Association between therapy outcome and right-hemispheric activation in chronic aphasia

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The role of the right hemisphere for language processing and successful therapeutic interventions in aphasic patients is a matter of debate. This study explored brain activation in right-hemispheric areas and left-hemispheric perilesional areas in response to language tasks in chronic non-fluent aphasic patients before and after constraint-induced aphasia therapy (CIAT). In particular, we analysed the relation between brain responses and therapy outcome. Using functional magnetic resonance imaging (fMRI), brain activation was measured during word-reading (REA) and word-stem completion (COM) in 16 chronic non-fluent aphasic and 8 healthy subjects. Before therapy, activation in right inferior frontal gyrus/insula (IFG/IC) was stronger in aphasics compared to controls during REA and in precentral gyrus (PCG) during COM. Therapeutic intervention per se did not change brain activation for either task across all aphasic subjects. However, therapeutic success correlated with a relative decrease of activation in right-hemispheric areas, including the IFG/IC. Most importantly, initial activation in right IFG/IC and other right-hemispheric areas correlated positively with subsequent therapy success. Thus, right-hemispheric activation prior to aphasia therapy strongly predicts therapeutic success, suggesting that brain activation in chronic aphasia indicates the patients’ potential for further language improvement.

Keywords: aphasia; recovery; CI aphasia therapy; right hemisphere; functional MRI

Abbreviations: AAT = Aachen Aphasia test; BI = behavioural improvement; CIAT = constraint-induced aphasia therapy; fMRI = functional magnetic resonance imaging


Introduction

Up to 38% of ischaemic stroke patients suffer from aphasia and nearly half of them develop persistent deficits (Wade et al., 1986; Pedersen et al., 1995). Nevertheless, patients generally undergo some degree of spontaneous recovery. This process depends on individual factors, e.g. the characteristics of the lesion and the capacity of the persisting functional network involved in language comprehension and production (Heiss et al., 1999). In aphasics, language-related cortical activations have been detected within perilesional areas of the language-dominant left hemisphere and within the right hemisphere at sites homotopic to left-sided fronto-temporal language areas such as the right inferior frontal gyrus and the adjacent insular cortex (IFG/IC) (Weiller et al., 1995; Ohyama et al., 1996; Zahn et al., 2004). Reactivation of perilesional areas has been suggested being most efficient in regaining language functions (Karbe et al., 1998; Rosen et al., 2000; Heiss and Thiel, 2006).

The role of the contralesional hemisphere for recovery remains controversial. Generally, stronger activation in right-hemispheric language areas has been shown in aphasics as compared to healthy subjects (Belin et al., 1996; Karbe et al., 1998; Cao et al., 1999). This activation might partially be interpreted in terms of transcallosal disinhibition, an anomalous response caused by damage of left-hemispheric parts of the language processing system, and does not reflect recovery (Price and Crinion, 2005). However, in some patients, right-hemispheric activation was associated with improvement of language functions (Thulborn et al., 1999; Winhuisen et al., 2005). There is evidence that the extent of right-hemispheric activation and its contribution for recovery depends on various conditions such as time since stroke onset (Hillis, 2006; Saur et al., 2006), localization and size of the lesion (Rijntjes, 2006), severity of aphasia (Heiss et al., 1999) and extent of improvement during therapeutic interventions (Musso et al., 1999). In particular, patients with less-severe
aphasia and smaller lesions may be able to restore activation within remaining language areas or perilesional areas of the left hemisphere. Patients with more severe aphasia usually show more extensive lesions and recruit undamaged right-hemispheric areas of the language processing network. The latter strategy is associated with less-efficient compensation but nevertheless leads to favourable recovery in some patients (Heiss and Thiel, 2006).

