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Neural correlates of recovery from aphasia after damage to left inferior frontal cortex

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Objective: To determine neural correlates of recovery from aphasia after left frontal injury. Methods: The authors studied the verbal performance of patients with infarcts centered in the left inferior frontal gyrus (IFG), using a battery of attention-demanding lexical tasks that normally activate the left IFG and a simpler reading task that does not normally recruit the left IFG. The authors used positron emission tomography (PET) and functional MRI (fMRI) to record neural activity in the same group of patients during word-stem completion, one of the attention-demanding lexical tasks. To identify potential neural correlates of compensation/recovery, they analyzed the resulting data for the group as a whole (PET, fMRI) and also for each participant (fMRI). Results: Patients with damage to the left IFG were impaired on all attention-demanding lexical tasks, but they completed the word-reading tasks normally. The imaging studies demonstrated a stronger-than-normal response in the right IFG, a region homologous to the damaged left IFG. The level of activation in the right IFG did not correlate with verbal performance, however. In addition, a perilesional response within the damaged left IFG was localized in the two patients who gave the best performance in the word-stem completion task and showed the most complete recovery from aphasia. Conclusions: Right-IFG activity may represent either the recruitment of a preexisting neural pathway through alternative behavioral strategies or an anomalous response caused by removal of the left IFG. Perilesional activity in the left IFG may represent sparing or restoration of normal function in peri-infarctual tissue that was inactive early on after injury. This activity may be of greater functional significance than right IFG activity because it was associated with more normal verbal performance.


Over the last hundred years, two mechanisms have been proposed to explain the recovery of language after left hemisphere lesions.1,2 Regions in the right hemisphere homologous to those damaged in the left hemisphere may be recruited to support residual or recovered language. In addition, language regions in the left hemisphere that are suppressed early on after injury may recover their normal functions at rest or during activation.

We used PET and functional MRI (fMRI) to examine the neural correlates of language recovery in a group of patients with nonfluent aphasia after left hemisphere injury. The authors studied the verbal performance of patients with infarcts centered in the left inferior frontal gyrus (IFG), using a battery of attention-demanding lexical tasks that normally activate the left IFG and a simpler reading task that does not normally recruit the left IFG. The authors used positron emission tomography (PET) and functional MRI (fMRI) to record neural activity in the same group of patients during word-stem completion, one of the attention-demanding lexical tasks.

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frontal infarcts. The experimental design addressed three main issues.

First, we enrolled patients by using strict anatomic criteria rather than the clinical symptoms used in earlier imaging studies of recovery from aphasia. This approach minimizes the anatomic variability that may occur when subjects are recruited by clinical deficits. Furthermore, recent developments in imaging and linguistics emphasize the relative modularity of language and its cortical representation. Hence, the most direct strategy for investigating the neural mechanisms of language recovery is to focus on the effects of restricted lesions on specialized language modules. A previous study investigated the effects of lesions restricted to the left posterior superior temporal gyrus (Wernicke area). We concentrated on lesions centered in the left posterior inferior frontal gyrus (Broca area).

Second, we used a language protocol that is specific for the damaged left IFG. This region of the brain is a critical module of the brain’s language system, and imaging studies with normal volunteers show that it becomes activated during many tasks that require the active processing of words (attention-demanding verbal tasks). Also, lesion studies indicate that damage to the left IFG creates problems with verbal fluency, phonologic processing, and word retrieval. Our strategy ensures that compensatory responses after left-IFG lesions will likely reflect specific changes within a damaged language system rather than nonspecific effects due to brain damage.

Finally, we examined patterns of functional activation on average in the group (PET, fMRI), but also individually in each patient (fMRI), because group analyses are appropriate for examining compensatory responses occurring at a distance from an injury site, but may miss compensatory responses near a lesion because of intersubject averaging. Furthermore, there have not been direct comparisons between PET and fMRI findings in patients with focal strokes, and it is unknown if the blood oxygenation level–dependent (BOLD) signal measured in fMRI is influenced by variations in baseline blood flow, which may occur near a stroke or at connected distant cortical sites.

