	374	2	Frontal + parietal	MCA- branch	No	MCA+

M = male, F = female; # Edinburgh-Handedness-test: 0 = left-handed in 10 items, 100 = right-handed in 10 items; NIHSS = National Institute of Health Stroke Scale: no deficit = 0, maximal deficit = 34; L = left, MCA = middle cerebral artery, MCA-trif = trifurcation of the MCA, SC = striatocapsular, M1/M2 = proximal/distal part of the MCA stem; *indicates recanalization was proven in MRI (MR angiography and/or perfusion-weighted imaging), MCA+ indicates M1 was detectable in colour-coded transcranial duplex sonography.

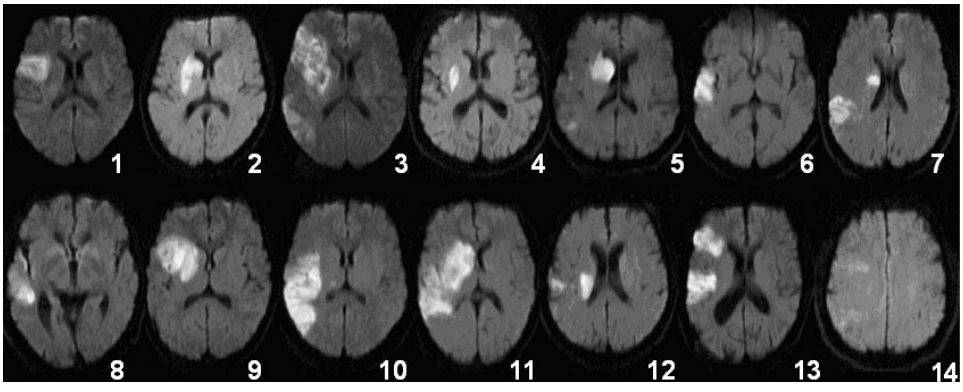

Fig. 1 Site of infarction of 14 patients. Axial diffusion-weighted MRI scans at the level of maximum infarct volume for each aphasic patient. Left side of the figure corresponds to the left side of the brain.

LRS_{range} = 0.11–0.81), improved significantly in the subacute phase (0.71; 0.33–0.92, $P < 0.001$) and showed further significant improvement in the chronic phase (0.91; 0.66–1.0, $P < 0.001$). In a one-factorial repeated-measures ANOVA, LRSs were different across examinations 1–3 [$F(2, 26) = 57.85$; $P < 0.001$]. Individual and mean language recovery curves are displayed in Fig. 2; scores of all tests at each examination are listed in Table 2; scores obtained in the AAT subtests are listed in Table 3 to characterize and quantify the patients' language performance with respect to different linguistic components at each examination.

All patients received standard language therapy throughout the whole observation period with at least 3 weeks as in-patient at a neurological rehabilitation clinic.

fMRI results

Language activation: control group and aphasic patients in different phases

The control group showed bilateral left lateralized language activation when analysed with the random effects model. The strongest activation was observed in posterior parts of the left superior and middle temporal gyrus (Wernicke's area), pars orbitalis and triangularis of the left inferior frontal gyrus (IFG) (including the anterior part of Broca's area) with dorsal extension to the premotor cortex (PMC), right insular cortex and right IFG (Broca-homologue), anterior parts of the left temporal lobe and the left fusiform gyrus. Additional activation was in the left occipitoparietal region and supplementary motor area (SMA, Fig. 3A and Table 4).

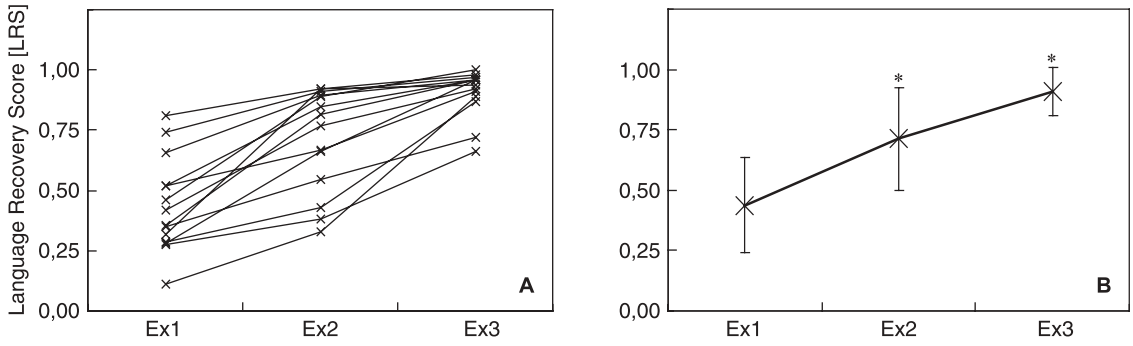

Fig. 2 Individual and mean Language Recovery Curves of 14 patients. (**A**) Plots of normalized overall LRS for each patient across the three sessions. Each patient had six separate language performance scores recorded at each fMRI session (comprehension task, AABT, AAT, TT, SP, CETI), creating six specific recovery curves per patient. The overall LRS represents a composite score, by normalizing and averaging the six language performance scores at each time. (**B**) Mean Language Recovery Curve; asterisk (*) indicates significant improvement (paired *t*-test, two-tailed).