Within this context, a big challenge is imposed by the question which brain processes are associated with therapeutically induced improvement of language functions in aphasic patients. Functional brain imaging, electroencephalographic (EEG) and magnetoencephalographic (MEG) methods provide important tools to study the effect of therapeutic interventions on brain activation (Thompson, 2004). However, only few studies with small samples (maximum of 10 patients) were conducted so far that explored the effects of aphasia therapy or language-related training programs on brain responses in aphasics (Belin et al., 1996; Musso et al., 1999; Leger et al., 2002; Abo et al., 2004; Peck et al., 2004; Crosson et al., 2005; Pulvermuller et al., 2005; Breier et al., 2006, 2007). Two studies included healthy subjects as reference for normal activation (Leger et al., 2002; Abo et al., 2004). Abo et al. (2004) investigated brain activation 7 months after aphasia treatment and found exclusively right-hemispheric activation in two completely recovered patients. In another study, individually different lateralization shifts in frontal areas were reported in two patients after receiving intention training (Crosson et al., 2005). Peck et al. (2004) investigated times to peak (TTPs) of right-frontal hemodynamic responses as an indicator for the speed of word-finding in aphasics and found that TTPs decreased in two patients and increased in one patient after an effective 2-week treatment. Furthermore, Musso et al. (1999) reported increased activation within the right superior temporal cortex that correlated with language performance after short-term therapy in four aphasics suffering from Wernicke’s aphasia. In contrast, reactivation of left-frontal, perilesional areas after long-term aphasia therapy was reported in a single non-fluent aphasic patient (Leger et al., 2002). The effect of melodic intonation therapy on neural activation has been investigated in seven non-fluent aphasics with positron emission tomography revealing that left-frontal activation increased while right-hemispheric activation decreased after treatment (Belin et al., 1996). Pulvermuller et al. (2005) reported that constraint-induced aphasia therapy (CIAT) led to bilaterally enhanced N300 components of evoked potentials in 10 patients. An MEG study with five chronic aphasic patients did not show an association between language improvement and MEG activity during CIAT (Breier et al., 2007).

Nevertheless, this study adverts that response to CIAT might be a function of the degree of activation prior to therapy.

Thus, results are fairly inconsistent and it remains controversial to what extent the right hemisphere contributes to therapy-induced improvements of language functions in aphasic patients. Studies with increased sample size and with more extended analyses of correlations between brain activation and therapy outcome are strongly needed. In particular, there is a lack of studies that investigate whether brain activation in chronic aphasia may predict the success of subsequent therapeutic interventions. This analysis should be a critical test of the question whether specific activation patterns in aphasic patients are associated with prognostic trends for therapeutic outcomes.

The present study aimed to investigate right-hemispheric brain function in chronic aphasic patients before and after participating in an effective treatment of language impairment. We used functional magnetic resonance imaging (fMRI) to measure brain activation in response to different language tasks in a final sample of 16 chronic non-fluent aphasic patients and in 8 healthy control subjects. In particular, we analysed the predictive value of brain activation for subsequent therapy outcome, and the relation between therapy outcome and therapy-induced changes in brain activation. Based on prior studies, we focused on the most relevant region involved in recovering from non-fluent aphasia—the IFG and adjacent IC (e.g. Rosen et al., 2000; Winhuisen et al., 2005).

Subjects and Methods

Subjects

Twenty-four right-handed patients with chronic non-fluent aphasia and eight control subjects participated in the study. Patients were recruited from several self-help groups and by public advertisement. The inclusion criteria were: (1) a lesion exclusively within the language-dominant left hemisphere, (2) evidence of persisting aphasia as assessed by the Aachen Aphasia Test (AAT) (Huber et al., 1984), (3) main deficits in language production but not in perception as indicated by several subtests of the AAT, (4) at least 12 months since the stroke accident and (5) no other significant illnesses precluding participation. Pre-morbid right-handedness was assessed with the Edinburgh Handedness Inventory (Oldfield, 1971). In case patients had difficulties with the questionnaire we interviewed their affiliates regarding the actions listed in the questionnaire. Eight of the 24 aphasic patients had to be excluded from further analyses. Five of these patients attended only one fMRI-session and three patients were not able to execute the tasks properly. Finally, 12 males and 4 females non-fluent aphasics, aged between 43 and 73 years [mean (SD) = 58.3 (9.6) years] took part in this study. Seven patients met the classification criteria for Broca’s aphasia, 7 for anomic aphasia, and 2 for global aphasia. Patients’ characteristics are listed in Table 1. Sites of infarctions are displayed in Fig. 1.

