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Therapy-induced brain reorganization patterns in aphasia

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Both hemispheres are engaged in recovery from word production deficits in aphasia. Lexical therapy has been shown to induce brain reorganization even in patients with chronic aphasia. However, the interplay of factors influencing reorganization patterns still remains unresolved. We were especially interested in the relation between lesion site, therapy-induced recovery, and beneficial reorganization patterns. Thus, we applied intensive lexical therapy, which was evaluated with functional magnetic resonance imaging, to 14 chronic patients with aphasic word retrieval deficits. In a group study, we aimed to illuminate brain reorganization of the naming network in comparison with healthy controls. Moreover, we intended to analyse the data with joint independent component analysis to relate lesion sites to therapy-induced brain reorganization, and to correlate resulting components with therapy gain. As a result, we found peri-lesional and contralateral activations basically overlapping with premorbid naming networks observed in healthy subjects. Reduced activation patterns for patients compared to controls before training comprised damaged left hemisphere language areas, right precentral and superior temporal gyrus, as well as left caudate and anterior cingulate cortex. There were decreasing activations of bilateral visuo-cognitive, articulatory, attention, and language areas due to therapy, with stronger decreases for patients in right middle temporal gyrus/superior temporal sulcus, bilateral precuneus as well as left anterior cingulate cortex and caudate. The joint independent component analysis revealed three components indexing lesion subtypes that were associated with patient-specific recovery patterns. Activation decreases (i) of an extended frontal lesion disconnecting language pathways occurred in left inferior frontal gyrus; (ii) of a small frontal lesion were found in bilateral inferior frontal gyrus; and (iii) of a large temporo-parietal lesion occurred in bilateral inferior frontal gyrus and contralateral superior temporal gyrus. All components revealed increases in prefrontal areas. One component was negatively correlated with therapy gain. Therapy was associated exclusively with activation decreases, which could mainly be attributed to higher processing efficiency within the naming network. In our joint independent component analysis, all three lesion patterns disclosed involved deactivation of left inferior frontal gyrus. Moreover, we found evidence for increased demands on control processes. As expected, we saw partly differential reorganization profiles depending on lesion patterns. There was no compensatory deactivation for the large left inferior frontal lesion, with its less advantageous outcome probably being related to its disconnection from crucial language processing pathways.

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Abbreviation: ICA = independent component analysis

Introduction

Recently, neural underpinnings of aphasia recovery in the domain of word processing, with or without lexical therapy, were investigated using functional brain imaging techniques (for overviews, see Zahn *et al.*, 2006; Crinion and Leff, 2007; Crosson *et al.*, 2007; Thompson and den Ouden, 2008; Meinzer *et al.*, 2011). Results did not reveal homogeneous recovery patterns across all patients, but several mechanisms underlying brain reorganization in aphasia have been proposed. Thus, the two brain hemispheres were shown to be engaged not only in word production of healthy participants (Abel *et al.*, 2011; Vigneau *et al.*, 2011) but also in the recovery of word production deficits in aphasia (Crosson *et al.*, 2007). The extent of brain damage influences the recovery pattern: if left-hemisphere damage is relatively restricted, reactivation and compensation seem to occur mainly in peri-lesional areas, resulting in relatively good recovery. The right hemisphere appears to take over, if left hemisphere language capacities have become insufficient, even though compensatory capabilities of the former have been reported to be restricted (Heiss and Thiel, 2006; Crosson *et al.*, 2007). Moreover, results indicate that brain areas involved in recovery (i) comprise right hemisphere areas homologue to damaged language areas and/or peri-lesional left-sided areas (Weiller *et al.*, 1995; Musso *et al.*, 1999; Thompson and den Ouden, 2008); (ii) already had the potential to subserve the language task before the stroke occurred (normal or 'redundant' activation)—instead of a takeover by unrelated brain areas (deviating or 'vicarious' activation) (Zahn *et al.*, 2006); and (iii) be affected by distant brain damage ('dynamic diaschisis') (Price *et al.*, 2001) as well as by inhibitory influences due to ipsilateral and contralateral connectivities (Heiss and Thiel, 2006).

However, the interplay of factors influencing aphasia recovery and associated patterns of brain reorganization still remains largely unresolved. Especially the high variability of extent and locus of brain lesions poses a major challenge (Cappa, 2000; Crinion and Leff, 2007). Thus, studies on therapy-induced recovery yielded equivocal findings on the involvement and contribution of brain areas, so that favourable activation patterns for patient subgroups could not be revealed, yet. In order to illuminate this issue, larger patient groups and a detailed characterization of brain damage and language performance are crucial (Crinion and Leff, 2007). An approach that relates lesion information from structural MRI with functional activation data, namely joint independent component analysis (ICA) (Calhoun *et al.*, 2006; Specht *et al.*, 2009), seems to be well suited to shed light on the variability of patient lesions. Specht *et al.* (2009) applied the joint ICA approach to data from a PET study in aphasic patients that included a lexical decision task. Results revealed patient-specific signal changes in bilateral language areas that were not detectable by standard group analyses. Compared with PET, the acquisition of functional data using functional MRI has the advantage of its non-invasive nature, its good availability in clinical settings, and its inclusion of random and thereby unpredictable events (event-related design) (Scott and Wise, 2003; Price, 2012).

Thus, we aimed to apply lexical therapy, which was shown to be effective in a previous study (Abel *et al.*, 2007), to a group of 14 patients with aphasic word retrieval deficits after left-hemisphere stroke. We intended to illuminate brain reorganization considering functional MRI time-series of (I-a) recovered word production before therapy in a picture naming task; (I-b) recovery induced by therapy, as well as aphasic brain activations in comparison to initial (II-a); and (II-b) repeated naming in healthy controls. Moreover, (III) we analysed the entire data set using joint ICA to reveal correlations between brain lesions and pre-post functional MRI activations that differed between patients and controls. We also examined correlations between resulting joint ICA parameter estimates and behavioural therapy gain.

We predicted peri-lesional activations and right hemisphere activations homologue to pooled lesion sites before therapy, signal changes in these bilateral naming networks due to therapy, and patterns of brain reorganization dependent on lesion localization. For the latter, we expected to find patient subgroups and their favourable recovery patterns.

Patients and methods

Patients

Inpatients of the aphasia ward at the University Clinic Aachen were included if they presented naming disorders in the chronic phase (>4 months) after a first-ever left-hemisphere stroke. Severity of the naming disorder had to be at least moderate, unless there appeared to be urgent demand for treatment of their milder naming disorder.

Exclusion criteria included presence of severe apraxia of speech or dysarthria, contraindications for functional MRI

examinations, or naming performance at a mastery level during pretesting (Supplementary material). The study was approved by the local ethics committee at the medical faculty (EK 124/05).

Overall study design

Pretesting for confrontation naming with depicted everyday objects was first performed on a laptop (Test T1) and at least 1 day later in the MRI-scanner (Test T2), leaving ~1 week to select a subset of items with low baseline performance in both pretests for the 4-week lexical therapy. Naming performance was assessed again in a post-test (Test T3) the week after therapy.

Behavioural tests and therapy

The material consisted of 132 black-and-white drawings from the Snodgrass and Vanderwart (1980) corpus. The complete list of items was presented for oral naming once per assessment inside as well as outside the scanner, and the subset of 60 items was used for training during therapy. In the naming test on a laptop, participants had 10 s to overtly name each picture successively presented via audio-visual presentation software (AVMP, 1997), which also does sound recordings of responses. During therapy, patients were asked to name pictures from the training subset, which were consecutively presented in a paper-pencil version. If the patient failed to produce the correct response, they were given increasing assistance according to a semantic or a phonological cueing- hierarchy (Supplementary material). A detailed description of diagnosis of the lexical impairment and the training procedures was presented elsewhere (Abel *et al.*, 2014).

Behavioural data analysis

Verbal responses to test items were rated according to a 4-point scale 'naming score', with the score 3 representing a spontaneously correct response and the score 0 indicating inappropriate wrong responses. Statistical analyses comprised tests for dependent samples (within-item comparisons) to test the null hypothesis that the difference in item scores is zero (Supplementary material). Therapy gain for each individual patient was evaluated, subtracting the naming score for each item before training (Test T2) from the score after training (Test T3). Moreover, we manually assessed response times (latencies) for the first complete naming response of each item.