Table 2 Scores of the aphasia test battery

Patient	Task (0–100)			AABT (0–240)			AAT (0–480)			TT (0–50)			SPS (0–30)			CETI (0–16)		
	Ex1	Ex2	Ex3	Ex1	Ex2	Ex3	Ex1	Ex2	Ex3	Ex1	Ex2	Ex3	Ex1	Ex2	Ex3	Ex1	Ex2	Ex3
01 HA	45	82	94	152	195	240	313	344	439	13	15	45	15	16	23	10	13	15
02 RD	10	89	95	135	212	240	288	384	455	11	41	47	14	21	29	3	13	16
03 RL	8	8	94	109	147	240	219	327	425	2	8	40	13	16	24	4	8	13
04 IK	10	80	95	168	214	240	214	366	470	5	6	50	5	20	26	3	11	15
05 PW	8	98	98	123	240	240	221	415	480	17	48	50	8	22	27	4	16	16
06 HS	5	88	94	181	238	240	287	393	441	5	16	39	21	23	27	5	13	15
07 MM	92	97	95	188	234	240	271	429	452	37	45	49	17	21	27	6	15	16
08 AK	94	97	97	240	240	240	410	446	454	43	43	44	21	22	26	8	16	16
09 TW	10	96	98	217	240	240	321	448	480	6	44	50	20	24	30	5	12	16
10 KO	10	83	98	68	142	216	36	85	419	2	14	46	5	13	22	2	3	13
11 BN	89	93	93	118	157	225	0	63	332	0	5	4	1	7	17	4	4	13
12 DR	10	76	94	143	218	240	262	307	424	12	11	40	15	17	20	2	3	9
13 PK	10	83	78	203	224	240	316	362	454	7	18	50	23	23	27	10	13	14
14 LJ	97	98	95	235	240	240	345	451	469	16	43	46	25	24	29	12	14	16
MEAN	36	83	94	163	210	237	250	344	442	13	26	43	15	19	25	6	11	15

Task indicates task performance in the scanner; AABT = Aachen Aphasia Bedside Test; AAT = Aachen Aphasia Test including subtests of repetition, written language, confrontation naming and comprehension; TT = Token Test; SP = analysis of spontaneous speech; CETI = Communicative Effectiveness Index.

The aphasic patients in the acute stage (Ex1) revealed only little language activation in the left IFG with two peaks in the pars orbitalis and triangularis. In the subacute stage (Ex2), there was strong bilateral activation in the language network with the highest peak of significance in the right IFG and adjacent parts of the insular cortex. In the chronic stage (Ex3), language activation returned to a more normal pattern with a re-shift of peak activation to the left hemisphere with highest activation in the left IFG, left temporal gyrus, SMA and right IFG (Table 4, Fig. 3A).

In a direct comparison of the subacute with the acute stage (Ex1 < Ex2), the strongest increase of activation was observed in the right IFG including the right insular cortex and SMA ('early upregulation'). The comparison of the subacute and chronic stage (Ex2 > Ex3) revealed a decrease of activation in the right Broca-homologue, which was evident after lowering the statistical threshold to a value of $P < 0.005$ uncorrected for multiple comparisons across the whole brain (Fig. 3B). In the comparison of the chronic with the acute stage (Ex3 > Ex1), an increase of activation was detectable in the right IFG and SMA as well as in left language areas (Table 5, 'late upregulation'). There were no language-specific activation changes in the comparisons of Ex1 > Ex2, Ex1 > Ex3 and Ex3 > Ex2.

A comparison of controls with patients in the acute phase (Ex1) revealed higher activation for controls in left- and right-hemisphere language areas. The comparison of controls with patients in the subacute phase showed higher activation for patients in the right and left IFG and SMA. The comparison of controls and patients in the chronic stage did not show any significant differences (no figure, Table 6).

Table 3 Subtest results of the AAT

	Type of aphasia			Repetition (0–150)			Written language (0–90)			Naming (0–120)			Auditory comprehension (0–60)			Reading comprehension (0–60)		
	Ex1	Ex2	Ex3	Ex1	Ex2	Ex3	Ex1	Ex2	Ex3	Ex1	Ex2	Ex3	Ex1	Ex2	Ex3	Ex1	Ex2	Ex3
01 HA	II/fluent	II	0-I	120	133	147	65	70	85	78	85	106	20	23	53	30	33	48
02 RD	II/non-fluent	I	0	137	148	150	35	55	84	54	95	117	38	44	55	24	42	49
03 RL	II–III/non-fluent	II	0-I	91	144	147	61	60	88	42	66	106	36	33	45	19	24	39
04 IK	II–III/non-fluent	I-II	0	52	110	150	35	70	90	36	98	115	40	39	56	51	49	59
05 PW	II/non-fluent	0-I	0	72	115	150	41	78	90	48	117	120	39	51	60	36	54	60
06 HS	II–III/fluent	I-II	I-anomic	85	117	130	37	80	87	85	100	116	16	43	53	21	53	55
07 MM	II/non-fluent	0-I	0	88	133	141	41	74	83	50	111	113	46	57	58	46	54	57
08 AK	I/fluent	0	0	127	139	139	74	82	84	108	113	114	49	56	57	52	56	60
09 TW	II/non-fluent	I	0	130	150	150	55	88	90	70	106	120	30	47	60	36	57	60
10 KO	III/non-fluent	III	I-anomic	0	5	127	0	0	74	0	0	104	26	35	58	10	28	56
11 BN	III/non-fluent	III	II-global	0	6	99	0	0	17	0	0	48	0	30	43	0	27	41
12 DR	II/fluent	II	I-anomic	139	145	141	25	56	80	47	49	107	26	33	41	25	24	45
13 PK	II/non-fluent	I-II	0	93	112	142	58	55	84	86	103	117	38	51	56	41	41	55
14 LJ	I–II/fluent	0	0	111	135	144	64	89	90	71	115	118	53	56	60	46	56	57
MEAN				89	112	140	42	61	80	55	83	109	33	43	54	31	43	53

0, no aphasia; I, mild aphasia; II, moderate aphasia; III severe aphasia as indicated by the AAT.