Control subjects [4 male, 4 female volunteers, aged between 51 and 69 years, mean (SD) = 57.6 (6.4) years, all right handed] did not report any prior head injuries, cerebral insults or language-related disorders. While control subjects were scanned once, patients were scanned directly before therapy onset (T1) and immediately after therapy (T2). There was a 2-week interval between pre- and post-scans. All subjects were native German speakers and provided informed consent to participate in

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Table I  Patient characteristics and behavioural data

<table>
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<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>SS T1</th>
<th>SS T2</th>
<th>TT T1 (reversed)</th>
<th>TT T2 (reversed)</th>
<th>AC T1</th>
<th>AC T2</th>
<th>SC T1</th>
<th>SC T2</th>
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</table>

M = male; F = female; T1 = pre therapy; T2 = post therapy; SS = spontaneous speech scale of the Aachen Aphasia Test; TT = Token Test of the Aachen Aphasia Test; AC = auditory comprehensibility scale of the Amsterdam Nijmegen Everyday Language Test, SC = semantic comprehensibility scale of the Amsterdam Nijmegen Everyday Language Test, GLS1 = global score of language skills before therapy; GLS2 = global score of language skills after therapy; BI score = score of behavioral improvement; X = missing value.

Fig. 1  Sites of infarction in aphasic patients (A1–A16). Transversal MRI scans are displayed at the level of maximum infarct volume. Right side of the figure corresponds to left side of the brain.
Aphasia treatment

Each patient participated in a 2-week constraint-induced aphasia therapy (CIA-therapy), a behavioural treatment based on constraint-induced therapy (CI-therapy), developed for patients with motor deficits after stroke (Miltner et al., 1999a; Liepert et al., 2000; Taub et al., 1999). The treatment intended to specifically practice language acts patients have difficulties with and was carried out by experienced clinical psychologists. One main element characterizing this method is restriction of compensatory strategies such as mimics, gesticulation, writing, drawing and utterances that can easily be produced by aphasic patients. Therapists systematically apply the behavioural techniques of shaping as a method of operant conditioning and reinforcing strategies, i.e. the patient is rewarded for each single improvement but never criticized or blamed for any failure. Increased usage of previously neglected utterances was achieved by intense exercising during 3 h per day for a total of 10 days. This intervention was previously reported to be effective in chronic non-fluent aphasics (Pulvermüller et al., 2001). Three of our patients (A1, A11 and A12) were trained in a two-person group setting, other patients in a single patient setting with two therapists each.

Behavioural evaluation

Aphasia diagnosis was obtained by the complete AAT (Huber et al., 1984). Behavioural assessment of different aspects of language was conducted directly before (T1) and after CIA (T2). We selected four tests to measure language performance including two subscales of the AAT—spontaneous speech (SS, consisting of the subscales communicative behaviour, articulation/prosody, automated speech, semantic structure, phoneme structure and syntax) and the Token Test (TT) and two subscales of the Amsterdam-Nijmegen Everyday Language Test (ANELT) (Blomert et al., 1994)—auditory (AC) and semantic comprehensibility of speech (SC). The spontaneous speech scale and the two scales of the ANELT were assumed to be most sensitive to therapy-induced changes in speech production. We also included the Token Test that was widely used in prior studies of language recovery (e.g. Heiss et al., 1999; Musso et al., 1999; Saur et al., 2006). As a global score for behavioural improvement (BI) the differences between test scores at T1 and T2 were z-standardized and averaged using the equation BI = [(SS2 − SS1)2 + (TT2 − TT1)2 + (AC2 − AC1)2 + (SC2 − SC1)2]/4. Behavioural measures were analysed using SPSS (Version 13.0, SPSS Inc., Chicago, IL). Patients’ scores of T1 and T2 were compared using t-tests. Effect sizes were calculated for significant effects [(M1 − M2)/SD1]. Statistical threshold was fixed to P < 0.05 for group comparisons. Data of TT and SS after therapy is missing for patient A5 because of problems with the time schedule.

Language tasks

The experimental paradigm included two covert language-related activation tasks: a simple reading task (REA) and a more complex word stem completion task (COM). Both tasks were available in two different versions, one for each time of measurement. Assignment of task version to scanning time points was balanced across subjects. Each task was performed during a separate scanning run. During the reading task participants were instructed to silently read the words presented at the screen. During the completion task the word stems had to be completed to one meaningful word silently.