The specific hypotheses we tested derive from a previous case report on a patient with a lesion involving the left IFG. Three months after the stroke, the patient was able to read words, an outcome consistent with neuroimaging studies that show only minimal left-IFG activation during highly automated tasks. In contrast, he was severely impaired on more demanding verbal tasks that are known to activate the left IFG. However, he was able to access words when given partial words as visual cues (word-stem completion, e.g., COU is presented, and patient generates “COUple”). This was surprising because this task also activates the left IFG. Therefore, we measured regional blood flow with PET while the patient was performing the word-stem completion task to image potential compensatory pathways. Normal activity was observed throughout the brain, except for a lack of activation within the damaged left IFG and a significantly increased activation in the right IFG that was outside the normal range. We suggested that the right-IFG response was supporting the patient’s normal performance on word-stem completion task. In the current study, we determine whether: 1) patients with chronic lesions in the left IFG commonly recruit the right IFG; 2) the right-IFG response underlies the recruitment of a novel pathway or is just a variant of the normal activation pattern; and 3) the magnitude of the right-IFG response correlates with verbal performance.

Methods and materials. Subjects. We studied four groups of subjects: 1) patients with left frontal lesions, 2) behavioral control subjects, 3) PET control subjects, and 4) fMRI control subjects.

Patients with left frontal lesions. By reviewing radiology files and hospital admissions to Washington University Medical Center in St. Louis, MO, we identified more than 300 patients who had strokes between 1995 and 1997. By screening these individuals, we identified six patients (three women; aged 32 to 72 years, mean age 47 years) with left-hemisphere strokes for participation in the study. The inclusion criteria were 1) a single left-hemisphere lesion that included the left inferior frontal gyrus and operculum, and could extend to neighboring cortex and adjacent subcortical white matter; and 2) an interval of at least 6 months since the acute event that caused the lesion. The five exclusion criteria were 1) more than one cerebral cortical lesion, as revealed by CT or MRI scans of the brain; 2) a stenosis greater than 50% of the lumen of the internal carotid artery as shown by doppler ultrasonography or cerebral angiography; 3) language comprehension too severely impaired for the patient to follow instructions; 4) a history or clinical evidence of dementia; and 5) other significant medical illnesses (e.g., cancer, congestive heart failure class IV) precluding participation in the study. The clinical profiles of the patients (Patients 1 through 6) are discussed in the results section. The data from one of these patients (Patient 3) have been reported previously.

Behavioral control subjects. Behavioral data from four language tasks were collected from six normal elderly control subjects (three women; aged 50 to 72 years, mean age 65 years) recruited from a subject registry of the Department of Psychology at Washington University in St. Louis.

PET control subjects. Six control subjects (three women; aged 29 to 45 years, mean age 36 years) were recruited by advertising in the Washington University community.

fMRI control subjects. Eight control subjects (three women; aged 19 to 28 years, mean age 24 years) were also recruited by advertising in the Washington University community. This control group was part of a previously published study, and their data were used for some analyses in this experiment. All subjects (patients and control subjects) were native English speakers with normal or corrected vision and were right-handed according to the Edinburgh handedness inventory. We obtained informed consent from all control subjects and patients or their next of kin, and the Human Studies and Radioactive Drug Re-
Avoid phrases such as "you drive it" or other forms of the verb trial, subjects generated a verb associated with a presented visual cue (e.g., see DRA, say "drama"). Subjects were instructed one word to complete a word stem presented as a single word.

Completed at least five words with a frequency greater than 1 per million. For the verb-generation task, stimuli were high-frequency (>5 per million) concrete nouns. For word reading, stimuli were familiar nouns, verbs, and adjectives with a frequency greater than 1 per million.

Analysis. Errors were scored as follows. For pseudoword reading, an error was no response, conversion to a real word, or a phonemic error. For stem completion, an error was no response, a proper name or place name, or a response that did not begin with the displayed letters. For verb generation, an error was no response, an associated word that was not a verb, or an inappropriate verb. For word reading, an error was no response or a paraphasic error (either phonemic or semantic). Errors due to difficulty with articulation were not counted. Median RT for each task was calculated for correct responses only. The percentages of correct responses and the median RT for each task were analyzed with a 1 between (control subject, patients), 1 within (pseudoword reading, word-stem completion, verb generation, word reading) repeated measures analysis of variance (ANOVA).