Event-related functional MRI design

Control subjects

Fourteen healthy volunteers, matched to the 14 patients for gender (four female, 10 male), age (median age 48 years, range 34–73 years), and handedness were recruited as control subjects. They performed the functional MRI experiment twice, comparable to patient test times T2 and T3 (mean intervals: patients 5.3 weeks; controls 6.5 weeks). They did not undergo any study-related training during the interval. All 28 participants gave their informed written consent to the study.

Stimuli and experimental design

Stimuli and task of the functional MRI paradigm were identical to those of pretest T1, so that the first scan completed pretesting and the second constituted the post-test. In the event-related experiment, each picture to be named was followed by a fixation cross after 1.2 s and a blank screen after another 4.8 s, plus a random jitter (mean duration 2 s, range 1–3 s), allowing ~8 s time for each naming attempt. Participants saw the pictures via video goggles and their responses were registered and recorded (Supplementary material).

Data acquisition

A gradient echo planar T_2* sequence for functional data and a high-resolution T_1-weighted anatomical scan were acquired on a 3 T MRI-scanner (Philips Achieva) (Supplementary material).

Data analysis

The anatomical image was segmented into compartments of grey matter, white matter, and CSF, using the unified segmentation procedure (Ashburner and Friston, 2005; Crinion *et al.*, 2007; Seghier *et al.*, 2008). Normalization parameters were estimated to be applied to the functional images later on. Functional images were further preprocessed using standard SPM8 analyses (Supplementary material).

At the second level, we performed (I-a) one-sample *t*-tests to investigate brain activations for picture naming (against implicit control) at pretest T2, as well as paired *t*-tests to compare activations (against implicit control) (I-b) between pre- and post-test (T2, T3) and between patients and their matched control subjects (II-a) at T2. We also (II-b) tested for an interaction of group and activation change over time from Tests T2 to T3.

The functional MRI-analyses were performed at a voxel-wise intensity threshold of $P < 0.01$ uncorrected with an extent threshold of $k = 11$ voxels. A Monte Carlo simulation with 10 000 simulations revealed that this cluster extent cut-off provided an experiment-wise threshold of $P < 0.05$ corrected for multiple comparisons (Slotnick *et al.*, 2003). As Slotnick's simulations lead to relatively liberal thresholds, we also provide critical cluster sizes from another program (AFNI 3dClustSim, http://afni.nimh.nih.gov/afni/) in the Table legends. For each activation peak of the study, activation tables also provide information about the presumed cognitive or language function subserved in healthy speakers, as taken from the literature. The behavioural analysis comprised the application of a noise cancellation tool (Cusack *et al.*, 2005) to sound recordings of vocal responses, as well as the transcription and classification of naming responses (see 'Behavioural data analysis' section).

Joint independent component analysis

Finally, we (III) performed analyses on the association between brain lesions and patient-specific activation patterns pre-post therapy, and we considered correlations of activations with therapy gain.

Following the procedure described by Specht *et al.* (2009), the automatically segmented anatomical image (see data analysis) was used as a starting point for lesion localization. The resulting CSF maps are parameter maps, where voxel

intensities indicate the probability of CSF within the respective voxel. Therefore, these maps highlight the localization and extension of a lesion more efficiently than the corresponding grey and white matter maps. Therefore, only the CSF maps were spatially normaliszed and finally smoothed with a Gaussian smoothing kernel of 8 mm full-width at half-maximum.

In contrast to ICAs, which are used for analysing time series in functional MRI and electroencephalography data, a joint ICA is a second-level analysis, resting on already processed parameter maps from different modalities, like segmented MRI data and contrast maps from an functional MRI first-level analysis of time series. The underlying assumption in a joint ICA is that these spatially independent sources are linearly mixed (Calhoun *et al.*, 2006; Specht *et al.*, 2009). In our study, for each subject a CSF map, taken as indicator for a lesion, as well as an activation contrast map from the individual functional MRI first-level analysis were entered into the joint ICA. As it was the aim to detect associations between lesion localization and recovery patterns, only the differential contrast between Tests T2 and T3 was entered into the analysis. Therefore, each individual subject contributed to the joint ICA with two images, the CSF map and the contrast image.

The analysis was performed using the Fusion ICA Toolbox (http://mialab.mrn.org/software/fit/, version 1.2c). For the joint ICA, the voxel intensities of the two modalities were normalized across all subjects and for each modality separately, such that both modalities had the same sum-of-squares. Using the minimum description length algorithm as implemented in the Fusion ICA Toolbox, the number of independent components to be derived was set to seven, and the infomax algorithm was used to decompose the data into independent component images and subject-specific mixing parameters (Supplementary material).

To identify relevant components, the resulting components were sorted with respect to their difference in the subject-specific mixing parameter between control and patient group. Only those components showing a significant group difference in the mixing parameter (component loadings) at $P < 0.05$ were considered. The corresponding joint component maps for CSF and for the functional activation contrasts were reconstructed into 3D images, z-scaled, and restrained by a brain mask. The reconstructed components were displayed with a threshold of $z > 3.09$. For cross validation, the mixing parameters were entered as predictors in a linear regression analysis (Supplementary material).

We also performed joint ICAs for the subset of trained compared to untrained items over time (for details, see Supplementary material), as previously presented for the general linear model analysis (Abel *et al.*, 2014).

Results

Patients

Twenty-three patients were considered for inclusion into the functional MRI therapy study. However, nine patients were excluded after pretesting either because of naming performance close to ceiling ($n = 4$), scanner artefacts ($n = 2$), or technical problems ($n = 3$). Fourteen right-handed patients with chronic aphasia (median time post-onset: 41 months) completed the therapy study (Supplementary Table 1).

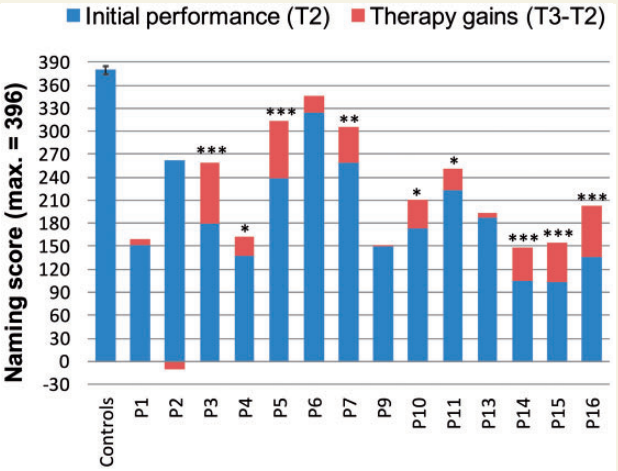

Figure 1 Behavioural therapy effects for healthy controls (group analysis) and for patients per subject (single case analysis). Statistical tests for improvement in performance after therapy [test for dependent samples (within-items comparison), T3 versus T2; exact Wilcoxon signed-ranks test, one-tailed, ***$P < 0.001$, **$P < 0.01$, *$P < 0.05$]. Group analysis for controls performed on individual naming scores, showing the mean performance including standard deviation (minimal mean decrease from Test T2 to T3: 1.1, SD = 9.8).

Behavioural analysis: therapy gain and response times

Nine of the 14 patients revealed significantly improved naming in the MRI scanner (Fig. 1). For the patient group, therapy gain in the total naming score was highly significant (group analysis, Wilcoxon signed-ranks test and t-test, Tests T3–T2, one-tailed, $P < 0.001$). Contrarily, the group of healthy controls already performed at ceiling during first testing and their naming performance remained perfectly stable at second testing (all statistical tests at one-tailed $P > 0.10$) (Supplementary material).

Considering naming response times for the group of patients (Table 1), mean response times at Test T2 were significantly longer than those of Test T3 (paired t-test, one-tailed, $P < 0.008$).

General linear model analysis

Lesions and recovered naming network

The lesion overlay for all 14 patients (Fig. 2A) revealed that lesions were consistently located in left-sided peri-sylvian regions, focusing on the insula extending to inferior frontal gyrus (IFG), lateral basal ganglia, and precentral gyrus, as well as to superior and middle temporal gyrus, angular gyrus and inferior parietal lobule, including sub-gyral

Table 1 Naming latencies for the group of 14 patients

	n	Mean (SD) at T2	Mean (SD) at T3
Responses both at T2 and T3	1118	1896 (1363)	1781 (1193)**

Mean naming response times and standard deviations (SD) (in ms) of first naming responses, taken from items rateable both at T2 and T3. A paired *t*-test was performed (**$P < 0.01$, one-tailed), in order to detect significant reductions in response times (i.e. priming). For comparison, latencies for picture naming in healthy speakers as taken from previous study are 751 (18) ms (Abel *et al.*, 2009), 789 (111) ms in the literature (van Turennout *et al.*, 2000), with the typical naming latency estimated at 600 ms in the review by Indefrey and Levelt (2004). If paired *t*-test and SD measures are performed on the basis of individual response times of each subject, the difference is not significant any more [mean response time in ms, 2077 (SD 790) at T2 versus 1920 (SD 450) at T3, $P = 0.923$].

white matter, and rarely extending to adjacent areas comprising supplementary motor area and precuneus. Medial areas like anterior cingulate gyrus (ACC), caudate, thalamus, and the hippocampal area were spared.