To examine the course of language-specific activation over time in defined language areas, overall language-specific activation of the patient group was computed across the three fMRI exams. Six peak voxels in the resulting activation pattern were identified in the left IFG (pars orbitalis and triangularis), left middle temporal gyrus, right insular cortex, right IFG (pars triangularis) and SMA (Fig. 3C). Plots of the parameter estimates (speech > reversed speech) for each of the six identified areas revealed different language recovery curves: left IFG and left posterior middle temporal gyrus showed a monophasic course with continuous increase of activation, whereas right insular cortex, right IFG and SMA showed a biphasic curve with an early increase and later decrease of activation. A two-factorial repeated-measures ANOVA with the factors time (Ex1-3) × region revealed that the course of activation over time was heterogeneous in the six tested regions (significant interaction effect region × time; $F(10, 130) = 5.21$, $P < 0.001$). Therefore, the effect of time was tested for each region separately with a one-factorial repeated-measures ANOVA and subsequent type-I error-adjusted paired *t*-tests. These further analyses showed that language-specific activations were significantly different when comparing Ex1, Ex2 and Ex3 in all tested regions ($P < 0.05$) except for the right IFG ($P = 0.086$). *Post hoc* paired *t*-tests (two-tailed) showed that the early increase of activation (Ex1 versus Ex2) was significant in all identified regions except for the pars triangularis of the left IFG. The late increase (Ex1 versus Ex3) was significant in all left-hemisphere regions and the right insular cortex. The decrease of activation (Ex2 versus Ex3) was significant only in the right insular cortex and right IFG. After Bonferroni–Holm correction for multiple comparisons ($k = 18$), only the early increase in the right insular cortex and SMA, and the late increase in the left middle temporal gyrus remained significant ($P < 0.0028$). In addition to the patient data, language-specific activation of the controls was added to the plots for visual comparison. *Post hoc* two-sample *t*-tests (two-tailed) of controls (C) and patients at the acute stage (Ex1) showed significantly higher activation for controls in the left middle temporal and right IFG ($P < 0.05$); comparison with patients at the subacute stage (Ex2) showed a trend towards higher activation for patients in the right insular cortex ($P < 0.064$); comparisons with patients at the chronic stage (Ex3) revealed no significant differences to controls in the depicted voxels.

Correlation of language impairment and language activation at different phases

In three separate linear regression analyses, the LRS of each patient at each time of testing was correlated with the respective language activation. In the acute phase, there was a strong positive linear correlation of LRS_{Ex1} with language activation with two large clusters in the left IFG ($r = 0.93$, $P < 0.001$) and SMA ($r = 0.88$, $P < 0.001$), and a small cluster in the pars triangularis of the right IFG ($r = 0.79$, $P < 0.001$, Tab. 4A). Put differently, the better the initial language performance,

