Functional Magnetic Resonance Imaging Before and After Aphasia Therapy
Shifts in Hemodynamic Time to Peak During an Overt Language Task

Kyung K. Peck, PhD; Anna B. Moore, PhD; Bruce A. Crosson, PhD; Megan Gaiefsky, MSc; Kaundinya S. Gopinath, MSc; Keith White, PhD; Richard W. Briggs, PhD

Background and Purpose—Comparing the temporal characteristics of hemodynamic responses in activated cortical regions of aphasic patients before and after therapy would provide insight into the relationship between improved task performance and changes in blood oxygenation level–dependent (BOLD) functional MRI (fMRI) signal. This study investigated differences in the time to peak (TTP) of hemodynamic responses in activated regions of interest (ROIs), before and after therapy, and related them to changes in task performance.

Methods—Three aphasic patients and 3 controls overtly generated a single exemplar in response to a category. For the patients, TTP of hemodynamic responses in selected ROIs was compared before and after language therapy. The timing differences between auditory cues and verbal responses were compared with TTP differences between auditory and motor cortices.

Results—The selected ROIs were significantly activated in both aphasic patients and controls during overt word generation. In the aphasic patients, both the timing difference from auditory cues to verbal responses and the TTP difference between auditory and motor cortices decreased after rehabilitation, becoming similar to the values found in controls.

Conclusions—Findings indicate that (1) rehabilitation increased the speed of word-finding processes; (2) TTP analysis was sensitive to this functional change and can be used to represent improvement in behavior; and (3) it is important to monitor the behavioral performance that might correlate with the temporal pattern of the hemodynamic response. (Stroke. 2004;35:554-559.)

Key Words: aphasia ■ hemodynamics ■ magnetic resonance imaging, functional ■ rehabilitation

An important issue for rehabilitation of language and cognition after brain damage is the manner in which therapeutic intervention changes brain systems responsible for relevant cognitive activities. Despite a number of studies on cortical activation during recovery from aphasia, there is limited understanding of cortical reorganization of language-related brain regions after stroke.

Previous functional MRI (fMRI) studies1,2 exploring language-related brain activation with aphasic patients used silent language generation paradigms. However, use of silent responses does not allow monitoring of task performance. Normal subjects are predictable in terms of response times, correctness, and (to a lesser extent) strategy used in language generation. Aphasic subjects are not consistent in these respects, and covert paradigms provide no verification that the task was performed as desired. Therefore, it is important to monitor verbal responses as an indicator of behavioral performance to assess directly the speed of response and its improvement after therapeutic intervention and to aid analysis and interpretation of neuroimaging data. The disadvantages of overt language paradigms include artifacts caused by tongue and jaw movement occurring during verbal responses and the challenge of hearing or recording responses in the presence of scanner noise. The former can be minimized by specialized data processing,3,4 and the latter can be achieved with a noise-canceling microphone and digital filtering.

Most fMRI studies measuring brain function during cognition have reported only spatial activation information.5 Time-resolved fMRI has been applied to investigate differences in the time course of the hemodynamic response between supplementary motor area (SMA) and primary motor cortex6–8 and between basal ganglia and the cerebellum9 for movement in control subjects.
TABLE 1. Demographics and Pretreatment Language Performance of Patients With Aphasia

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex/Age</th>
<th>Years of Education</th>
<th>Months After Onset</th>
<th>Lesion Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/46</td>
<td>12</td>
<td>48</td>
<td>Parietal frontotemporal (Ins, STG, PMC, operculum, caudate, putamen, globus pallidus thalamus, PVM, &amp; CR)</td>
</tr>
<tr>
<td>2</td>
<td>F/79</td>
<td>12</td>
<td>44,74,12</td>
<td>Frontotemporal/parietal (STG, MC, PMC Broca’s area, SSC, SMG, Ins, caudate, thalamus)</td>
</tr>
<tr>
<td>3</td>
<td>F/48</td>
<td>14</td>
<td>8</td>
<td>Frontotemporal/parietal (Ins, STG, MC, PMC, SSC, SMG)</td>
</tr>
</tbody>
</table>

Lesion locations from T1-weighted spoiled GRASS images. Ins indicates insula; STG, superior temporal gyrus; PMC, premotor cortex; PVM, periventricular white matter; CR, corona radiate; MC, motor cortex; SSC, somatosensory cortex; SMG, supramarginal gyrus.