Figure 2B presents previously recovered naming networks of aphasic patients, i.e. brain activations for picture naming before the training had started. Activations were absent in lesioned peri-sylvian regions (as shown in Fig. 1A). But there were also left peri-lesional activations, i.e. activation increases around the pooled lesion sites for the group. The highest activation peak was found in left fusiform gyrus. Some activation extended to left cuneus and precuneus, posterior cingulate, a sub-gyral area medial to IFG pars triangularis [Brodmann area (BA) 45], and supplementary motor area proper; however, activations widely and predominantly extended to the right, including cuneus and further visual areas, fusiform gyrus, lingual/parahippocampal gyrus, superior parietal lobule, pre-supplementary motor area, precentral gyrus/rolandic operculum, and insula/IFG (Table 2).

Therapy-induced recovery

Comparing pre- to post-training naming activation (contrast I-b), we found activation decreases due to training—but no increase—involving right middle temporal gyrus/superior temporal sulcus, thalamus, hippocampus, paracentral lobule, and posterior cingulate, bilateral cerebellum, precuneus, mid-cingulate, and supplementary motor area, as well as left IFG pars triangularis (BA 44/45), middle/medial frontal gyrus, pre- and postcentral gyrus, and inferior parietal lobule (BA 40) (Fig. 2C and Table 2).

Comparison between patients and controls

The comparison between patients and healthy speakers revealed (II-a_1) that there was more activation before training at Test T2 for controls in the left-sided naming network damaged in patients (peak: left superior temporal gyrus) and in further areas involving right superior temporal gyrus, precentral gyrus, and insula (Fig. 2D). Left postcentral gyrus, rolandic operculum, posterior ACC and mid-cingulate gyrus, thalamus, and caudate were less activated for patients as well. Visual inspection in comparison with the lesion map revealed some left hemisphere areas with less activation in patients despite preservation of respective brain tissue, especially in left cingulate areas and caudate. Conversely, (II-a_2) there was a small activation spot for patients in right precuneus (BA 7) ($k = 18$) (Table 3).

Moreover, (II-b) the interaction between subject group and time (patients versus healthy speakers at T2 versus T3) revealed that due to therapy, there was a significant decrease specific to patients in left posterior ACC and caudate, in right middle temporal gyrus/superior temporal sulcus, thalamus, hippocampus, and posterior cingulate cortex, as well as in bilateral precuneus (Table 3 and Fig. 3A). The plot of significant activation contrast estimates (Fig. 3B) illustrates that for healthy participants, there was even an increase in left ACC, but there was no pre-post decrease for control subjects and an increase in a cluster of 77 voxels comprising left ACC and caudate instead (Supplementary Table 2 and Supplementary Fig. 1).

We additionally applied the finite impulse response basis set to estimate the responses at five time points following the picture stimulus for patients and controls to detect possible deviations from the haemodynamic response function for the former group (Bonakdarpour *et al.*, 2007). The time course of naming (Fig. 4) reveals that were is no systematic difference in extent or strength of brain activations between both groups (see Supplementary material for details and further analyses).

Specific therapy-induced recovery in joint ICA

Using joint ICA, three (out of seven retained) components were identified (Fig. 5), which showed a significant group difference in the subject-specific mixing parameter, of which two components were also significant after correction for multiple comparisons. The first component (C4, group difference $P < 0.001$) demonstrated an association between a large lesion in left IFG and adjacent subcortical areas, including basal ganglia, and functional recovery, as reflected by decreased peri-lesional activation within IFG pars triangularis (BA 45), as well as bilaterally decreased activation within superior frontal (BA 9) and calcarine gyri. At the same time, increased activation was found within right orbito-medial prefrontal cortex (BA 11) and left thalamus. In addition, the individual component loadings correlated negatively with therapy gain ($r = -0.560$; $P < 0.037$) (Table 4).

The second component (C7, group difference $P < 0.004$) demonstrated that patients with lesions covering the posterior and middle part of the temporal lobe and sparing the inferior temporal gyrus showed decreased activations within bilateral IFG pars orbitalis and middle occipital gyrus, right superior temporal gyrus, and left superior frontal gyrus. Corresponding increased activation was found in

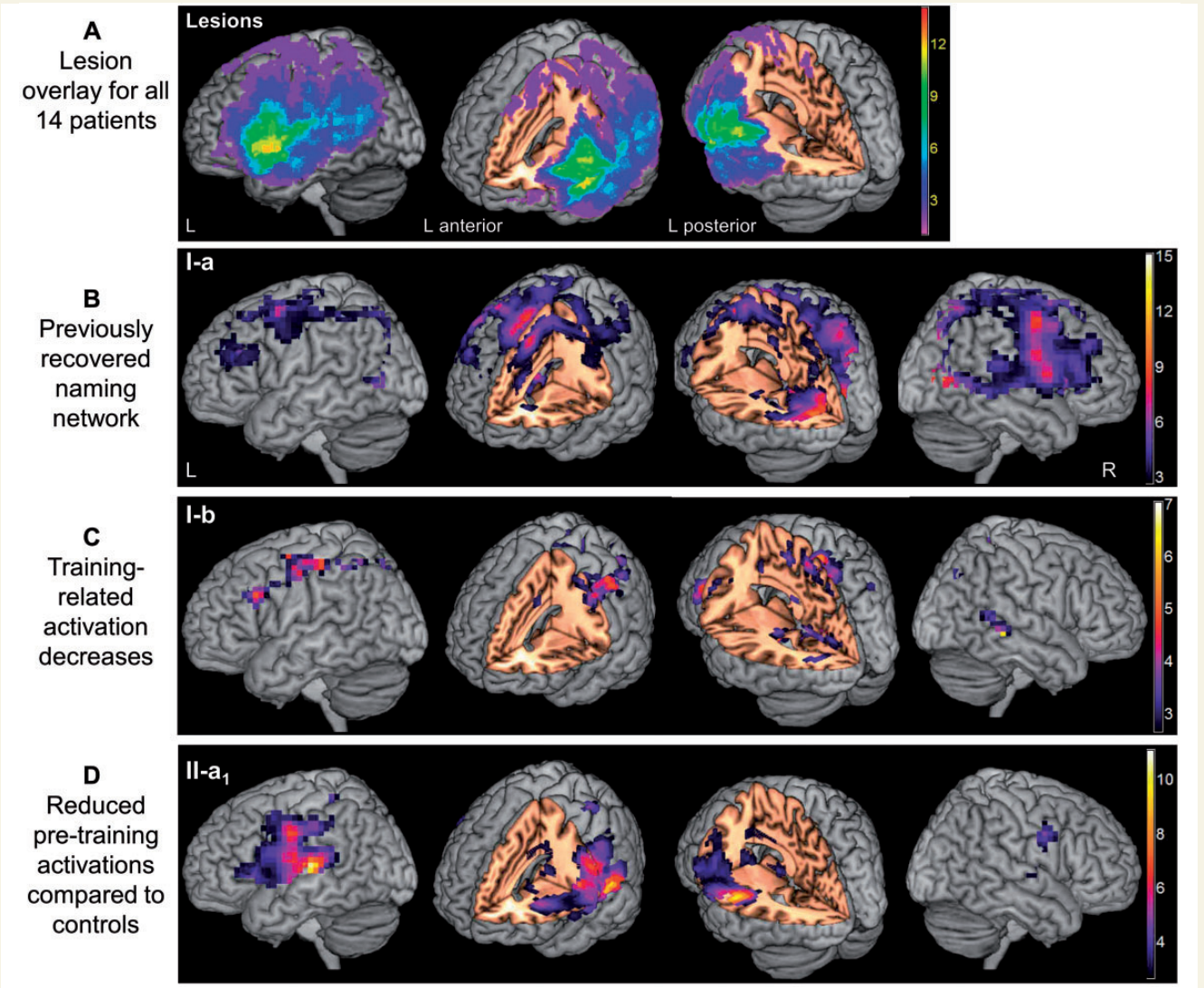

Figure 2 Lesion extension and brain activations for aphasia recovery in the group of 14 patients. View of the left (L) hemisphere surface, left anterior cut, and left posterior cut of a lesion overlay of all 14 patients (**A**), and contrasts of (I-a) brain activations for recovered word production before training (**B**), (I-b) decreasing brain activations due to training (**C**), and (II-a_1) lower pre-training activations compared to healthy control subjects (**D**), additionally shown on the right (R) hemisphere surface (*cf.* Table 2 and 3) (*t*-tests, Monte Carlo-corrected, $P < 0.05$, 11 voxels).

the more anterior left superior frontal gyrus and right caudate.