PET imaging. Apparatus. Patient 3 was scanned on a Siemens 953B scanner (Erlangen, Germany) in 3D acquisition mode to acquire 31 slices with a resolution of 5 mm full width at half maximum (FWHM) and an axial field of view of 10.5 cm. All other patients and controls were scanned on a Siemens 961 EXACT HR scanner in 3D acquisition mode to acquire 47 parallel slices with a resolution of 4 mm FWHM and an axial field of view of 14.7 cm. Stimuli were presented on a monitor that was suspended at 45 degrees in front of the subjects as they lay on the scanner bed.

Tasks and procedures. Subjects were scanned during word-stem completion (four scans), pseudoword reading (four scans), and a visual-fixation control task (maintaining fixation on a crosshair at the center of the screen) (two scans). Data for pseudoword reading will be reported separately and will not be considered here. The order of tasks was counterbalanced across subjects. Stimuli were presented every 5 seconds, with a stimulus that persisted for 4.25 seconds.

Image and statistical analysis. For each scan, 12 to 16 mCi of O15-labeled water was administered as an IV bolus. Brain radioactivity was measured over a 40-second period to estimate blood flow. Images were reconstructed and analyzed.

### Table: Clinical characteristics of patients with left frontal lesions

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Patient no.</th>
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<td>1</td>
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<tr>
<td>Age, y</td>
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<tr>
<td>33</td>
<td>36</td>
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<tr>
<td>Sex</td>
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<tr>
<td>M</td>
<td>F</td>
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<tr>
<td>Lesion size, cm³</td>
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<tr>
<td>10.7</td>
<td>18.1</td>
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<tr>
<td>Years after stroke</td>
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<tr>
<td>2.3</td>
<td>1.5</td>
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<tr>
<td>Initial aphasia type</td>
<td></td>
</tr>
<tr>
<td>Broca’s Broca’s Broca’s Broca’s Global Global</td>
<td></td>
</tr>
<tr>
<td>WAB Aphasia Quotient at time of experiment</td>
<td></td>
</tr>
<tr>
<td>97</td>
<td>89.5</td>
</tr>
<tr>
<td>WAB Aphasia Classification at time of experiment</td>
<td></td>
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<tr>
<td>No aphasia Anomic NA Anomic Anomic Broca’s</td>
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A measure of aphasia severity that ranges from 1 to 100. A score higher than 93.8 indicates no aphasia.

* WAB = Western Aphasia Battery.
Figure 1. Lesion anatomy. Structural MRI scans from six patients enrolled in this study, labeled P1 through P6 in ascending order of lesion size. Above each label is a 3D-rendered brain viewed from the left side. The lesion does not reach the surface of the brain in P1. The quality of the images was poorer in P3. On the right, horizontal T1-weighted MR images of each lesion. Each brain has been standardized to the Talairach and Tournoux atlas. Selected sections from $z = 0$ to $z = 30$ mm above the anterior–posterior commissure reference line.
smoothed with a Butterworth filter to a FWHM of approximately 14 mm. They were normalized for individual variations in global blood flow and transformed to a stereotactic space using Automated Image Registration software (Freeware Software, UCLA, CA). Then they were screened for motion using a visually based rating system. Individual difference images (i.e., word stem-fixation point) were created for each subject by subtracting the PET peak detection algorithm. Regions of differential activation between groups were localized by subtracting the PET control group's averaged word-stem fixation image from the patients' averaged word-stem fixation image. Only regions with a magnitude difference greater than 80 PET counts were selected for further statistical analysis. This threshold was selected to ensure replication of the result in a separate sample of subjects. The regions of interest were applied to individual word-stem visual fixation images and regional magnitude values were computed. These magnitudes were then compared between groups (patients versus control subjects) using a two-tailed unpaired t-test and a Bonferroni correction for the number of regions.

MRI. Apparatus and MR sequences. A Siemens MAGNETOM Vision 1.5 T system (Erlangen, Germany) with a standard head coil was employed for MRI. High-resolution structural images were obtained using a sagittal T1-weighted sequence (echo time [TE] = 4 ms, repetition time [TR] = 9 msec, inversion time [TI] = 300 ms, flip angle = 12°, 160 slices, 1 × 1 × 1 mm voxels). T2-weighted images were also collected (TE = 80, TR = 2500, flip angle = 90°, 12 slices, 1.2 × 0.9 × 5 mm voxels). fMRI series were collected using either an asymmetric spin-echo (ASE) (TR = 2364 msec, TE = 50 ms, a = 90°, 8-mm slices, in-plane resolution 3.75 × 3.75 mm) (patients) or a gradient-refocused echo (GRE) (TR = 2200 ms, T2* = 50 ms) (fMRI controls) sequence sensitive to blood oxygenation level–dependent (BOLD) contrast. Each scan consisted of 128 whole-brain echoplanar imaging acquisitions. Stimuli were projected with a Sharp LCD projector (640 × 480 pixel resolution) onto a translucent screen at the end of the MR bore. The subject was able to see the screen through a mirror placed on the head coil. A microphone was placed outside the scanner’s bore for recording vocal responses.