Pineiro et al10 explored the rate and maximum increase of hemodynamic response during a motor task in patients after subcortical stroke using blood oxygenation level–dependent (BOLD) fMRI and compared them with data from control subjects. They found that the average magnitude of the BOLD response in sensorimotor cortex can be reduced (approximately 30%) in stroke patients even if infarcts do not involve that cortex. Musso et al11 investigated changes in brain activity associated with language comprehension training of aphasic patients using positron emission tomography (PET) and found a correlation between increased activation in right temporal cortex and training effect. Heiss et al12 measured regional cerebral glucose metabolism during word repetition in aphasic patients using PET and found that the patterns of speech-associated activation of glucose metabolism were related to improvement in language performance as measured by the Token test. These studies indicate that functional imaging can be used to characterize rehabilitation outcomes. However, studies of the effect of rehabilitation on the relationship between behavioral performance and temporal BOLD hemodynamic response parameters during overt language tasks in aphasic stroke patients have not been reported.

In this study BOLD fMRI was used to examine brain function of aphasic patients and controls overtly generating words and to explore changes in the temporal characteristics of aphasic patients' hemodynamic response resulting from therapy. Time to peak (TTP) values of the hemodynamic response in right hemisphere pre-SMA, Broca’s area homologue, and motor and auditory cortices were measured before and after therapy. Differences in TTP of auditory and motor cortices were compared with response latencies between auditory cues and verbal responses. For aphasic patients, TTP differences for the regions of interest (ROIs) were hypothesized to decrease after therapy as a result of faster verbal output, reflected in a decrease of the timing difference between auditory cues and word generation.

Subjects and Methods

Patients

Three right-handed patients with chronic nonfluent aphasia due to left hemisphere stroke participated in fMRI scanning sessions before and after 8 weeks of rehabilitative intervention. At least 6 months had elapsed since stroke onset, and it was therefore expected that there would be no additional spontaneous reorganization of neural activity. Patient 2 had experienced 3 strokes; the most recent was 44 months before onset of the study. T1-weighted structural images were interpreted to allow localization of lesions; these data are summarized in Table 1. Response to treatment is described in Table 2.

Aphasia Treatments

Each treatment was divided into three 2-week phases, with treatment occurring 5 days per week. A unique 50-picture set was trained during each phase. Ten items from each of these treatment phases plus 10 additional never-treated items constituted the probe set. Before each treatment, patients named the probe pictures. Treatment was initiated after a stable baseline performance on naming probes was achieved.

Intention Treatment

This treatment (received by patients 1 and 3) was designed to engage right hemisphere initiation mechanisms. Intention can be defined as preparation for action, including initiation of action. This treatment assumes (1) that intention mechanisms for hand movement and spoken language overlap enough that language initiation can be facilitated when preceded by hand movement, (2) that using a left hand movement specifically activates right hemisphere initiation mechanisms, and (3) that activating right hemisphere initiation mechanisms facilitates participation of right hemisphere mechanisms in word production. Patients were seated directly in front of a computer monitor. A flashing star and tone signaled trial onset. Patients opened a box to the left of the monitor with the left hand and pressed a button to display an object picture on the monitor. Patients named the picture. Therapists gave the correct name for incorrect responses and asked patients to repeat the name while making a nonsymbolic circular left hand gesture. The amount of cuing before naming trials decreased between phase 1 and phase 2, and the patient used the circular left hand gesture to initiate naming trials in phase 3. Since this treatment was designed to enhance initiation, it should decrease the time between stimulus presentation and word production in the fMRI paradigm (see below) if successful.

Attention Treatment

This treatment (received by patient 2) was designed to engage intact right hemisphere attention mechanisms to facilitate word finding. Attention can be defined as preparation to process and manipulate incoming information. This treatment assumes (1) that the hemispace to which one attends (left versus right) will tend to engage attention mechanisms in the contralateral hemisphere, (2) that as language mechanisms may be damaged in aphasia, and (3) that engaging intact contralateral attention mechanisms will improve performance on concurrent language tasks when ipsilesional attention mechanisms are damaged, as Coslett13 demonstrated. The patient was seated with a computer monitor 45° to her left. A tone signaled trial onset. The patient turned her head 45° to the left to name the picture of an object on the monitor. Therapists corrected errors and asked the patient to repeat the correct name while continuing to look at the monitor 45° to her left. The amount of cuing before naming trials decreased during each phase, and the position of