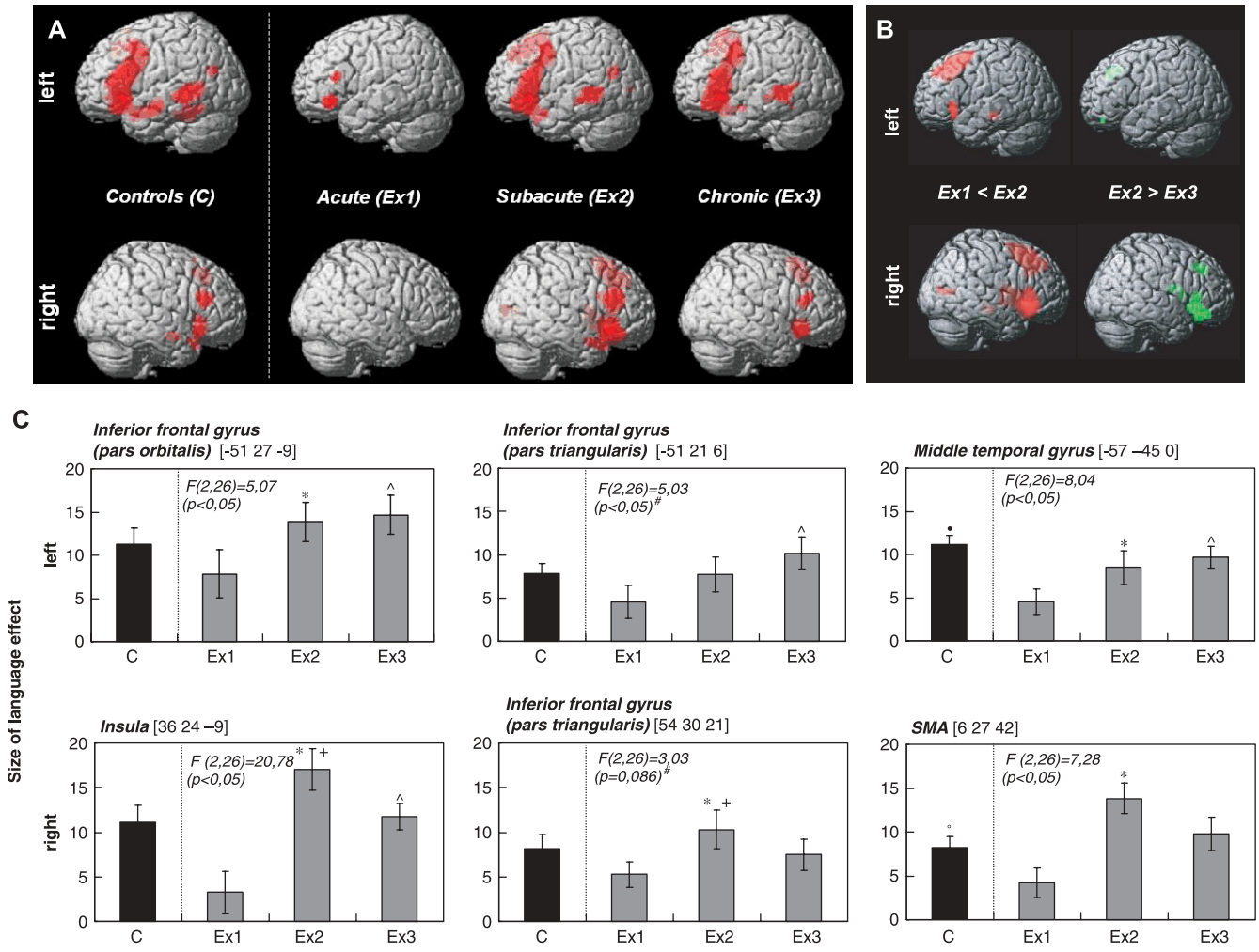

Fig. 3 (**A**) Three phases of language reorganisation. Language activation in controls and aphasic patients in the acute, subacute and chronic stage after stroke. Results of the group analyses of 14 controls and 14 patients repeatedly measured in the acute, subacute and chronic stage after stroke. Results are surface-rendered onto a canonical brain with the left side in the upper and the right side of the brain in the lower row. Red areas represent all voxels, which are significant at $P < 0.05$ (corrected for multiple comparisons). (**B**) Up- and downregulation in the language network. Direct comparison of Ex1 < Ex2 ($P < 0.05$ corrected) and Ex2 > Ex3 ($P < 0.05$ uncorrected for display purposes). (**C**) Plots of parameter estimates (language effect) for the peak voxel of six different regions. Plots of parameter estimates (intelligible language > reversed language) in the peak voxel of six left- and right-hemisphere regions. C, controls; Ex1–3, examinations 1–3. To test whether activations in each region are different at examinations Ex1–Ex3, a repeated-measures ANOVA was used and *F*-values with corresponding *P*-values were computed. #*P*-values are corrected for non-sphericity. *Post hoc t*-tests were performed to test for changes (i) between examinations (paired *t*-tests) and (ii) between examinations and controls (two-sample *t*-tests). *t*-tests (two-tailed) significant at $P < 0.05$: *Ex1 versus Ex2, +Ex2 versus Ex3, ^Ex1 versus Ex3, •C versus Ex1; ◦C versus Ex2, C versus Ex3 not significant in any region.

the higher the activation in these areas. In three patients, the identified peak in the left IFG was located in the infarct; therefore, the corresponding effect sizes were low (marked black in the plot). There was no negative correlation between LRS and language activation in the acute phase, and neither positive nor negative correlations in the subacute and chronic stage.

Correlation of improvement of language performance and consecutive changes of language activation

Previous analyses of the behavioural data had shown significant improvements of language function between the three examinations, whereas analyses of the changes in language activation had shown increases in activation between Ex1 on the one hand and Ex2 and Ex3 on the other, and a decrease in language activation from Ex2 to Ex3. Thus, three further linear regression analyses were carried out between these language improvements and concurrent changes of activation. Only the correlation of early *relative improvement* of language function ($LRS_{Ex2/Ex1}$) and *increase* of language activation (Ex2 > Ex1) was significant. This correlation revealed strong activation in the SMA ($r = 0.92$, $P < 0.001$) and right IFG including right insular cortex ($r = 0.88$, $P < 0.001$; Fig. 4B). In other words, the higher the initial improvement, the higher the increase of activation in these

Table 4 Language activation of controls and aphasic patients in the acute, subacute and chronic stage after stroke