Task and procedures. Subjects were scanned during word-stem completion and visual-fixation tasks. In contrast to the PET session, word-stem completion was performed covertly (without vocalization) to minimize potential susceptibility artifacts caused by mouth movements. Previous experiments had shown that left inferior frontal and temporal cortices are similarly active during either covert or overt versions of the word-stem completion task. Each scan began with a 19-second period of visual fixation followed by alternating 30-second periods of word-stem completion and visual fixation. Each scan included about 30 word-stem completions, and each patient was scanned between three and six times. Patient P3 was not scanned with fMRI.

Image and statistical analysis. The lesions were segmented using Brainvox (University of Iowa, Iowa City, IA) on the magnetization-prepared rapid gradient-echo (MPRAGE) images. The fMRI data were corrected for physical artifacts, realigned within-across scans, and normalized to a mode intensity value of 1,000. After subtraction of linear trends on a voxel-by-voxel basis, voxels that were significantly activated during word-stem completion were identified using a Wilcoxon rank-sum statistic. Wilcoxon statistical images were transformed into z-maps. The MPRAGE and statistical functional images were normalized to atlas space using an affine (12-parameter) transformation. To avoid distortion by lesions, the damaged tissue was masked and excluded from the transformation. Atlas-transformed single-subject z-maps were either multiple comparisons–corrected to an overall p value of < 0.01 for individual analysis or summed and divided by the square root of n and then multiple comparisons–corrected for group analysis. Parametric tests could not be used to assess regional differences because the two groups were scanned with different MR sequences that yield different signal-to-noise ratios. Therefore, we selected a nonparametric analysis that compares the relative rank of activation z-scores of specific regions, and we used a Mann–Whitney U test to test for rank difference between groups.

Results. Clinical profiles and lesions. The table shows the clinical characteristics of the patients. The clinical records stated that just after their strokes, four patients were diagnosed with Broca’s aphasia (Patients 1 through 4) and two with global aphasia (Patients 5 and 6) at the time of the experiment (range 0.5 to 7.5 years postonset), a standardized language examination revealed variable degrees of recovery. One patient with Broca’s aphasia (Patient 1) had recovered fully, and two patients with Broca’s aphasia (Patients 2 and 4) were anomic. One patient with global aphasia (Patient 5) had recovered to anomic aphasia, whereas the other (Patient 6) had recovered to Broca’s aphasia. Patient 3, who was acutely classified with Broca’s aphasia, had recovered to a mild expressive aphasia.

Anatomically, the posterior left IFG, anterior insula, and frontal isthmus, i.e., the white matter underlying the frontal operculum, were damaged in all patients. These were the only regions damaged in Patient 1. Patient 2’s lesion extended anteriorly in the anterior IFG and the middle frontal gyrus. The lesions of Patients 3 through 6 extended posteriorly in the ventral motor cortex and posterior insula, and in the periventricular white matter. Figure 1 shows the 3D surface rendering and selected horizontal MR sections of the lesions.

Behavior. Figure 2a shows the data from the behavioral session in five patients and six control subjects. Overall, the patients were less accurate than the control subjects (main effect of group, F[1,9] = 9.7, p = 0.013) and were more impaired on the attention-demanding verbal tasks (word-stem completion, verb generation, pseudoword reading) than on word reading (task by group interaction: F[3,27] = 2.95, p < 0.05; patients versus controls: word-stem completion, 63% versus 90%; p = 0.026; verb generation, 40 versus 84% p = 0.015; pseudoword reading, 40 versus 82% p = 0.051; word reading 94% correct versus 100% p = 0.083). There was no overall difference in reaction time.
between the two groups on correct trials ($F_{[1,8]} = 3.98, p = 0.081$) or on any task by group interaction ($F_{[3,24]} = 0.5, p = 0.674$). During the PET session, the patients performed less accurately than the control subjects (patients: 58% correct; control subjects: 87% correct, $F_{[1,7]} = 48.95, p = 0.0002$), but again there was no significant difference in reaction time on correct trials.