During the reading condition, four activation periods were presented in the scanner. Before the first and after the last period and between periods, a fixation cross was presented as low-level baseline condition. Each of the six baseline periods and each of the four stimulus sequences lasted 30.1 s (seven volumes). Each stimulus sequence included 14 one- or two-syllable German nouns with a presentation time of 1.9 s per stimulus and an interstimulus interval of 0.25 s. There was no repetition of words between periods or time points. The average word frequency was high (mean = 101.9, SE = 7.3, reference 500 000 spoken German words) corresponding to Ruoff (1990). The nouns were matched between the two versions according to word frequency and length.

During the completion task, also four task blocks and six fixation periods were presented, each lasting 30.1 s (seven volumes). Each stimulus sequence included seven three-letter word stems (e.g. ‘HAL’) with a presentation time of 3.4 s per stimulus and an interstimulus interval of 0.9 s. There was no repetition of word stems between blocks or time point. It was assured that there were at least three meaningful and high frequent completions possible for each word stem (Ruoff, 1990). Word stems of the two versions were matched according to the most frequent completion in German language (Ruoff, 1990). The paradigm induced a continuous word generation task comparable to previous studies (e.g. Cao et al., 1999; Rosen et al., 2000; Blasi et al., 2002; Perani et al., 2003).

Pre-tests with an independent sample of aphasics were carried out to assure that non-fluent aphasics were able to solve the tasks. Based on these tests, the presentation parameters were chosen. In a final pre-test, we conducted the tasks with six non-fluent chronic aphasics and asked for comprehensibility, feasibility and speed of the tasks. Each patient reported the tasks to be adequate in speed and complexity, whereas the completion task was rated as more difficult but solvable when using the presentation parameter described earlier. However, to assess the task performance of patients during the scanning session, patients underwent a brief interview after completing the fMRI-session. Additionally, the study was aborted if patients still reported to have problems with reading or word stem completion after two test trial sessions.

MRI and fMRI data acquisition and analysis

In the 1.5 T magnetic resonance scanner (Magnetom Vision plus, Siemens, Medical Systems, Erlangen, Germany), two runs of 67 volumes were measured using a T2*-weighted echo-planar sequence [time to echo (TE) = 60 ms, flip angle = 90°, matrix = 64 × 64, field of view (FOV) = 192 mm, scan repeat time (TR) = 4.3 ms]. Each volume comprised 40 axial slices (thickness = 3 mm, no gap, in plane resolution = 3 × 3 mm2) parallel to the intercommissural plane (AC–PC plane). Additionally, a high-resolution T1-weighted anatomical volume was recorded (192 slices, TE = 5 ms, matrix = 256 × 256 mm2, resolution = 1 × 1 × 1 mm3, duration = 12 min). Analysis of anatomical data confirmed exclusively left-hemispheric lesions in the patients (Fig. 1).
Imaging data were pre-processed and analysed using Brain Voyager QX (Version 1.7.; Brain Innovation, Maastricht, The Netherlands). The volumes were realigned to the first volume in order to minimize effects of head movements on data analysis. The further data pre-processing comprised spatial (6 mm full-width half-maximum isotropic Gaussian kernel) as well as temporal smoothing (high-pass filter: 3 cycles per run). Anatomical and functional images were co-registered and normalized to the Talairach space (Talairach and Tournoux, 1988).

Statistical analysis of fMRI-data was performed by multiple linear regression of the signal time course at each voxel. The expected blood oxygen level-dependent (BOLD) signal change for each event type (predictor) was modelled by a canonical hemodynamic response function (modified gamma function). Statistical parametric maps resulting from the whole brain, voxelwise analysis were inspected within and outside the defined region of interest (ROI). The right IFG/IC and the left IFG/IC were defined a priori as ROI using the Talairach daemon (http://ric.uthscsa.edu/projects/talairachdaemon.html).