Region	Side	MNI			
		x	*y*	*z*	*t*
Controls (*n* = 14)					
Middle/superior temporal gyrus (posterior part)	L	−60	−45	3	8.92
IFG,	L				
Pars triangularis		−42	12	24	8.87
Pars orbitalis/insula		−45	24	−6	6.26
Insula	R	33	24	−6	7.62
IFG, pars triangularis	R	54	27	21	5.53
Middle temporal gyrus (anterior part)	L	−57	−9	−15	7.22
Inferior temporal gyrus (fusiform gyrus)	L	−42	−45	−18	6.38
Middle occipital gyrus	L	−36	−66	24	6.15
Medial frontal gyrus (SMA)	M	9	18	48	6.09
Patients (*n* = 14) Examination					
Examination 1: Acute Phase					
IFG	L				
Pars orbitalis		−51	36	−9	5.22
Pars triangularis		−48	27	18	4.72
Examination 2: Subacute Phase					
IFG	R				
Pars orbitalis/insula		36	24	−9	10.51
Pars triangularis		54	30	21	6.66
Medial frontal gyrus (SMA)	M	6	27	42	9.12
IFG	L				
Pars orbitalis/insula		−51	30	−9	8.23
Pars triangularis		−48	24	18	7.59
Middle temporal gyrus	L				
Posterior part		−63	−39	0	6.66
Angular gyrus		−39	−63	24	5.31
Anterior part		−51	12	−21	5.24
Superior temporal gyrus anterior part	R	48	18	−27	6.06
Examination 3: Chronic Phase 1					
IFG	L				
Pars orbitalis/insula		−51	27	−9	8.32
Pars triangularis		−48	27	18	7.48
Middle temporal gyrus	L				
Posterior part		−57	−45	0	7.66
Anterior part		−57	0	−15	4.97
Medial frontal gyrus (SMA)	M	−6	15	51	7.53
IFG	R				
Pars orbitalis/insula		33	21	−9	7.02
Pars triangularis		51	30	21	5.01

Peak voxels for the language contrast (intelligible speech > reversed speech) in 14 healthy control subjects and 14 patients repeatedly measured in the acute, subacute and chronic stage after stroke ($P < 0.05$, corrected for multiple comparisons across the whole brain, $t > 4.71$). MNI indicates coordinates that refer to the Montreal Neurological Institute reference brain; SMA = supplementary motor area; R = right; L = left.

areas. Using the early *absolute improvement* of language function ($LRS_{Ex2\text{-}Ex1}$) as variable, the same analysis showed a similar pattern of activation, but results were less significant.

Table 5 Comparison of language activation at different phases of recovery

Region	Side	MNI			
		x	*y*	*z*	*t*
Examination 2 > 1 (early increase)					
IFG, pars orbitalis and insular	R	33	21	−9	6.28*
SMA	M	9	18	48	4.56
Insula	L	−33	24	−3	3.36
Examination 2 > 3 (decrease)					
Middle occipital gryus	R	36	−84	9	3.36
IFG, pars orbitalis	R	36	30	−12	2.74°
Examination 3 > 1 (late increase)					
IFG, pars orbitalis and insula	R	33	21	−9	4.43
IFG, pars orbitalis	L	−42	21	−6	3.73
SMA	M	−6	9	57	3.57
Inferior temporal gyrus	L	−48	−48	−12	3.17

Coordinates represent voxels significant at $P < 0.001$ uncorrected for multiple comparisons across the whole brain ($t > 3.14$); *$P < 0.05$ corrected ($t > 4.71$); °$P < 0.005$ uncorrected ($t > 2.61$).

Table 6 Comparison of aphasic patients with controls

Region	Side	MNI			
		x	*y*	*z*	*t*
Controls > Examination 1					
Inferior temporal gyrus	L	−42	−45	−18	5.15
IFG, pars trinagualris	L	−42	12	24	4.46
IFG, pars orbitalis/insula	R	33	24	−3	4.31
Superior temporal gyrus	L	−63	−51	3	4.31
Middle temporal gyrus	L	−57	−12	−12	4.28
IFG, pars orbitalis/insula	L	−30	21	−3	4.28
Examination 2 > Controls					
IFG	R	36	30	−12	3.56
SMA	M	−9	33	42	3.27
IFG, pars orbitalis/insula	L	−45	36	−9	3.08°

Coordinates represent voxels significant at $P < 0.001$, uncorrected for multiple comparisons across the whole brain ($t > 3.14$); °$P < 0.005$ uncorrected ($t > 2.61$).

Discussion

This is the first functional imaging study examining patients during all phases of language recovery, beginning in the acute stage during the first days after stroke and following up until the chronic stage. Patients were examined three times with fMRI, performing the same language comprehension paradigm at each time of scanning. This allows us to describe the process of language reorganization and to delineate a systematic model with three phases of language recovery (Fig. 5).

Contrasting speech with reversed speech evoked an activation of the areas crucial to language comprehension, which is consistent with previous studies on language