We also analyzed the accuracy and reaction time data at the single-subject level. Figure 2b shows that all patients performed within normal limits on word reading, but that five of the six patients were impaired on the more attention-demanding verbal tasks. In contrast, Patient 1’s performance was normal on all tasks. Patient 6 was tested both at the acute (within 3 weeks) and chronic (6 months) stage of recovery, and the patient’s performance on the word-stem completion task improved over time, changing from no correct responses to 65% of the responses correct.

**PET (overt task).** During the overt word-stem completion task, control subjects activated the visual cortex (lingual, fusiform, and inferior temporal gyri), auditory cortex (superior temporal gyrus), IFG, supplementary motor area (SMA), left putamen, and cerebellum (figure 3, top row). Responses were strongly lateralized to the left hemisphere in the IFG and anterior fusiform–inferior temporal gyrus. The response in the left IFG included a more dorsal response extending posteriorly into the precentral gyrus (motor cortex) and a more ventral response near the operculum. Patients activated similar regions to control subjects except for a stronger activation in the right IFG, both dorsally and ventrally, and barely any response in the damaged left IFG (see figure 3, bottom row). The anterior fusiform–inferior temporal gyrus response remained lateralized to the left hemisphere. (For atlas coordinates, please access the Web version of this article at www.neurology.org)

Four regions, including right dorsal and ventral IFG, SMA, and right transverse temporal gyrus (T2G) (near the primary auditory cortex) (figure 4; see figure 5 for atlas coordinates and statistics), were significantly more active in patients than in control subjects after Bonferroni correction. Magnitude differences were consistent across subjects and were not carried by outliers (see figure 5).

**fMRI (covert task).** Controls activated a network similar to the one recruited by the overt version of the word-stem completion task except for regions involved in overt vocalization (e.g., motor cortex, medial cerebellum, and putamen) (figure 6, top row). Again, the left IFG was strongly active, both dorsally and ventrally; but a weaker significant response was also recorded in the right IFG. In patients with frontal lesions, strong right-IFG responses were replicated both dorsally and ventrally, with little activity detected in or near the damaged left IFG (see figure 6, bottom row). (For atlas coordinates, please access the Web version of this article at www.neurology.org)

The presence of significant right IFG activity in control subjects may indicate that this region is normally recruited during word-stem completion, and that its detection in patients with left frontal lesions represents a variant of the normal activation pattern. To examine the relative lateralization of the IFG response in patients and control subjects, we created multiple comparison–corrected ($p < 0.01$ level) statistical maps for each subject (figure 7). In four of the eight control subjects, the response was entirely lateralized to the left IFG (see figure 7, top row). In the remaining four control subjects, the response was more bilateral, but still stronger on the left side (figure 7, middle row). All five patients showed a response in the right IFG (see figure 7, bottom row). Statistical analyses showed that the right dorsal IFG was more strongly active in patients than in control subjects (Mann–Whitney U test: $p = 0.0042$). In contrast, there was no difference between groups in SMA (Mann–Whitney U test, $p = 0.949$), which served as a control region. This difference in the strength of the right-IFG response cannot be explained by differences in age between patients and control subjects (patients, mean age = 47; control subjects, mean age = 24 years). In fact, recent studies failed to find any difference between young and elderly control subjects in the degree of lateralization of frontal activity during verbal processing. 36

Figure 8 provides a complete view of the functional anatomy of covert word-stem completion (as compared with visual fixation) in each patient. All patients show a dorsal (about $z = 30$) (green arrows) and ventral (about $z = 12$) (red arrows, particularly evident in Patients 2 and 5) right-IFG response. The functional topography of this activation is equivalent to the one found in the left IFG of control subjects (compare with figure 6). Time-course analyses indicated that right-IFG activity is task-specific, increasing during word-stem completion and decreasing during visual fixation.

A second potential compensatory mechanism was identified in Patients 1 and 2, who had the best aphasia scores and communication skills in the group. In addition to a right-IFG response, these patients activated tissue near the infarct in the left IFG. Perilesional activity was localized both in dorsal and ventral left IFG in Patient 1, and in ventral IFG in Patient 2 (yellow arrows). Time-course analyses indicated that this activity was also task-specific (see figure 8).