Random effect group analyses were performed for each relevant contrast: (1) activation in controls, (2) activation at T1 in aphasics, (3) comparison of aphasics and control subjects, (4) activation changes in aphasics from T1 to T2. To strike a balance between type I and type II errors, results were considered being statistically significant for clusters with peak $t$-values of $P<0.005$ and at least 108 activated $1 \times 1 \times 1 \text{mm}^3$ voxels within the ROI (Straube et al., 2006, 2007). Exploratory analysis of activation in the right hemisphere outside the IFG/IC was conducted on a significance level of $P<0.001$. Although not the focus of our study, given the heterogeneity of lesions in the patients, we also investigated brain activation in left-hemispheric areas in the patients. Voxelwise random effects analyses were not appropriate to measure activation at T1 or activation change from T1 to T2 due to the enormous individual differences of infarction sites. Therefore, group analyses were conducted with $t$-tests (using SPSS software) across the parameter estimates of the peak activation of significant clusters (according to the ROI thresholds) in the IFG/IC or the frontal perilesional area of each patient. The perilesional areas were defined as the brain tissue in the frontal cortex that surrounded the lesion within a distance of about 5 mm for all coordinates $y>0$. In case we detected two or more significant clusters, the mean parameter estimates for the peaks of those clusters were used for further analyses. Based on activation in the main effect analysis, additional correlation analyses between BI scores and brain activation of aphasics were performed on a significance threshold of $P<0.05$.

**Results**

**Behavioural results**

From T1 to T2 assessment, patients improved significantly regarding spontaneous speech ($t=4.81$, $P<0.001$), auditory comprehensibility ($t=3.60$, $P<0.01$) and semantic comprehensibility ($t=2.45$, $P<0.05$). Performance of language comprehension, measured by the Token Test of the AAT did not differ between time points. Behavioural data pre- and post-therapy are listed in Table 1. Effect sizes were calculated for significant results, showing medium-sized effects for behavioural changes in spontaneous speech ($d_{SS}=0.41$) and auditory comprehensibility ($d_{AC}=0.51$) and a small-sized effect for changes in semantic comprehensibility ($d_{SC}=0.25$). Test scores before CIAT did not correlate significantly with behavioural improvement score (BI), indicating that therapy-induced behavioural changes were not related to severity of aphasia.

**fMRI results**

**Activation at T1 in aphasics and controls**

**Reading.** Inspection of activation in control subjects within and outside the ROI indicated a neural network involving left IFG/IC, right superior frontal gyrus, bilateral lingual gyrus, superior temporal gyrus, middle and inferior occipital gyri. In the ROI analysis, patients exhibited activation of right IFG/IC and left IFG/IC or frontal perilesional tissue. The mean $t$-value of individual peaks within the left-hemispheric ROI was mean ($t=4.91$). Exploratory analysis of other right-hemispheric regions in the patient group revealed activation in precentral, middle frontal, middle and superior temporal gyri, putamen, inferior to middle occipital and lingual gyr. Voxelwise activation within the right hemisphere is displayed in Fig. 2 and corresponding statistics are listed in Table 2. Compared to controls, patients showed significantly stronger activation within right IFG/IC ($t=4.59$; $P<0.005$; 940 voxels, peak voxel: $x=42$, $y=15$, $z=-2$).

**Fig. 2** Sagittal and transversal view of activated clusters in regions of interest at T1 in controls ($x=42$, $y=22$, $z=10$) and aphasics ($x=42$, $y=22$, $z=10$) during reading (REA). Voxelwise random effect analyses within the left hemisphere were not conducted in aphasics due to the variety of lesions. IFG/IC = inferior frontal gyrus and insular cortex.
Word-stem completion. Control subjects recruited a widespread network of activations within and outside the ROI including bilateral IFG/IC, precentral gyrus (PCG), superior temporal gyrus, precuneus, fusiform gyrus and middle occipital gyrus, and right medial frontal gyrus and lingual gyrus. In the ROI analysis, aphasics exhibited activation of right IFG/IC and left IFG/IC or frontal perilesional tissue. The mean \( t \)-value of individual peaks within the left-hemispheric ROI was mean \( t \) = 4.32. Exploratory analysis of other right-hemispheric regions showed activation in PCG (one cluster extending from IFG/IC to PCG), middle, medial and superior frontal gyri, lingual, middle temporal gyrus (MTG) and fusiform gyrus. Voxelwise activation within the right hemisphere is displayed in Fig. 3 and corresponding statistics are listed in Table 3.

During the completion task, no between-group effects were found within the ROI. Exploratory analysis showed that aphasics exhibited significantly stronger activation than controls in one cluster within the right PCG \( t = 5.26; P < 0.001; 918 \) voxels; peak voxel: \( x = 25, y = -28, z = 52 \).