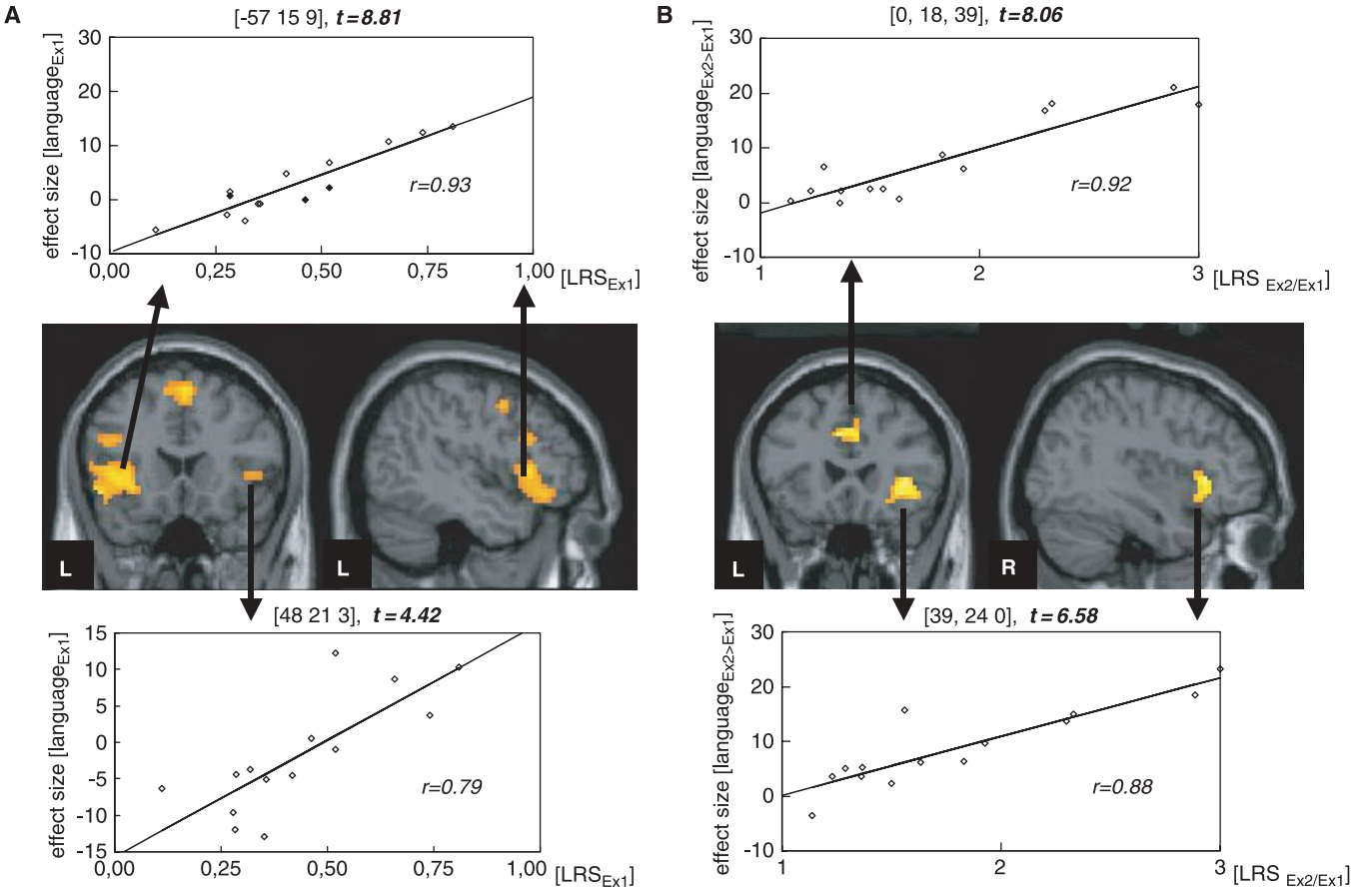

Fig. 4 Correlation of initial impairment and language activation (**A**) and early improvement and increase of language activation (**B**). **A:** Results of the simple regression analysis of initial language impairment (LRS_{Ex1}) and language activation (contrast image = [1 1 −1 −1]). All voxels are significant at $P < 0.001$ (uncorrected for multiple comparisons, $t > 3.93$). At [−57 15 −9], peak is located in infarcted tissue in three patients (marked with filled claver). **B:** Results of the simple regression analysis of early language improvement ($LRS_{Ex2/Ex1}$) and increase of activation (contrast image = [−1 −1 1 1 1 1 −1 −1]). All voxels are significant at $P < 0.001$ (uncorrected for multiple comparisons, $t > 3.93$).

comprehension with PET and fMRI (Scott *et al.*, 2000; Crinion *et al.*, 2003; Scott and Wise, 2004; Gitelman *et al.*, 2005). This activation was more or less detectable bilaterally in all healthy controls. The strong bilateral frontal activation and activation of the SMA may partly be explained by the executive component of the task with a forced-choice decision and a motor response; pure listening to the sentences without any judgement might have resulted in less frontal activation. This was demonstrated by Crinion *et al.* (2003), who contrasted the implicit comprehension of simple narrative speech with listening to reversed versions of the narratives. The result showed that normal comprehension, free of particular task demands, engages regions distributed between the two temporal lobes, more widely on the left. The only frontal contribution in their study was confined to the left ventrolateral prefrontal cortex. In our study, all of the items in the control condition ('reversed speech') required a button press, whereas in the 'intelligible speech' conditions button presses were required for half of the items only (i.e. the violated sentences). Therefore, executive activation due to decision making and the motor response should be minimized by contrasting speech with reversed speech.

The repeated fMRI examinations of patients in the acute, subacute and chronic stage revealed three distinct phases of language recovery. In the acute phase, weak activation of the left IFG was observed. At this time, patients' speech was disrupted after the stroke, resulting in a low LRS in the aphasia exams. At the next examination, ∼2 weeks later, fMRI revealed strong upregulation of the entire language network with the highest increase of activation in the right IFG. Parallel language testing showed significant improvement of language performance in the same time period. In the chronic stage, months after the stroke, fMRI activation was normalized and peak activation 're-shifted' to the left hemisphere. This normalization of activation was associated with further significant improvement of language impairment resulting in an almost complete recovery in most patients.