We examined the relationship between performance and IFG activation (left or right) by plotting response magnitude in right and left IFG against accuracy on the word-
stem completion task as measured in the behavioral session and Aphasia Quotient (AQ) on the Western Aphasia battery. These results should be considered exploratory because of the small number of observations. We found no systematic correlation between right-IFG activity and word-stem accuracy (right dorsal IFG Spearman Rho = 0.1, p = 0.84; right ventral IFG Spearman Rho = −0.1, p = NS). Similarly, there was no correlation with AQ (right dorsal IFG Rho = 0.3, p = NS; right ventral IFG Rho = 0.2, p = NS).

Discussion. This study identifies two potential functional anatomic correlates of language recovery in patients with chronic damage to left frontal cortex. During a word-stem completion task that specif-
ically activated the left IFG in normal subjects, we observed a significantly increased activation in the right IFG. In addition, we recorded activity near the infarct (perilesionally) in the two patients whose lesions were more restricted to the left IFG, and had the best language function.

**Anatomy of lesions and behavior.** The clinical–anatomic profile of our group of patients agrees well with other studies on the left frontal operculum. For example, Patient 1, whose lesion was restricted to the left posterior IFG (and anterior insula) and who had minimal white matter involvement, fully recovered from an acute Broca’s aphasia. This is consistent with previous studies showing that a complete recovery can be expected following lesions that are limited to the posterior aspect of the left IFG (Broca’s area). Also, the three patients with the least recovery (Patients 4, 5, and 6) had lesions that extended posteriorly into lower motor cortex and deep into the white matter underneath the operculum and adjacent to the lateral ventricles. Consistently, a more severe aphasia that does not fully recover has been associated with damage to Broca’s region plus neighboring cortex and underlying white matter.

We selected a group of patients with lesions involving the left IFG who were homogeneously impaired on tasks that normally activate the left IFG. We were successful because our patients, as a group, were impaired on many attention-demanding verbal tasks, including word-stem completion, verb generation, and pseudoword reading. In contrast, they performed normally on a word-reading task that does not activate the left IFG. The im-

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**Figure 5.** Regional magnitude (PET counts) differences during word-stem completion–visual fixation in six patients (closed circles) and six controls (open circles). R dIFG = right dorsal inferior frontal gyrus; R vIFG = right ventral inferior frontal gyrus; SMA = supplementary motor area; R TTG = right transverse temporal gyrus.

**Figure 6.** Group averaged functional MRI statistical maps during covert word stem completion–visual fixation, control subjects (n = 8) (top) and patients (n = 5) (bottom). z Maps are uncorrected for multiple comparisons, and thresholded to a value of z = 2. SMA = supplementary motor area; dIFG = dorsal inferior frontal gyrus; vIFG = ventral inferior frontal gyrus.
Impairment relates to the selection or retrieval of accurate responses rather than the preparation of a vocal response, because reaction times for correct trials were normal. In addition, this result rules out the possibility of inattentiveness or distractibility as an explanation for the behavioral and imaging differences. Our findings are in agreement with clinical studies showing that patients with left frontal lesions have problems with word fluency and retrieval, and a neuropsychological study that showed a selective deficit in patients with left-IFG lesions during verb generation. The exact verbal processing deficit remains unclear, however. The left IFG may play a role in retrieving lexical or phonologic information during attentive verbal processing. Alternatively, it may not be involved in retrieval per se but in the selection of relevant responses and suppression of alternative competing responses.

Potential metabolic correlates of recovery. I: Right inferior frontal gyrus. At the group level, control subjects activated a large set of occipital, parietal, and frontal regions during both overt (PET) and covert (fMRI) word-stem completion. These regions have been reported in earlier studies. The basic pattern observed in control subjects was maintained in patients with left frontal lesions in both PET and fMRI studies. The strong similarities in PET and fMRI measurements within and across groups are important because they indicate that BOLD fMRI responses are not impaired in the presence of a stroke lesion, and related metabolic effects on surrounding and distant cortical tissue.