Relation between brain activation at T1 and therapy outcome
We tested whether brain activation at T1 correlated with the amount of language improvement during therapy, as indicated by BI scores. During reading, BI showed a positive correlation with activation in right IFG/IC at T1 \( r = 0.56; P < 0.05; \) peak voxel: \( x = 48, y = 2, z = 21 \). Furthermore, outside the ROI, BI was positively correlated with activation in PCG \( r = 0.78; P < 0.01; \) peak voxel: \( x = 52, y = -11, z = 25 \) and MTG \( r = 0.53; P < 0.05; \) peak voxel: \( x = 58, y = -46, z = -9 \). Thus, activation of right IFG/IC, PCG and MTG during reading predicted therapy-related behavioural outcome. Figure 4 displays the corresponding scatter plots.

For the completion task, BI was positively correlated with activation in two clusters within right IFG/IC (cluster 1 with \( r = 0.81, P < 0.005, \) peak voxel: \( x = 35, y = 22, z = 11 \); cluster 2 with \( r = 0.58, P < 0.05, \) peak voxel: \( x = 52, y = 17, z = 2 \). Thus, as in the reading task, activation in right IFG/IC predicted therapy-related behavioural outcome during word stem completion (Fig. 5). There was no significant correlation between activation in left IFG/IC and perilesional areas and BI for both tasks.

Therapy-induced changes in brain activation
For both hemispheres, there were no statistically significant differences of activation between T1 and T2 across the
whole group of aphasics. Evidently, aphasics exhibited similar activations at both time points. In the next step, we tested whether therapy-induced activation changes within the highly predictive clusters correlated with BI scores. To quantify changes in brain activation, we used the difference activation at T2 minus activation at T1. Positive correlations would indicate that a stronger increase or at least a less decrease of activation across time points is

Table 3 Activated clusters within right hemisphere in aphasics before therapy and controls during word stem completion (COM)

<table>
<thead>
<tr>
<th>Region of right hemisphere</th>
<th>Aphasics</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>x</td>
<td>y</td>
</tr>
<tr>
<td>ROI (P &lt; 0.005) In inferior frontal gyrus/insula</td>
<td>40</td>
<td>6</td>
</tr>
<tr>
<td>Non ROI (P &lt; 0.001) Superior temporal gyrus</td>
<td>52</td>
<td>-39</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Precentral gyrus</td>
<td>43</td>
<td>18</td>
</tr>
<tr>
<td>Medial frontal gyrus</td>
<td>13</td>
<td>-84</td>
</tr>
<tr>
<td>Lingual gyrus</td>
<td>34</td>
<td>-81</td>
</tr>
</tbody>
</table>

Coordinates refer to the most significant voxel within each cluster. t = t-value of most significant voxel; voxel = number of voxels within referred activated cluster.

Fig. 4 (a–c) Significant correlations of behavioural improvement (BI) with activation at T1 and (d) Significant correlations of BI with activation change from T1 to T2 during reading (REA). IFG/IC = inferior frontal gyrus and insular cortex (x = 48, y = 2, z = 2); MTG = middle temporal gyrus (x = 58, y = -46, z = -9); PCG = precentral gyrus (x = 52, y = -11, z = 25).

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associated with more behavioural improvement. Negative correlations would indicate that a stronger decrease or at least less increase of activation across time points is associated with more behavioural improvement.

During reading, no significant correlation between changes in brain activation and BI was detected for the ROI analysis within both hemispheres. Analysis of activation within PCG and MTG indicated that activation change within the MTG was negatively correlated with BI ($r = -0.69; P < 0.005; x = 58, y = -46, z = -9$; see Fig. 4).

During the completion task, negative correlations between BI and activation change were found for the two clusters in right IFG/IC (cluster 1: $r = -0.68; P < 0.005; x = 52, y = 17, z = 2$; cluster 2: $r = -0.55; x = 35, y = 22, z = 11$). Figures 4 and 5 display the corresponding scatter plots for the peak voxels. Visual inspection of the scatter plots revealed that activation during both tasks decreased in aphasics with higher BI scores and increased in aphasics with lower BI scores.

We found no significant correlation of activation change within left IFG/IC and perilesional frontal regions and BI.