The third component (C5, group difference $P < 0.020$) highlighted an association between a focal lesion of middle frontal gyrus/dorsal part of IFG pars opercularis and bilaterally decreased activations within the IFG pars triangularis. In addition, decreased activation was seen in left IFG pars orbitalis, and left cerebellar areas, and this decreased activation extended to the inferior occipital gyrus (Fig. 5). Increased activation was found in right orbitomedial prefrontal cortex as well as in the middle/superior frontal gyrus. The remaining four components did not show significant group differences with respect to the mixing parameter.

We also found significant effects for the regression analyses on the complete set (Supplementary Fig. 4) and on the subsets of trained versus untrained items (Supplementary Fig. 5) over time.

Discussion

Behavioural therapy effects

Our behavioural results corroborate previous findings on the effectiveness of lexical therapy even in the chronic phase of recovery (Wisenburn and Mahoney, 2009). Patients were <1 s slower than healthy participants in

Table 2 Brain activations for word production in the group of aphasic patients

Extent	Cluster *P* unc.	*t*-value	Voxel *P*	Coordinates *x*, *y*, *z* (mm)			Structure (Brodmann area)	Presumed function in healthy subjects
I-a. Main effect of naming before training								
6106	0.000	14.15	0.000	−34	−56	−14	L FG	Visual-semantic[1]
		11.60	0.000	22	−80	10	R cuneus	Visual[7]
		11.51	0.000	30	−64	−10	R FG	Visual-semantic[1]
		10.94	0.000	38	−68	6	R middle occipital gyrus	Visual[1]
		10.75	0.000	−10	−80	18	L cuneus	Visual[7]
		10.52	0.000	26	−72	30	R superior occipital gyrus	Visual[1]
		10.51	0.000	34	28	2	R insula/ IFG	Lexico-semantics[2]
		10.11	0.000	6	16	54	R pre-SMA/ superior frontal gyrus (8)	Sequencing motor plans, response inhibition[1]
		9.52	0.000	18	−48	−10	R lingual/ parahippocampal gyrus (19)	Visual[3]/ semantic[4]
		9.45	0.000	30	−36	−14	R FG/ parahippocampal gyrus	Semantics[1,4]
		9.16	0.000	−30	28	26	L frontal lobe sub-gyral, medial to 45	45: word retrieval[1]
		9.00	0.000	−26	−72	38	L superior occipital gyrus/ precuneus	Visual/ semantics, visual imagery[1] (visuo-cognitive)
		8.78	0.000	18	−64	6	R calcarine/ posterior cingulate (30)	Visual/semantic[1]
		8.59	0.000	46	0	50	R precentral gyrus/ middle frontal gyrus (6)	Articulation[1]
		8.36	0.000	−22	−64	14	L posterior cingulate	Semantics[1]
		7.87	0.000	58	8	10	R precentral gyrus/ rolandic operculum	Articulation[1]
		7.79	0.000	58	0	26	R precentral gyrus (6)	Articulation[1]
		7.72	0.000	−14	0	58	L SMA proper (6)	Articulation[1]
		7.68	0.000	6	−28	−10	R midbrain, near red nucleus	Motor
		7.64	0.000	22	−64	54	R superior parietal lobule	Visual, attention, working memory[5]
I-b. Naming pre-post training: More activation before training								
86	0.013	6.30	0.000	54	−36	−6	R MTG/STS	Sentence/ text[2], phonology[6]
		5.14	0.000	22	−32	6	R thalamus (pulvinar)	Attention[5]
		4.73	0.000	30	−32	2	R hippocampus	Word acquisition, semantic retrieval[1]
282	0.000	6.25	0.000	6	−56	−14	R cerebellum (culmen: IV,V)	Articulation[1]
		6.01	0.000	−2	−60	−14	L cerebellum (culmen: IV, V)	Articulation[1]
		5.64	0.000	−10	−60	−18	L cerebellum (declive: VI)	Articulation[1]
131	0.003	5.35	0.000	6	−44	62	R paracentral lobule (5)	Somatosensory
		4.38	0.000	2	−56	54	R precuneus	Semantics, visual imagery[1] (visuo-cognitive)
		3.71	0.001	−18	−72	50	L precuneus	Semantics, visual imagery[1] (visuo-cognitive)
42	0.069	4.93	0.000	−50	20	30	L IFG, pars triangularis (44/ 45)	Word retrieval, semantic decisions[1]
		3.05	0.005	−42	4	38	L precentral gyrus (9)	Articulation[1]
		2.70	0.009	−34	12	34	L middle frontal gyrus	Word retrieval[1]
81	0.016	4.88	0.000	−46	−28	54	L postcentral gyrus	Somatosensory[1]
		4.68	0.000	−38	−4	58	L precentral gyrus (6)	Articulation[1]
		4.48	0.000	−46	−12	46	L postcentral gyrus (4)	Articulation[1]
73	0.021	3.89	0.001	18	−48	30	R mid cingulate/ precuneus	Semantics/ visual imagery[1]
		3.39	0.002	6	−36	26	R posterior cingulate gyrus (23)	Semantics[1]
		3.34	0.003	−6	−28	26	L mid cingulate gyrus	Semantics[1]
26	0.143	3.80	0.001	−34	−56	54	L inferior parietal lobule (40)	Articulatory loop[1]/ phonology[6]
		3.73	0.001	−46	−44	50	L inferior parietal lobule	Articulatory loop[1]/ phonology[6]
		3.57	0.002	−26	−48	50	L superior parietal lobule	Visual, attention, working memory[5]
22	0.175	3.71	0.001	−2	−20	58	L SMA proper (6)	Articulation[1]
		3.00	0.005	−2	−20	70	L medial frontal gyrus (6)	Articulation[1]
11	0.334	3.14	0.004	−6	8	34	L mid cingulate gyrus	Semantics[1]
		2.79	0.008	2	8	46	R pre-SMA	Sequencing motor plans, response inhibition[1]

Areas of significant brain activations in the group of all 14 patients (I-a) when naming at T2 was compared to the rest (all 132 items, one-sample *t*-test), and (I-b) when naming pre- and post-training were compared, with significant activations only present for T2 > T3 (paired *t*-tests). Activations were thresholded at Monte Carlo-corrected $P < 0.05$ with at least 11 voxels (according to more conservative AFNI cluster simulations, the threshold is 31.2 and 44.7 voxels for one-tailed and two-tailed statistics, respectively). Co-ordinates refer to MNI space.

For the huge cluster of the main effect (I-a), a maximum of the 20 highest peaks within the cluster extent are shown on subsequent lines that were more than 16 mm apart.

R = right hemisphere; L = left hemisphere; FG = fusiform gyrus; unc = uncorrected.

[1]Price (2012); [2]Vigneau *et al.* (2011); [3]Price (2000); [4]Price (2010); [5]Cabeza and Nyberg (2000); [6]Abel *et al.* (2009*a*); [7]Vigneau *et al.* (2006).