Beyond this overall time course of language activation, left- and right-hemisphere language areas revealed different patterns of progression of language activation across

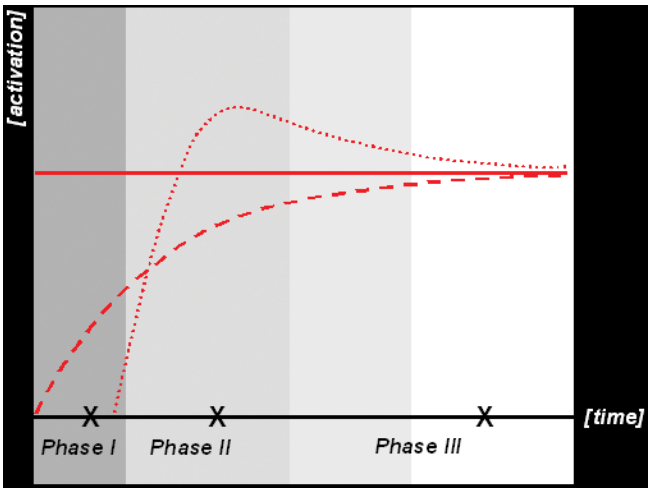

Fig. 5 Model with three phases of language recovery after stroke. Three phases of language recovery: Acute Phase I characterized by loss of function; Subacute Phase II by an upregulation of the language network; Chronic Phase III by a consolidation and normalization of activation. Diagrammed activation of controls (—), left language areas (---) and right language areas of aphasic patients (···). Crosses (X) indicate time of fMRI (examinations 1, 2 and 3).

examinations. The right IFG and SMA showed a clear biphasic course with an early strong increase and a later decrease of activation, while left-hemisphere language areas showed a monophasic course with a continuous increase of activation during recovery. This model of language recovery with three distinct phases of fMRI activation is new. However, our observations reflect the optimal course of language recovery after stroke derived from a highly selected patient group, all able to perform early fMRI and all presenting with an embolic first-ever stroke hitting an otherwise 'healthy' brain with high plastic potential.

In earlier longitudinal studies on language recovery, the acute stage had been neglected (Heiss *et al.*, 1999; Leger *et al.*, 2002; Cardebat *et al.*, 2003; Fernandez *et al.*, 2004; de Boissezon *et al.*, 2005). For example, Fernandez *et al.* (2004) showed activation of homotopic right language areas in a patient with conduction aphasia 1 month after stroke, whereas large perilesional left involvement occurred later after 12 months. This fits well with our phase-model; the study by Fernandez *et al.* may tap into the second, 'subacute' phase with a recruitment of right language homologues and then into the third 'chronic' phase with an increase of left perilesional activation. The momentum of the early upregulation in the language network may have not been captured by their study. The question remains as to which conclusions can be drawn from language-related activations in the acute phase, only hours and days after the stroke. At this time, only little activation in the left IFG had been observed. Looking at individual data, only 6 of the 14 patients showed activation in left language areas. The correlation of initial language impairment and language activation revealed that better language performance was linked to higher activation in the left IFG. This is the key message of the early activation in the acute stage: remaining language ability directly after stroke is related to left IFG activation. Many reasons for impaired language performance and a lack of early activation can be thought of: (i) a loss of function and activation is directly caused by the infarction itself; (ii) the infarction causes a disruption of the language network, that is, infarction results in a dysfunction (and missing activation) in remote areas in terms of diaschisis (Monakow, 1906; Price *et al.*, 2001); (iii) preceding hypoperfusion causes neuronal dysfunction in tissue that cannot be activated despite missing infarction on MRI (Weiller *et al.*, 1993; Garcia *et al.*, 1996); (iv) preceding hypoperfusion leads to a failure of cerebral autoregulation, thus a lack of activation is due to a failure of blood oxygenation level-dependent (BOLD) response rather than a functional deficit (Krainik *et al.*, 2005); and finally (v) persisting hypoperfusion with a prolonged penumbra is the reason for functional impairment (Hillis *et al.*, 2002; Reineck *et al.*, 2005). In a random effects model with a heterogeneous patient group in which each individual presents with an infarction of a different part of the MCA territory, activation patterns at the different phases reflect an 'average pattern' of the group, and each of the above-mentioned mechanisms may contribute to the effect, especially in the acute phase. However, in our study, all patients except one showed complete recanalization in MR angiography and perfusion-weighted imaging or ultrasound before the first fMRI examination. Therefore, persisting vessel occlusion with a prolonged penumbra as the reason for impaired function and reduced activation in the acute phase can be ruled out in our study.

The upregulation of the entire language network and especially of the right inferior frontal cortex must be regarded as an early mechanism, which begins hours to days after the stroke. The great impact of this effect may first be explained by the fact that the right inferior frontal cortex was intact in all patients and thus could be activated in all patients. There is a long debate in the literature of language recovery [for review, *see* Price and Crinion (2005)] concerning the functional relevance of right language activation and especially right inferior frontal activation. On the one hand, this activation was interpreted as a 'maladaptive strategy', that is, this activation reflects disinhibition rather than functioning of right frontal areas due to infarction of left frontal areas (Naeser *et al.*, 2005). Application of slow, inhibitory repetitive transcranial magnetic stimulation (rTMS) (1 Hz) to the pars triangularis of the right IFG (anterior portion of the Broca-homologue) caused an improvement of picture naming in four patients with non-fluent chronic aphasia, suggesting that a suppression of this area modulates the prefrontal/temporoparietal connections relevant for picture naming (Naeser *et al.*, 2005). However, in contrast to our study, Naeser's study was done in the chronic stage, possibly capturing a maladaptive mechanism that had manifested itself over the course of years. Disinhibition of the undamaged hemisphere in the acute phase after stroke was also observed in the motor system by means of transcranial magnetic

stimulation (Liepert *et al.*, 2000). On the other hand, right inferior frontal activation was attributed to functional recovery by demonstrating a worsening of aphasia after targeting this activated area with 4 Hz rTMS (Winhuisen *et al.*, 2005).