TABLE 2. Summary of Treatment Data for Patients With Aphasia

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Treatment Type</th>
<th>Accuracy Before Treatment</th>
<th>Accuracy After Treatment</th>
<th>Z Score/Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Intention</td>
<td>60.8%</td>
<td>74.4%</td>
<td>3.23/P&lt;0.01</td>
</tr>
<tr>
<td>2</td>
<td>Attention</td>
<td>42.3%</td>
<td>73.5%</td>
<td>5.78/P&lt;0.01</td>
</tr>
<tr>
<td>3</td>
<td>Intention</td>
<td>51.4%</td>
<td>84.5%</td>
<td>4.54/P&lt;0.01</td>
</tr>
</tbody>
</table>
the picture changed from the left side of the monitor during phases 1 and 2 to the center of the monitor in phase 3. Because this treatment was designed to enhance attention, it should increase the speed of information processing during the word production. Thus, if successful, it should decrease the time between stimulus presentation and word production.

Control Subjects
Three right-handed (Edinburgh Handedness Inventory) native English speakers with no history of neurological or psychiatric disturbance served as controls. Control 1 was a 74-year-old woman with 9 years of education, control 2 was a 42-year-old woman with 12 years of education, and control 3 was a 59-year-old woman with 13 years of education.

fMRI Paradigm
The rehabilitative intervention was designed to engage medial frontal regions. Because fluency tasks show greater medial frontal involvement than naming tasks (pilot data from our laboratory), a modified verbal fluency task, modeled after the word generation task used by Crosson et al., was used. Subjects were informed that during the fMRI study they would be fitted with headphones that would allow them to hear the name of a category (eg, farm animals or tools). Subjects were instructed to generate 1 exemplar of the given category (eg, “spices” for a cue, “cinnamon”). Categories were selected to evoke emotionally neutral words. Participants were instructed to respond at a normal conversational volume and to rest quietly between trials. Subjects were instructed to respond with “no” if they were unable to hear a category, understand the name of the category, or produce a response after attempting initiation. This task was practiced outside of the scanner environment until it was clear that subjects understood the task and were able to comply. A total of 45 unique categories were presented across 5 runs (9 categories per run). Variable interstimulus intervals separated the stimuli within each run and were established according to the following procedure. So that hemodynamic responses return to baseline levels before ensuing stimuli on a majority of trials, the “average” interstimulus interval for each nonfluent patient was set to the mean response time, determined individually in pilot studies, plus 1.2 SDs. For all patients, this meant that variable rest intervals of 21.6, 23.2, 24.9, and 26.6 seconds were randomized over the course of the runs. For the 3 control subjects, the rest intervals were 13.3, 14.9, 16.6, and 18.3 seconds; these values were determined on the basis of unpublished pilot data acquired in our laboratory (Megan Gaiefsky, MSc, unpublished data, 2002). An audio presentation device (Resonance Technology, Inc) including nonmagnetic headphone and microphone set, CD player, and speaker was used to deliver auditory cues and record subject responses.

Patient 1 correctly responded to 24 and 32 stimuli during the scans before and after therapy, respectively. Patient 2 correctly responded to 18 stimuli during the scan before therapy and 23 stimuli at the scan after therapy. Patient 3 provided 41 correct responses during the scan before therapy and 44 correct responses during the scan after therapy.

Imaging Sequences
fMRI data were acquired with a GE 3T Signa LX scanner with a quadrature radio frequency coil. Thirty-two contiguous sagittal slices covering whole brain were acquired with the use of a 1-shot spiral sequence (repetition time [TR] 1660 ms; echo time [TE] 18 ms; 70° flip angle; 64×64 matrix; 200-mm field of view; 4 mm in thickness). An additional 6 images (9.96 seconds) were added to the beginning of the run to allow MR signal to reach equilibrium. The smallest out-of-plane head motion typically occurs with acquisitions in the sagittal plane. Anatomic images were obtained with both a MR angiogram (TR 17 ms; TE 4.9 ms; 50° flip angle; 256×128 matrix; 200-mm field of view; 4 mm in thickness) and a T1-weighted spoiled gradient-recalled acquisition in the steady state (GRASS) sequence (TR 23 ms; TE 6 ms; 25° flip angle; 256×192 matrix; 1.3 mm in thickness; 124 slices; 240-mm field of view). Foam padding limited head motion during scanning.