Table 3 Brain activations for word production in aphasic patients versus healthy controls

Extent	Cluster *P* unc.	*t*-value	Voxel *P*	Coordinates *x*, *y*, *z* (mm)			Structure (Brodmann area)	Presumed function in healthy subjects
II-a$_1$. More activation for controls compared to patients before training (T2)								
848	0.000	10.66	0.000	−50	−24	10	L STG (41)	Auditory processing[1]; feedback[5]
		7.23	0.000	−46	−12	14	L rolandic operculum (13)	Articulation[1]
		6.94	0.000	−58	−8	34	L postcentral gyrus	Articulation[1]
19	0.239	4.89	0.000	−30	−36	62	L postcentral gyrus (3)	Articulation[1]
75	0.028	4.77	0.000	54	0	34	R precentral gyrus (6)	Articulation[1]
		3.86	0.001	34	−20	10	R insula-p	Articulation[1]
		3.57	0.002	50	−12	2	R STG (22)	Auditory processing[1]; feedback[5]
50	0.065	4.14	0.001	−18	0	18	L caudate (caput)	Suppr. of irrelevant words[1]
		3.70	0.001	−6	−20	10	L thalamus (medial dorsal ncl.)	Articulation[1]
37	0.107	3.73	0.001	−2	32	26	L ACC-p	Motor execution/ suppr.[1], cognitive control[6]
		2.95	0.006	−2	8	42	L mid cingulate gyrus (32)	Semantics[1]
31	0.137	3.56	0.002	−14	0	34	L mid cingulate gyrus	Semantics[1]
		3.03	0.005	−10	−12	34	L mid cingulate gyrus	Semantics[1]
II-a$_2$. More activation for patients compared to controls before training (T2)								
18	0.251	3.41	0.002	6	−68	50	Right precuneus (7)	Semantics, visual imagery[1] (visuo-cognitive)
II-b. More activation decrease pre-post training (T2 versus T3) for patients compared to controls								
196	0.004	4.89	0.000	−14	12	30	L ACC-p	Motor execution/ suppr.[1], cognitive control[6]
			0.000	−10	16	22	L ACC-p	Motor execution/ suppr.[1], cognitive control[6]
		4.77						
			0.000	−6	4	22	L caudate (head)	Suppr. of irrelevant words[1]
		4.76						
17	0.332	3.90	0.001	−6	−28	22	L posterior cingulate	Semantics[1]
16	0.347	3.44	0.002	−2	−48	62	L precuneus (5)	Semantics, visual imagery[1]
		2.74	0.008	2	−60	54	R precuneus	Semantics, visual imagery[1]
12	0.417	3.42	0.002	50	−36	−6	R MTG/STS	Sentence/ text[2], phonology[4]
		3.33	0.003	62	−32	−2	R MTG/STS	Sentence/ text[2], phonology[4]
18	0.318	3.19	0.004	14	−32	6	R thalamus (pulvinar)	Attention[3]
		3.06	0.005	22	−36	10	R hippocampus	Word acquisition, semantic retrieval[1]
28	0.215	3.15	0.004	26	−44	30	R posterior cingulate	Semantics[1]

Areas of significant brain activations comparing naming of all 14 patients to their 14 matched controls (II-a) at T2. (II-b) Pre- versus post-training (interaction of factors group and time), with activations only being significant for the contrast [(T2 > T3) for patients > (T2 > T3) for controls], revealing stronger decrease of activation for patients. Contrasts were calculated applying paired *t*-tests, and activations were thresholded at Monte Carlo-corrected $P < 0.05$ with at least 11 voxels (according to more conservative AFNI cluster simulations, the threshold is 31.2 and 44.7 voxels for one-tailed and two-tailed statistics, respectively). Co-ordinates refer to MNI space.
R = right hemisphere, L = left hemisphere; MTG = middle temporal gyrus; STS = superior temporal sulcus; STG = superior temporal gyrus; a = anterior; p = posterior; suppr. = suppression.
Plots of brain areas with significant Group × Time interaction (contrast II-b) can be found in Supplementary Fig. 1, created to ease understanding of underlying activations for patients/controls at T2/T3.
[1]Price (2012); [2]Vigneau *et al.* (2011); [3]Cabeza and Nyberg (2000); [4]Abel *et al.* (2009*a*); [5]Ridderinkhof *et al.* (2004); [6]Badre and Wagner (2004).

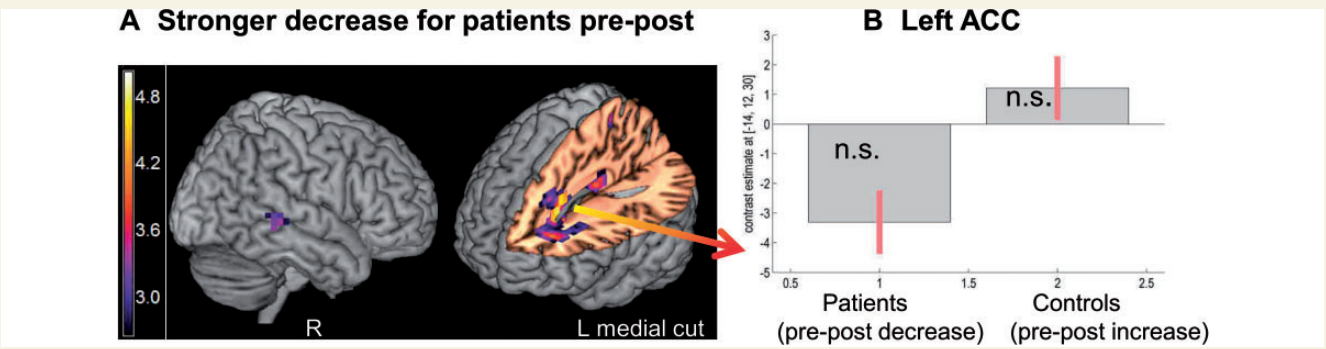

Figure 3 Patient-specific pre-post activation decreases. (**A**) Brain activations for the interaction of Group (patients, controls) × Time (T2, T3) (II-b), (**B**) showing the activation contrast estimate at the maximum activation voxel in the left ACC. View of the right (R) hemisphere surface and a left (L) medial cut of brain activations for the complex activation contrast II-b [(T3-T2) for controls > (T3 > T2) for patients] (paired *t*-test, Monte Carlo-corrected, $P < 0.05$, 11 voxels). Label for significance (sign.)/ no significance (n.s.) refers to the contrast T2 versus T3 for patients (I-b) and controls, respectively (paired *t*-tests, Monte Carlo-corrected, $P < 0.05$, 11 voxels) (*cf.* Table 3 and Supplementary Fig. 1).