The most striking difference was the near absence of activation in the damaged left IFG, and the significantly increased response in the right IFG, in patients as compared with control subjects. The right IFG activation involved separate dorsal and ventral foci, and was independent of overt verbalization, which is similar to the pattern observed in the intact left IFG. Although some control subjects recruited the right IFG during word-stem completion, the relative frequency and absolute magnitude of this response was clearly outside the normal range. This demonstrates that the right-IFG response is not a variant of the normal pattern of activation as previously proposed. Finally, the strength of right-IFG activation did not correlate with behavioral performance on the word-stem completion task, indicating that behavioral differences between groups cannot explain this anomalous response.

Figure 7. Individual functional MRI statistical maps during covert word stem completion-visual fixation in single subjects. Coronal sections through left and right IFG. Yellow arrows point to dorsal left IFG response; red arrows point to dorsal right IFG response. z Maps are Bonferroni corrected for multiple comparisons (z = 5.21).
What potential mechanisms of compensation/recovery could explain this activation pattern? One possibility is that the right frontal response reflects the recruitment of a novel pathway through mechanisms of neural plasticity (such as growth of new synapses) that allows this system to take over the set of functions originally localized in the left IFG. This possibility is unlikely for several reasons. Right-IFG responses have been recorded acutely (24 hours) and subacutely (within 3 weeks) after the onset of a left-frontal stroke. These rapid adjustments are inconsistent with the growth of new anatomical pathways.

Another hypothesis is that the right-IFG response reflects a switch in processing strategy that allows patients to solve the word-stem completion task. Words are encoded in various representations (semantics, phonologic, orthographic) that can be differentially damaged by focal brain lesions. Left frontal lesions cause phonologic and word-retrieval deficits. Priming studies in normal subjects and studies in split-brain patients have suggested that phonologic codes are localized in the left hemisphere, whereas orthographic and semantic codes may be more bilaterally organized. After a lesion in the left IFG, a strategy based on phonology may no longer be available, and a less efficient strategy (e.g., orthographic processes) based on more bilateral frontal representations may be recruited. A problem with this hypothesis is the lack of a correlation between right-IFG response and accuracy on the word-stem completion task. Such a correlation might be expected if alternative word codes supported performance.

A final hypothesis, which we favor, is that the anomalous right-IFG response reflects a loss of mechanisms that normally regulate the level of activation in homologous frontal areas. Several results, including the topography of the response, the independence from overt verbalization, and the presence of some right-IFG activity in control subjects, are consistent with the idea that right- and left-IFG are homologous regions. Moreover, left and right dorsal IFG activity can be tightly regulated by stimulus material in certain tasks. Left frontal responses predominate during the encoding of words, right frontal responses predominate during the encoding of non-nameable faces, but bilateral responses occur during encoding of nameable objects. Thus, the anomalous right frontal response after left frontal damage may reflect the loss of active inhibition or competitive interaction from the homologous left frontal area, or an inefficient “dead end” strategy. This interpretation may explain the detection of anomalous right frontal responses just 24 hours after a stroke, and the lack of a correlation with accuracy during word-stem completion. The idea of a reciprocal regulation of activity in homologous cortical regions is not novel; it has been proposed by theories addressing the functional roles of callosalconnec-

Figure 8. Individual functional MRI statistical maps during covert word-stem completion–visual fixation in single patients (P1 through P6), superimposed on individual structural MRI. z Maps are uncorrected for multiple comparisons, and thresholded to a value of $z = 2$. The green arrows indicate responses in right dorsal IFG. The red arrows indicate responses in right ventral IFG and frontal operculum. These responses are more evident in P2 and P4, but were significant in all patients. The yellow arrows indicate the presence of left perilesional IFG responses in P1 and P2. Note that P1 has both left dorsal and ventral IFG responses, whereas P2 has only a ventral response. Right column: Individual time-courses of blood oxygenation level–dependent (BOLD) response in right dorsal IFG. X-axis = time; Y-axis = % change in MR signal. Left column: Individual time-courses of BOLD response in left ventral perilesional IFG in patients P1-P2.
at the acute stage, and that does not progress to complete infarction. It is possible that penumbral tissue near the infarct is not viable early on after injury and therefore cannot be recruited to support behavior. In the course of recovery, this tissue may return to a metabolically normal state and become functionally relevant for task performance.

Future studies will need to combine metabolic and activation measures prospectively and longitudinally in patients with frontal injury to clarify the relative roles of right-frontal and perilesional left-frontal mechanisms in recovery from aphasia.

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