**Discussion**

The purpose of this study was to investigate the relation between right-hemispheric activation and outcomes of an aphasia therapy in chronic non-fluent aphasia. Using a simple reading task and a more complex word-stem completion task we measured brain activation in regions associated with language processing in aphasic and healthy control subjects. At the behavioural level, aphasics subjects improved regarding language production skills consistent with findings of prior reports on CIAT effects (Pulvermüller et al., 2001). We observed that activation within the right hemisphere predicts therapy success and that change in brain activation across scanning sessions correlates with the behavioural data. In the following paragraphs, the fMRI
findings will be discussed in relation to each step of data analysis.

Brain activation in controls and aphasics

Controls activated a distributed neural network including bilateral language-related areas during reading and word-stem completion, supporting that right-hemispheric regions engage in language processing in healthy right-handed subjects as stated previously (Karbe et al., 1998; Heiss et al., 1999). Compared to controls, aphasics activated a similar network with stronger activation in right IFG/IC during reading and in right PCG during completion. The lack of significant differences in right IFG/IC may be due to the more bilateral and widespread activation within both hemispheres of controls during completion compared to the reading task (Figs 3 and 4). The differences in central processing between aphasics and controls might be particularly conspicuous when solving simple tasks. The cognitive demands of a reading task in healthy controls might be very low compared to aphasics while the word-stem completion task might be a highly demanding task for both experimental groups.

Numerous studies demonstrated that right IFG/IC and PCG are associated with language processing in post-stroke aphasia, even though it is not resolved yet to what extent this process reflects restoration or a compensation of language functions (Weiller et al., 1995; Cao et al., 1999; Zahn et al., 2004; Winhuisen et al., 2005; Saur et al., 2006). Extended activation of the unaffected hemisphere has previously been linked to poor recovery and extended lesions (Naeser et al., 2004; Heiss and Thiel, 2006), and has mainly been interpreted in terms of enhanced transcortical disinhibition due to large left-sided infarctions of patients (Price and Crinion, 2005). However, right-hemispheric activation was assumed to reflect the recruitment of language-related areas at least in some aphasics (Winhuisen et al., 2005). This assumption is partially underpinned by the finding that even control subjects activated a bilateral language network including classic left-hemispheric areas and also homologue regions within the right hemisphere. This indicates that the language tasks we used inherently activated language-processing regions within the right hemisphere.

Relation between pre-therapy brain activation and therapy outcome

Right-hemispheric activation in aphasics has mainly been suggested to signal an inferior strategy (Karbe et al., 1998; Rosen et al., 2000; Heiss and Thiel, 2006). This might implicate that subjects with stronger right-lateralized activation might benefit more from intense language training resulting in more efficient strategies of language processing. A critical test of the question whether right-hemispheric activation is associated with good or bad prognoses of further improvement in language functions following therapeutic interventions is the investigation of the relation between pre-therapy activation and therapy outcome. Does activation in language-related right-hemispheric areas predict therapy outcome? Effectively, we found positive correlations between activation of right frontal language-related areas (IFG/IC and PCG) and BI scores in the aphasic group indicating that brain activation prior to treatment can predicted therapeutic success of chronic, non-fluent aphasics. These findings suggest that, even if stronger activation of right language-related areas reflects an inferior strategy of recovery in the chronic state, this strategy seems to be crucial for subsequent improvements of language functions after interventions. Thus, this effect might be based on a greater potential for further improvement if the current reorganization strategy was suboptimal.

An alternative explanation, however, is that the detected positive correlation traces back to differences in cognitive effort while solving the reading and completion tasks. A relation between effort and activation would be in line with an earlier study, hypothesizing an association between the amount of neural activation and the computational demands of a task (Just et al., 1996). Aphasics with more effort might be those patients who experience more difficulties with the tasks. They might also be those patients who show more sedulity during training and therefore benefit most according to language improvement. Thus, individual differences in motivation and effort might influence both—extent of brain activation and therapy outcome.

Breier et al. (2007) found that response to CILT was a function of the degree of late activity within the right hemisphere prior to therapy in 5 non-fluent aphasics. Even though they analysed a small sample of five patients, these findings are in line with our hypothesis of the predictive value of pre-therapy right-hemispheric activation and suggest that some degree of participation in language function by the right hemisphere prior to therapy may facilitate the effects of CILT.