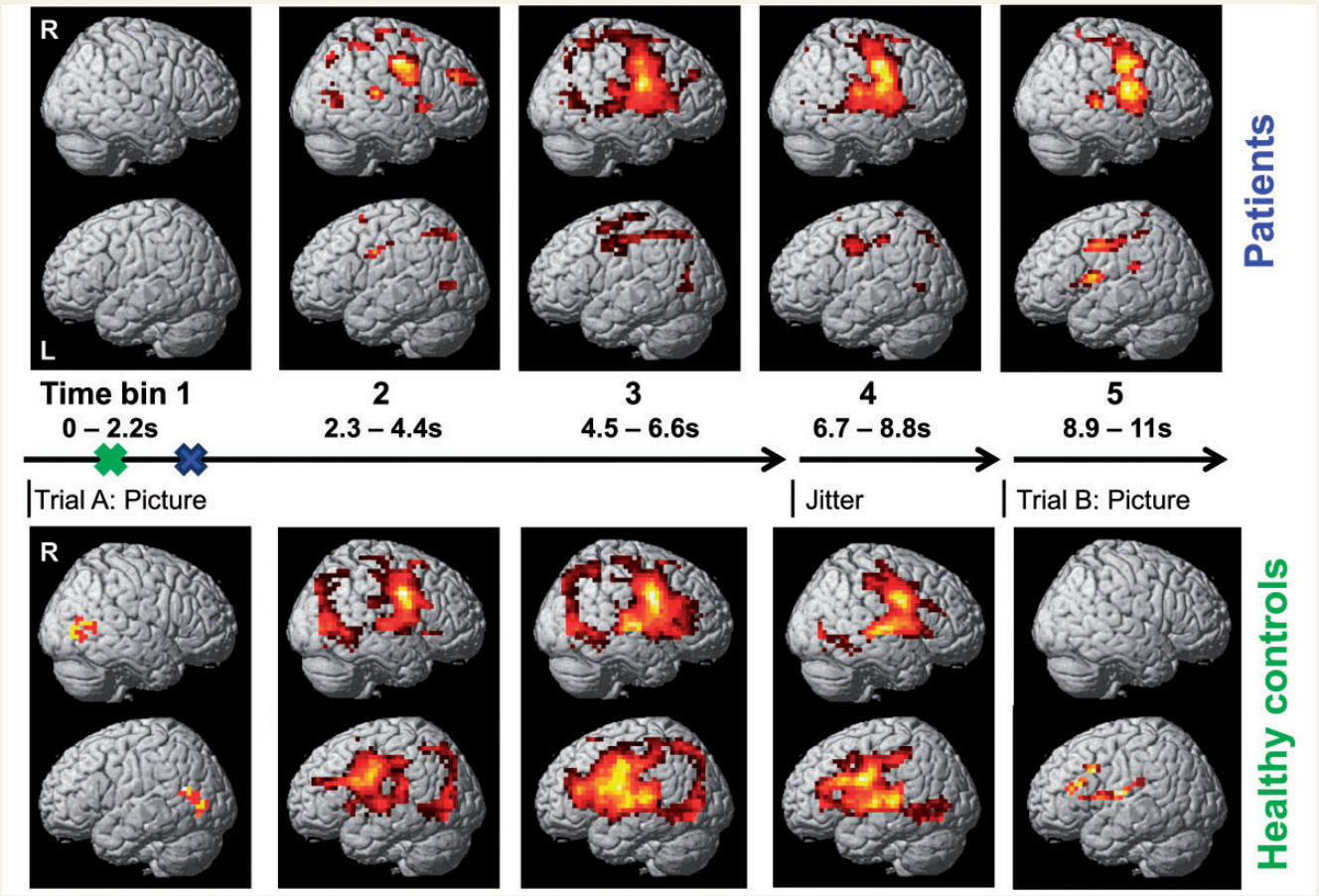

Figure 4 Time course of picture naming activation during the first scan for the group of patients and healthy controls. Activations as revealed by application of a finite impulse function for picture naming at pre-test T2 (contrast Ia) (one-sample *t*-test, Monte Carlo-corrected $P < 0.05$, 11 voxels). The green and blue crosses indicate the mean response time as estimated for healthy subjects and found for patients, respectively (see text and Table 1). Location of global activation maxima: For patients, time Bin 1: none above threshold; Bin 2: right cuneus ($t = 10$); Bin 3: right postcentral gyrus ($t = 14$); Bins 4 and 5: right precentral gyrus ($t = 13$ and $t = 8$); for controls, Bin 1: left inferior occipital gyrus ($t = 4$); Bins 2 and 3: right precentral gyrus ($t = 18$ and $t = 13$); Bins 4 and 5: left precentral gyrus ($t = 9$ and $t = 5$). Significant group-specific effects were restricted to time Bins 2 and 3 as depicted in Supplementary Fig. 2, pre-post activation changes over time can be found in Supplementary Fig. 3.

similar settings of confrontation naming in previous studies (van Turennout *et al.*, 2000; Abel *et al.*, 2009*a*), but nevertheless there was a significant priming effect for patients between test times. The variability of therapy outcomes offers a good starting point for the subsequent correlation analysis with therapy gain in the joint ICA approach.

General linear model analysis

Lesions and recovered naming network

As would be expected, the patients' lesions involved language areas of the left hemisphere (Price, 2012), mainly insula as well as Broca's and Wernicke's area, and there were peri-lesional and contralateral brain activations before training. Group analyses might under-estimate particularly the involvement of peri-lesional areas due to high variability of lesion sites. However, it remains unclear whether the observed peri-lesional activations were actually functional or an attempt to access Broca's area, for example. The right-sided activations were not restricted to areas homologous to lesion sites, which might be attributed to the presence of a premorbidly bilateral naming network (see below).

Brain mechanisms underlying recovery

To be able to interpret our results against a theory of neural rehabilitation, Table 5 gives an overview of the spectrum of possible brain mechanisms underlying aphasia recovery both for cross-sectional between-group and longitudinal within-group comparisons. We make a distinction between (i) enhanced and reduced activation when activations in patients are compared to controls; and (ii) increased and decreased activations when the aspect of activation changes over time is concerned. Most references

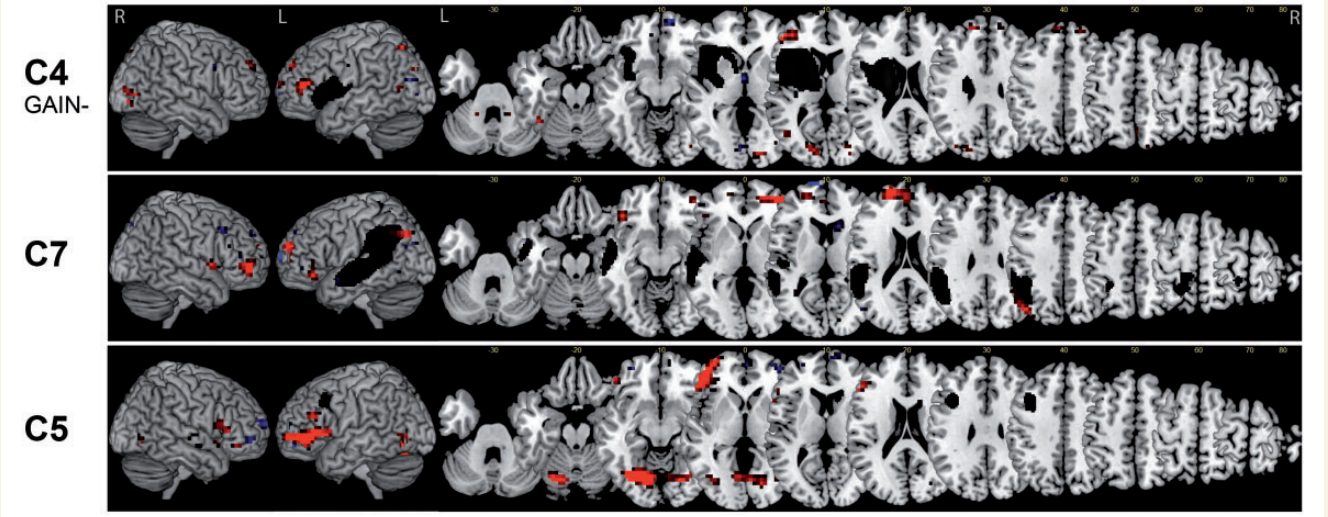

Figure 5 The three components of the joint ICA. Render of the right (R) and left (L) hemisphere and axial slices, revealing lesion localization/extension and associated brain activations for naming pre-post in the 3 out of 7 components (C4, C7, and C5) that revealed differences in brain activation between patients and healthy subjects, with C4 at $P < 0.001$, C7 at $P < 0.004$, and C5 at $P < 0.020$, the latter component not surviving the Bonferroni correction at 5% (see also Table 4). Colour coding: 'Positive' direction = decreasing activation pre-post in red; 'negative' direction = increasing activation pre-post in blue. GAIN$^-$: for component C4, there was a negative correlation with therapy gain (see also Fig. 1).

are given alongside the discussion of our data in the remainder of the article.

Strong activation in patients might be associated with enhanced/increased demands in the short run, as well as rewiring in the long run, i.e. growth and strengthening of connectivities and re-routing. The application and build-up of new strategies in non-language areas as well as the impact of recognition and familiarity can be assigned to these mechanisms. Moreover, the task may require more effort in areas subserving executive control processes. Maladaption, on the other hand, has been reported to occur in right IFG pars triangularis (Naeser *et al.*, 2011); however, right hemisphere involvement including IFG pars opercularis after therapy has been shown to be favourable (Crosson *et al.*, 2007).

On the contrary, activation decrease due to therapy has been linked to more efficient processing of tasks involving priming and learning in healthy participants (Henson, 2003; Horner and Henson, 2008; Abel *et al.*, 2012*a*). In aphasic patients, activation decrease has been associated with higher efficiency due to therapy (Breier *et al.*, 2007; Richter *et al.*, 2008). However, reduced and decreased activation might also be related to (persistent) malfunctioning due to the left-hemisphere brain damage itself, disconnection, or missing inputs. In addition, any abnormal reduction might be related to differences in task performance, e.g. fewer (successful) attempts to produce a response. This might be especially the case for reductions in the unimpaired right hemisphere. Altogether, increases and decreases of activation might be intertwined, such that a lower degree of pre-post decrease was shown to be specific to trained items and a higher degree of decrease was associated with low gain in performance (for details see Abel *et al.*, 2014).