In our study, the early improvement of language function was highly correlated with an increase of activation in the right IFG. This correlation provides further evidence for the functional significance of right frontal areas in recovery from aphasia. Whether the temporary increase in the right IFG represents real right-hemisphere language processing and/or reflects increased traffic in a relay station remains unclear. The latter possibly may be important, as the Broca-homologue may have to relay most of the information between the language-relevant areas in both hemispheres. Therefore, this view may be favoured if we assume that the BOLD signal mainly reflects neuronal activity triggered by post-synaptic input. Mechanistically, the right inferior frontal activation may reflect reduced trans-hemispheric inhibition due to the altered left-hemispheric functioning. With gradual recovery of activation in left-hemispheric language areas (monophasic activation course), these areas may exert their inhibitory influence again, resulting in a decrease of right frontal signal (biphasic activation course). An alternative explanation from a more cognitive point of view may be derived from the assumption that frontal activation in attentional and control areas depends on the level of task performance and practice (Kelly and Garavan, 2005). Little or no right-hemisphere activation in the very acute stage may reflect that overall language activation is reduced and the demand for cognitively controlling language performance is low. In the intermediate stage, the language areas are recovering but are working at a suboptimal level such that there is a major requirement for cognitive control, reflected in larger-than-normal bilateral activations in the inferior frontal regions. Finally, in the third stage, with continuously improving language performance language function increasingly engages classic language-specific perisylvian areas of the left hemisphere, resulting in a lower requirement for control from these frontal systems (Duncan, 2001).

We postulate that this transition into the third phase is restricted to patients with a potential of left-hemispheric recovery with a return of left (perilesional) function after the acute injury. Consequently, patients with extensive disruption of left language zones remain in the second phase because (i) intensive right-hemisphere activation is necessary to compensate for the stroke and (ii) the inhibitory influence of left language areas remains absent. This persistence of right frontal activation may indicate a chronic disturbance of hemispheric balance, which might indeed be disadvantageous for language processing (Naeser *et al.*, 2005). However, these suggestions should be investigated in detailed longitudinal studies of patients with different degrees of impairment and different sites of lesion, in single-subject studies as well as in subgroup analyses.

Finally, some remarks have to be added concerning the study design. First, the control subjects were scanned only once. Normal subjects tend to show a steady decrease of activation with each scan of the same task, owing to practice (Henson, 2003). Two points may be made with respect to the need of repeated measurements of healthy subjects: (i) the practice effect is particularly large when subjects find the task difficult and demanding (Johnson, 2000). In our study, control subjects performed the task nearly error-free, demonstrating low task demands; thus the effect of practice can be assumed to be weak for healthy subjects. However, the comparison of patients at Ex3 with control subjects *measured a third time* may have resulted in 'higher' activation for patients; actually, we found no significant differences for this comparison. (ii) Effects of practice are greater when there is a shorter lag between the trials. In our study, the short interval was between the acute (Ex1) and subacute (Ex2) examination. If practice had influenced our findings, then we would have expected a decrease of activation between Ex1 and Ex2, which is quite the opposite of what was actually found. Moreover, in the longer period from the subacute to the chronic stage, we observed a differential evolution of activation in left and right language areas rather than an overall decrease of activation typical for repetition priming. Overall, practice may be a contributing factor, but the changes after a stroke, especially in the first phase, are so rapid and massive that they should exceed any practice effects. Second, because of the imposed selection and exclusion criteria with patients being able to sustain an fMRI session during the first days after stroke, a considerable number of aphasic patients screened during the study period were rejected. Thus, the results are limited to somewhat less severely impaired patients who were clearly aphasic at the first exam but were able to understand the task. Therefore, it remains unclear whether our results are specific to this level of aphasia severity or may be generalized to more severe types of aphasia. Third, a greater variance in performance with inclusion of more patients with poor recovery at Stage 3 probably would have facilitated the correlation analyses of activation and language performance in the chronic stage.

The model of three phases of language recovery may have implications for future concepts of aphasia treatment. The early (compensatory) upregulation of the language network after vessel recanalization could be utilized for an early unspecific language therapy mostly consisting of stimulation techniques, because all potential areas of language processing are activated with the goal to compensate the deficit. The other implication concerns the chronic phase of language recovery. We propose that an intensive training in the chronic stage may evoke recurrent phases of upregulation in the language network as the neural correlates of a systematic model-orientated therapy.

Conclusions

We examined aphasic patients with fMRI performing a comprehension task throughout three major phases after stroke. At each time of fMRI, detailed language examinations were

carried out. Thus, we were able to relate fMRI activation patterns to language recovery. We have suggested a model with three phases of language recovery, which might be transferable to other systems as a general concept of reorganization of function after focal brain damage. Correlation analysis of early language activation and language performance corroborated that intact *left* language areas are important for early language processing. In addition, the correlation of an early increase of activation with and improvement of language function has shown the functional significance of *right* frontal areas in the subacute stage of language recovery. These results advance our understanding of the dynamic process of language recovery and might have implications for the specificity of therapeutic strategies in the treatment of aphasia.

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