Therapy-induced changes in brain activation

We did not find activation changes from T1 to T2 across the whole group of 16 aphasics due to CI-aphasia therapy. Nevertheless, suggesting that a lack of therapy-induced activation changes may also be a result of individual differences in behavioural improvement, we investigated correlations of BI scores with activation changes.

Furthermore, activation change in left perilesional regions was not associated with therapy success. This stands in contrast to several prior studies that reported that reactivation of perilesional regions is associated with language improvements (e.g. Belin et al., 1996; Leger et al., 2002). This might indicate that a reactivation of perilesional tissue is not necessarily associated with therapy success. Nevertheless, analysing activation change in a stroke-patient group, especially within the damaged hemisphere, is accompanied by various limitations due to the individuality of lesion characteristics and activation patterns. Therefore, methodical
problems such as differentiation between lesion and remaining grey matter, the use of individual local peaks of activation for statistical analyses, and averaging of activation within perilesional areas might contribute to the lack of solid results.

We found negative correlations between BI and activation changes in right IFG/IC and MTG, suggesting that patients indeed show different reorganization strategies depending on therapy outcome. Activation within the right IFG/IC represents a compensatory strategy due to the loss of left-frontal classical language processing areas. The MTG has previously been reported to be activated bilaterally during retrieval of phonological and semantic codes during word reading (Hagoort et al., 1999). Visual inspection of the scatter plots showed that activation in these areas decreased in aphasics with more improvement and increased in aphasics with less improvement. Thus, the negative correlation did not simply reflect a stronger decrease of activation in patients with better therapeutic outcomes but indicates individual differences in strategies used to improve language function probably due to the characteristics of the remaining neural network.

Breier et al. (2007) did not find a significant correlation between changes in right-hemispheric activation and changes in language performance after therapy. Pulvermuller et al. (2005) reported a medium positive correlation between increase of the early negativity source strength bilaterally and improvement in Token test score after CIAT. This is not consistent with our findings. One point to mention is that different behavioural measures were applied. Pulvermuller et al. (2005) used the Token test, mainly associated with language comprehension, whereas we used a score that included the Token test and tests concerning spontaneous speech as an overall indicator for language performance. Nevertheless, the patients with little improvement in our study also showed increased activation. Therefore another explanation for the contrary results might be differences in patients’ characteristics that result in different strategies to improve language function.

The reduction of right-hemispheric activation in aphasics characterized by high improvement might indicate a new strategy of increased efficiency of language processing as previously suggested by Breier et al. (2007). As a result of sufficient improvements, less effort might be required at T2 compared to T1 to solve the language tasks. In contrast, patients with poor improvement may attempt to put more effort in using additional strategies after therapy but fail to restore more efficient language capacities. This is reflected by increased activation in those patients.

Limitations
Some limitations of the current study should be mentioned. The results were obtained in patients with chronic aphasia during intense treatment long after a stroke. This seems to be a special condition, and conclusions have to be drawn with caution. Our study focused on activation within the right hemisphere. Further investigations should use samples with similar lesions of the left hemisphere to increase the power for reliable analysis of left-hemispheric perilesional activation. The absence of treatment effects in left-hemispheric areas might be due to the difficulty in analysing patients with a great variety of lesions. Another limitation is that, although we used two tasks to increase the reliability of our findings, other language tasks such as auditory tasks or overt language production might reveal further therapy effects. Furthermore, although we tried to use a homogeneous sample of non-fluent aphasics, some patients had additional impairments in speech comprehension which might have affected the results. Future studies might also investigate more ROIs than the IFG/IC to increase the chance to detect main effects of treatment.

Conclusions
Taken together, our findings suggest that activation of right language-related areas is associated with word reading and word-stem completion in healthy controls and chronic non-fluent aphasics. Compared to controls, aphasics exhibited stronger activations in right language-related areas probably being a result of less-effective strategies for language processing. Activation of language-relevant right-hemispheric regions before CIAT is highly predictive for therapy outcome. During therapy, activation of these regions decreased in aphasics with high improvements, and increased in aphasics with less-behavioural improvements. These data provides evidence that right-hemispheric brain activation before and after therapeutic intervention is strongly correlated with individual differences in language improvement in chronic aphasia. Any analysis that is limited to the group level seems to be insufficient in order to detect these individual and partially opposite effects.

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