Therapy-induced recovery

Even though activation increases have regularly been found in functional MRI aphasia therapy studies—most of which constitute a series of a few single cases—while decreases are reported much more rarely, we only found activation decreases when comparing activations before versus after therapy. We attribute this finding to more ease in processing, i.e. higher efficiency (Table 5). Our complementary analyses on specific therapy effects for the same patient group (Abel *et al.*, 2014) revealed that left IFG was a positive predictor of therapy outcome and that less activation decrease due to therapy in left-hemisphere temporo-parietal language areas was positively correlated with therapy gain. An increase in right middle temporal gyrus/superior temporal sulcus was previously associated with low performance in verbal fluency (Szaflarski *et al.*, 2013). Conversely, decreased activation in the same area due to therapy, as revealed by our study, might be favourable for therapy outcome.

Comparison between patients and controls

There were only minor differences between the naming network for patients before therapy and for healthy controls when the left-sided brain regions in patients found inactive due to damage are taken into account. Compensatory brain activations in patients mainly encompassed the strongly bilateral naming network of healthy speakers (see also Abel *et al.*, 2009*b*), which corresponds to the notion of

Table 4 Results for the joint ICA

Extent	z-value	Voxel *P*	Coordinates *x, y, z* {mm}			Structure (Brodmann area)	Presumed function in healthy subjects
Component C4 (correlates with therapy gains*): positive direction							
32	6.91	0.000	−50	40	14	L IFG pars triangularis (45)	Word retrieval, semantic decisions[1]
47	4.96	0.000	18	−88	2	R calcarine (18)	Visual[1]
20	4.51	0.000	−14	56	34	L superior frontal gyrus (9)	Semantics[1]
17	4.49	0.000	−14	−84	10	L calcarine (17)	Visual[1]
13	4.17	0.000	18	52	34	R superior frontal gyrus (9)	Semantics[1]
Component C4 (correlates with therapy gains*): negative direction							
13	4.42	0.000	10	60	−10	R OMPFC (11)	Cognitive control[2]
16	4.18	0.000	−2	−4	−2	L thalamus	Articulation[1]
Component C5: positive direction							
108	7.88	0.000	−50	40	−2	L IFG pars triangularis (45)	Word retrieval, semantic decisions[1]
237	7.27	0.000	−18	−72	−14	L cerebellum (VI)	Articulation[1]
15	4.64	0.000	−50	32	22	L IFG pars triangularis (45)	Word retrieval, semantic decisions[1]
20	4.52	0.000	58	28	6	R IFG pars triangularis (45)	Sentence/ text; L: word retrieval
Component C5: negative direction							
18	5.23	0.000	2	56	−6	R OMPFC (11)	Cognitive control[2]
20	4.35	0.000	14	68	14	R superior frontal gyrus, medial (10)	Cognitive control[2]
10	4.12	0.000	38	52	−2	R middle frontal gyrus, orbital (46)	Cognitive control[2]
Component C7: positive direction							
61	7.64	0.000	34	52	−6	R inferior/ middle frontal gyrus, pars orbitalis (47)	Semantics; L: selection/ retrieval or semantic concepts/ words[1]
117	7.41	0.000	−18	56	22	L superior frontal gyrus (10)	Semantics[1], cognitive control[2]
27	5.16	0.000	−42	−72	34	L middle occipital gyrus (19)	Visual[1]
15	4.99	0.000	58	8	2	R STG-a (22)	Early auditory processing of compex words[1]; feedback[2]
22	4.93	0.000	−42	32	−10	L IFG pars orbitalis (47)	Selection/ retrieval or semantic concepts/ words[1]
27	4.28	0.000	−22	−84	18	L middle occipital gyrus (19)	Visual[1]
Component C7: negative direction							
11	5.76	0.000	−14	68	14	L superior frontal gyrus, medial (10)	Cognitive control[2]
11	3.93	0.000	14	20	10	R caudate (head)	Suppression of irrelevant words[1]

Naming from pre- to post-training for those 3 out of 7 joint ICA components (C4, C5 and C7), which revealed significant differences ($P < 0.05$) in brain activation between patients and healthy controls. Positive direction = decreasing activation pre-post; negative direction = increasing activation pre-post.

*For component C4, there was a negative correlation with therapy gain ($r = -0.560$, $P < 0.037$). R = right hemisphere; L = left hemisphere; OMPFC = orbitomedial prefrontal cortex.

[1]Price (2012); [2]Ridderinkhof *et al.* (2004).

Table 5 Spectrum of possible brain mechanisms underlying aphasia recovery and reorganization as found in group comparisons and/or over time

Brain signals before therapy (comparison to controls)		Brain signal changes due to therapy (comparison pre-post or Time × Group interaction)	
Enhancement of activation*	**Reduction of activation**	**Increase of activation***	**Decrease of activation**
Enhanced demands and rewiring:	**Different task performance**	**Increased demands and rewiring:**	**Persistent malfunctioning in LH**
Storage of knowledge in language areas	**Malfunctioning in LH:**	Storage in language areas*	**Higher efficiency**
New strategies in non-language areas	Local brain damage	New strategies in non-language areas	Priming
Maladaption in RH	Disconnection	Recognition and familiarity	Learning
Recognition and familiarity	Missing inputs	More effort for executive control	
More effort for executive control			

Overview of brain mechanisms presumably involved in aphasia recovery, mirrored by changes of activations and their probable locus in the brain.

LH = left (damaged) hemisphere; RH = right hemisphere; *Enhanced/increased activations, presumably and particularly associated with mechanisms of strategy use and rewiring (i.e. storage of new information), might be characterized by high interindividual variability. Therefore, enhanced/increased activations may rarely be found for a group analysis of patients, but more often for lesion subgroups in the joint ICA and even more so in an analysis of three single cases previously reported elsewhere (Abel *et al.*, 2012*b*, see also text).

'redundancy recovery' (Zahn *et al.*, 2006) at least at the group level.

The present observation of left hemisphere regions that were unaffected by damage but revealed deviating activations may be attributed to a disconnection from crucial areas of the naming network. Along the same lines, Cao *et al.* (1999) found less activation in undamaged left-hemisphere areas for silent naming and verb generation among their seven patients included, especially in left SMG, angular gyrus, and inferior parietal sulcus. The authors attributed the reduction to a disconnection of left-sided areas from the rest of the language network, which instead were connected with homologue areas for compensation of the functional loss. Task-dependent activity reductions have been attributed to dynamic changes in effective connectivity to anatomically remote brain lesions (dynamic diaschisis; Price *et al.*, 2001). Anatomical connections between frontal and temporo-parietal language areas appear to exist via dorsal and ventral language pathways (Saur *et al.*, 2008; Axer *et al.*, 2012). Their disconnection has been associated with impaired repetition and comprehension performance in acute aphasia (Kuemmerer *et al.*, 2013). In chronic patients, preserved inter-temporal connectivities have been associated with better receptive language performance (Warren *et al.*, 2009). Thus, the preservation of effective and anatomical connectivities appears to play a major role in aphasia recovery. Contrary, the right-sided cluster in our study, which showed reduced activation as well, may instead be explained by the fewer overt naming attempts in patients, requiring less articulatory and auditory processing.

Moreover, our patients might rely strongly on pre-linguistic features in right precuneus as a strategy for lexical access. This area is part of the default network, which is usually deactivated during task performance (Raichle and Snyder, 2007); however, our control group revealed a positive brain signal here as well, even though it was significantly lower than in patients. Increased left (Musso *et al.*, 1999; Calvert *et al.*, 2000) and bilateral (Fridriksson *et al.*, 2007) precuneus activation have previously been found to be present in aphasia recovery. Calvert *et al.* (2000) detected more left precuneus activation compared to controls in a semantic task and attributed this activation to a cognitive strategy in order to solve the task by stronger reliance on visual processing. The area has also been linked to visual imagery and semantics (Price, 2010).

Following our argument of higher efficiency in areas with decreased activation from pre- to post-training, right hippocampus (related to learning and memory) and thalamus (related to attention) became less involved after therapy. Decreases of precuneus and also of posterior cingulate activation speak for decreased involvement of previously required cognitive strategies. Likewise, Raboyeau *et al.* (2008) reported a decrease in these two areas, which was correlated with training-related improvement of word retrieval in aphasia.