Image Processing
Reconstructed fMRI data were realigned with the use of 3-dimensional rigid-body registration. Linear trends of the time series of each run were removed, and 5 runs were concatenated. Deconvolution analysis in AFNI16 software was used to estimate, to 26.5 seconds (16 images) for patients and 19.9 seconds (12 images) for control subjects, the hemodynamic response function of the fMRI signal on a voxelwise basis with the use of stimulus-based vectors. R values indicated goodness of fit of multiple linear regression, and F statistics measured significance of the regression. Activation maps were generated by thresholding at $R^2 > 0.21$ ($F > 10$).

TTP Analysis
Maximally activated pixels in the auditory cortex, Broca’s area homologue, motor cortex, and pre-SMA in the right hemisphere were used for the TTP analysis because these regions were activated reliably in aphasic patients. The TTP was measured by fitting the hemodynamic response with a 4-parameter gamma variate function with Matlab, as follows: $S(t) = A(t - \tau) \alpha \exp[-(t - \tau)/\beta] + B$, where $A$ is a constant, $\alpha$ and $\beta$ account for the shape of the curve, $\tau$ accounts for the shift in time, and $B$ is the baseline (Figure 1). TTP values were corrected for differences in timing of acquisition of the slices.

Behavior Performance
Cool Edit 2000 (Syntrium Software) was used to record subject responses directly to a personal computer and to reduce the amount of scanner noise in the responses recorded during functional scans. The timing difference between the auditory cue and the verbal response was compared with the difference in TTP of the hemodynamic response between the auditory cortex and the motor cortex.

Results
TTP in Aphasic Patients Before and After Therapy
TTP values of aphasic patients before and after therapy are summarized in Figure 2. For patient 1, from before to after therapy, the TTP in right Broca’s area homologue, motor cortex, and pre-SMA decreased by 5.2, 0.9, and 2.7 seconds, respectively, but that of the auditory cortex increased by 1.5 seconds. For patient 2, the TTP of right auditory cortex, Broca’s area homologue, motor cortex, and pre-SMA decreased by 1.3, 1.8, 3.5, and 2.9 seconds from before to after therapy. From before to after therapy, TTP of patient 3 increased by 0.2, 1.2, and 0.9 seconds in the auditory cortex, Broca’s area homologue, and motor cortex but decreased in the pre-SMA by 2.8 seconds. Two left hemisphere regions (auditory cortex and pre-SMA) were also analyzed. For all patients, left auditory cortex showed no change in TTP from before to after treatment scans, while left pre-SMA TTP decreased by 2.34 seconds for patient 1, 3.13 seconds for patient 2, and 1.06 seconds for patient 3.

Correlation Between Behavior Performance and TTP: Patients and Control Subjects
Figure 3 compares the average timing delay (mean and SD) between auditory input and verbal response with TTP difference between the auditory cortex and the motor cortex in aphasic patients observed before and after therapy and controls. Average time delay between auditory input and oral response was $8.4 \pm 3.7$, $5.1 \pm 5.7$, and $5.3 \pm 2.4$ seconds before therapy and $4.0 \pm 2.4$, $4.1 \pm 3.3$, and $5.3 \pm 1.8$ seconds after therapy in patients 1, 2, and 3, respectively. The response time after therapy was
shortened by 4.3 seconds in patient 1 and by 1.0 second in patient 2, reflecting an improvement in task performance after rehabilitation. For patient 3, the response latency did not change. Differences in TTP between auditory and motor cortices were 4.7, 2.9, and 1.3 seconds before therapy and 2.3, 0.7, and 1.9 seconds after therapy in patients 1, 2, and 3, respectively. The difference in TTP between auditory and motor cortices was shortened after therapy in patients 1 and 2 by 2.4 and 2.2 seconds and was lengthened by 0.6 second in patient 3. The Pearson correlation coefficient between the average time delay (auditory input versus oral response) and the TTP difference (auditory versus motor cortex) before and after therapy in the aphasic patients was 0.82 (α=0.05). The average time delay between auditory input and verbal response was 6.3 seconds before therapy and 4.5 seconds after therapy for the 3 patients compared with 3.4 seconds for the 3 control subjects. Correspondingly, the average difference in TTP between auditory and motor cortices was 2.9 seconds before therapy and 1.7 seconds after therapy for the patients compared with 1.4 seconds for the control subjects. Thus, both task performance and TTP values after therapy were close to values of control subjects, showing improvement compared with values before therapy.