Unexpectedly, we did not observe neural priming effects in healthy controls, even though activation reductions due to repeated task performance appear to be the rule (Henson, 2003). Nevertheless, this fits well with the findings of van Turennout *et al.* (2003), who reported activation decrease in occipito-temporal and left inferior frontal regions for repeated naming that diminished over a 3-day interval. Similar to our control group, activation increase was found in left insula and basal ganglia, especially for long lags. Turennout and coworkers (2003) argue that early changes of representations in occipito-temporal and inferior frontal areas were replaced by automated and efficient name retrieval in insula and basal ganglia later on; the latter could still be found weeks later in our healthy subjects, accompanied by increased posterior ACC activation. Since activation of ACC previously was found for the processing of personally familiar faces (Donix *et al.*, 2010), involvement of this control area might also be indicative of recognition processes and familiarity effects *per se*.

Given that this reorganization of brain circuitry related to priming and learning usually does occur, it may still not work properly in patients due to malfunctioning. Left ACC and caudate had already been abnormally reduced before training, and there was no amelioration but even further decrease due to training. Both areas have also been associated with language control (including error-related processing) and the suppression of irrelevant words (Price, 2010). We conclude that this decrease may represent the continuing functional deficit in higher-order priming/learning processes. This functional deficit might indeed be secondary, i.e. both areas might be inactive due to missing input from language-related areas. In accordance with this view, increased right ACC activation has been implicated in training-induced improvements by Raboyeau *et al.* (2008). Thus, decreased activation over time might not generally be indicative of higher efficiency, especially when activation had already been reduced compared to healthy controls before training started.

Joint ICA: specific therapy-induced recovery

The large IGF lesion (component C4) probably disconnected anterior from posterior brain regions both via dorsal and ventral language pathways (Saur *et al.*, 2008; Axer *et al.*, 2012). The negative correlation with therapy gain reveals that this recovery pattern was not successful for this subgroup of patients. Furthermore, the regression analysis on therapy effects showed that the lesion maps in particular contributed to this component. Naeser *et al.* (1989) showed that the extent of white matter damage in a region deep to Broca's region was an important indicator of severity of speech impairment in non-fluent aphasic patients. A lesion in left IFG pars triangularis (BA 45) was also correlated negatively with outcome after semantic therapy (Marcotte *et al.*, 2012). In both studies, a

disconnection might have contributed to the behavioural effects, just as in our patient subgroup. Thus, Broca's area and superior frontal gyri (BA 9) associated with word retrieval and semantics (Price, 2012) may be able to work more efficiently, but since they work relatively independent of more posterior left-sided regions, the information cannot be transmitted to the language area including Wernicke's area. Maybe even more crucial, the disconnection to the hippocampal formation may impair explicit learning of linguistic knowledge and optimal cognitive strategies (see also Goldenberg and Spatt, 1994), preventing further improvements. Moreover, the impairment of various pathways may render re-routing by means of therapy impossible; this may be the reason why there was no change of activation in the right Broca homologue. Thus, preserved ventral and dorsal connectivities via the frontal lobe appear to be crucial for therapy-induced improvements of aphasic word retrieval.

The other two components probably indicated spared long-range connectivities, since neither the large lesion associated to component C7 nor the more focal lesion associated with the component C5 extend into subcortical structures. The regression analysis on therapy effects indicated that lesion and activation maps equally contributed to the former component. The brain areas with significant signal change resemble those previously found for patient groups with good language recovery: compensatory activation for damage of posterior language zones in recovered aphasia was shown to include bilateral IFG and homologous right temporal areas (Weiller *et al.*, 1995). Moreover, compensatory activation for lesions in anterior language zones was shown to involve peri-lesional left IFG (Calvert *et al.*, 2000*a*, *b*) or right homologous IFG (Miura *et al.*, 1999) activation. We found the very same areas to show decreased activation after intervention for the two lesion subgroups.

A consideration of differential effects of trained versus untrained items over time (see Abel *et al.*, 2014) again revealed a frontal and a posterior component with specific activation patterns, corroborating the importance of bilateral thalamus (for the former), as well as the engagement of areas related to error suppression (left caudate) next to the disengagement of homologous right-hemisphere areas (middle temporal gyrus, superior occipital gyrus and angular gyrus) associated with compensation of language functions (for the latter).

Previous single case (Vitali *et al.*, 2007) and group studies (Blasi *et al.*, 2002; Musso *et al.*, 1999) on training-induced reorganization in aphasia after frontal or temporal damage revealed activation changes in right-sided language areas homologous to the respective lesion site. A correlation with improved language performance due to therapy was rarely found for right hemisphere activations (Crosson *et al.*, 2005; Raboyeau *et al.*, 2008), but more frequently for bilateral (Fridriksson *et al.*, 2006, 2007; Meinzer *et al.*, 2007; Menke *et al.*, 2009) and left-sided (peri-lesional) activations (Leger *et al.*, 2002; Cornelissen *et al.*, 2003; Vitali *et al.*, 2007; Meinzer *et al.*, 2008). High interindividual variability of the right hemisphere as 'backup' resource was emphasized by Cappa (2000) (see also Gainotti, 1993). Our joint ICA reveals that the IFG might have the highest compensatory potential at least for our patient subgroups and therapy method.

(Series) of single cases usually also report increases, while the rare group studies also report decreases in activations measured by functional MRI (Blasi *et al.*, 2002; Richter *et al.*, 2008; Menke *et al.*, 2009). We presume that increases might be attributed to rewiring of connectivities in the language system due to new associations, decreases might be related to enhanced efficiency due to priming and learning. It is likely that the re-wiring of connectivities strongly varies between patients, especially in the previously non-dominant right hemisphere, where new connectivities have to be established. Recent findings revealed that the extent of right-sided anatomical connectivities, which are heterogeneous in the healthy population, might play a role in the variable reorganization patterns and behavioural improvements in aphasia. Functional MRI case series also might be helpful to shed light on the interplay between the two presumed mechanisms of recovery. A previous analysis of three single cases including Patients P11 and P15 from the current study (Abel *et al.*, 2012*b*) revealed increases over and above decreases from pre- to post-training (contrast I-b) [see also pre-post comparisons for naming with distractors in three single cases from Dressel *et al.* (2011)].

An influence of the applied cueing-therapy method, which is known to feature word priming (Abel *et al.*, 2007) instead of (re-)learning of linguistic rules or compensatory strategies, remains to be investigated. Moreover, we cannot reveal the impact of treatment-induced changes over and above repeated exposure to the stimuli, as our control group did not receive multiple stimulus exposure or training in-between the two scans. However, it remains unclear whether repetition suppression related to priming and greater efficiency induced by therapy methods featuring priming differ at all.

Perani *et al.* (2003) examined functional MRI activations for a semantic fluency task in aphasic patients and attributed extensive prefrontal activations to mental effort to achieve lexical retrieval. Along the same lines, the increase of activation in prefrontal areas, which was found for all three components in our study, can be attributed to higher demands on control processes (Ridderinkhof *et al.*, 2004), which might be implemented in language performance and learning. Moreover, the joint ICA illustrates that various mechanisms of recovery and reorganization might be involved together, including activation decreases due to higher efficiency and increases due to higher demands on control processes.

Conclusion

The present study investigated therapy-induced changes of brain activation patterns in a group of 14 patients with

chronic aphasia and word-finding difficulties using functional MRI. Moreover, we combined functional MRI with joint ICA for the first time to investigate the relationship between brain reorganization patterns due to therapy and lesion sites. Behaviourally, the majority of cases and the patient group improved significantly during the 4 weeks of lexical therapy.

We assessed brain activations before therapy to determine already recovered naming networks and compared pre–post therapy activations to reveal neural changes due to therapy. We found bilateral compensation in a premorbidly existing language network (redundancy recovery), recruitment of non-language areas to subserve other strategies for naming attempts (visuo-cognitive strategy in precuneus), and persisting deficits affecting higher-order cognitive functions (ACC and caudate). The exclusive presence of therapy-related activation decreases—which have been related to higher processing efficiency—without any sign of increases in the group analysis may be caused by the high variability of individual rewiring of connectivities.

To account for high lesion variability, we related lesion information from structural MRI with functional data of therapy-induced brain reorganization, using joint ICA. As a result, significant differences in brain activation between patients and healthy controls were found for three of seven joint ICA components. All three lesion patterns involved deactivation of left IFG; however, large IFG lesions appear to be less advantageous, perhaps due to persisting disconnection of pathways preventing successful information transmission between language areas. Moreover, there was no compensatory deactivation in contralateral IFG for large IFG lesions, which might be—at least functionally—disconnected. On the contrary, right IFG compensation could be found for the small prefrontal lesion, and right IFG and homologous superior temporal gyrus compensation for temporo-parietal lesions.

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Supplementary material

Supplementary material is available at *Brain* online.

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