**Discussion**

Using a category member generation task in fMRI, we measured the verbal response times and changes in TTP of BOLD hemodynamic responses of the right hemisphere homologues of stroke-damaged left hemisphere regions in 3 aphasic patients performing overt word generation tasks before and after therapy. All patients demonstrated improvements in language production, as evidenced by increased percentage of correct objects named on the therapy probes (Table 2) and by increases in category generation from before fMRI to after fMRI. This increase in category member generation suggests generalization of training effects from the picture-naming task that was used during training to other word-finding tasks. After therapy, the TTP of the activated ROIs in right auditory cortex, Broca’s area homologue, motor cortex, and pre-SMA significantly decreased in 2 aphasic patients. Decreased TTP of the hemodynamic response appears to reflect more rapid response by these regions after therapy. Findings from this study indicate that not only is the single subject level of analysis with the use of an ROI approach a viable one for analysis of patient fMRI data, but consideration of TTP may reveal additional important information about an individual patient’s performance and response to rehabilitative interventions. Furthermore, in populations with variability in terms of structural damage (e.g., stroke), analysis at the individual level is the most accurate way to capture and analyze variability in performance.

Using PET, Musso et al11 reported a correlation between increased activation in the right temporal cortex and com-
hension scores in Wernicke’s aphasia. Our results indicate that temporal as well as spatial aspects of brain activation are correlated with functional performance measures, such as response time, which reflects the speed of word finding and generation. Our data show a relationship between verbal response time and the TTP difference between the hemodynamic responses of auditory and motor cortices.

Several other factors should be considered when the data are interpreted. Liu and Gao, in a study of the linearity of the BOLD response in primary visual cortex, found that the TTP of the hemodynamic response was proportional to the stimulus duration. This suggests that the changes in TTP we observed are indicative of the time spent on the task between auditory stimulus presentation and verbal response. It has also been shown that contributions from large draining veins can affect the percent signal change and time to onset of the hemodynamic response observed in BOLD fMRI. However, to the extent that slice positioning and voxel selection were reproducible, this should not be a confounding factor in our study. Finally, it has been reported that, within a brain region, for a given subject, reproducibility of percent signal change and time to peak are good, with time to onset somewhat less reproducible. Evidence also exists that within-region response stability is sufficient to permit second resolution of changes in relative timing between regions.

It is well known that brain activation obtained during a covert language task is different from that obtained during overt verbal responses. In addition, artifacts due to task-related correlation, head motion, prolonged responses, and unpredictable responses, produced when aphasic patients speak out loud during an fMRI scan, are serious technical issues. To minimize these problems, it is important to give good instructions, to repeat the guidelines between functional runs, and to apply proper data analysis tools. One advantage of overt language production in fMRI studies is the ability to monitor task performance. This is especially important for aphasic patients because their response is variably delayed from the stimulus. Task performance data provide information to aid in analyzing and understanding the aphasic patient’s brain activation, as well as an additional factor with which to characterize rehabilitation outcome.

An unresolved issue in stroke rehabilitation is whether recovery from aphasia after left hemisphere lesions is mediated by the preserved and recovered left hemisphere areas or by readaptation of the homologous right hemisphere regions. Our finding supports the hypothesis that regions in the right hemisphere play an important compensatory role in the chronic stages of rehabilitation-aided recovery of language function after left hemisphere damage.

In summary, we used time-resolved fMRI to investigate the TTP of the BOLD hemodynamic response in aphasic patients before and after rehabilitation, comparing verbal response timing and TTP of BOLD hemodynamic response before and after therapy. Several preliminary conclusions may be drawn from this study: (1) it is important to record behavioral performance that may relate to the temporal characteristics of the hemodynamic response; (2) language therapy increased the speed of word-finding processes by several seconds; and (3) TTP analysis also detected this change in brain function with therapy.

Our data suggest that time-resolved fMRI can be used to evaluate quantitatively whether brain rehabilitation functionally improves speed of processing in regions that compensate for damaged cortical areas. This capability to provide temporal as well as spatial information about brain activity and function indicates that fMRI will likely play an increasing role in monitoring rehabilitation outcomes and in providing insight into how to design more effective rehabilitative interventions.

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