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Technical Note

Hemodynamic response function in patients with stroke-induced aphasia: Implications for fMRI data analysis

B. Bonakdarpour,[a,*] T.B. Parrish,[c] and C.K. Thompson[a,b]

[a]Department of Communication Sciences and Disorders, Northwestern University, 2240 Campus Drive, Evanston, IL 60208, USA
[b]Department of Neurology, Northwestern University, Evanston, IL, USA
[c]Department of Radiology, Northwestern University, Evanston, IL, USA

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Functional MRI is based on changes in cerebral microvasculature triggered by increased neuronal oxidative metabolism. This change in blood flow follows a pattern known as the hemodynamic response function (HRF), which typically peaks 4–6 s following stimulus delivery. However, in the presence of cerebrovascular disease the HRF may not follow this normal pattern, due to either the temporal signal to noise (tSNR) ratio or delays in the HRF, which may result in misinterpretation or underestimation of fMRI signal. The present study examined the HRF and SNR in five individuals with aphasia resulting from stroke and four unimpaired participants using a lexical decision task and a long trial event-related design. T1-weighted images were acquired using an MP-RAGE sequence and BOLD T2*-weighted images were acquired using Echo Planar Imaging to measure time to peak (TTP) in the HRF. Data were analyzed using Brain Voyager in four anatomic regions known to be involved in language processing: Broca's area and the posterior perisylvian network (PPN) (including Wernicke's area, the angular and supramarginal gyri) and right hemisphere homologues of these regions. The occipital area also was examined as a control region. Analyses showed that the TTP in three out of five patients in the left perisylvian area was increased significantly as compared to normal individuals and the left primary visual cortex in the same patients. In two other patients no significant delays were detected. We also found that the SNR for BOLD signal detection may by insufficient in damaged areas. These findings indicate that obtaining physiologic (TTP) and quality assurance (tSNR) information is essential for studying activation patterns in brain-damaged patients in order to avoid errors in interpretation of the data. An example of one such misinterpretation and the need for alternative data analysis strategies is discussed.

Introduction

Functional MRI (fMRI), a now widely used method for studying brain function, is based on a vascular response that is triggered by neuronal activation. The vascular response results from variations in deoxygenated hemoglobin concentration, i.e., the Blood Oxygen Level Dependent (BOLD) contrast, which can be measured in fMRI experiments (Ogawa et al., 1990). The activation-induced vascular response is known as the hemodynamic response function or HRF (see Huettel et al., 2004). In most individuals the signal starts to rise (increased cerebral blood flow and blood volume) shortly after stimulus onset and reaches a peak 5 to 6 s post-stimulus onset. This is followed by a slow decrease in MR intensity (decreased flow with nominal change in volume) that dips below baseline at roughly 10 s post-stimulus. In the next 10–20 s, the BOLD signal returns to baseline as blood volume decreases and vascular physiology returns to normal.

The shape of the BOLD signal response may vary with the properties of the evoking stimulus (Hund-Georgiadis et al., 2003) as well as the underlying neuronal activity (Buxton, 2002; Thierry et al., 2003). The shape of the HRF is particularly important when studying patients with occlusive cerebrovascular disease and cerebral infarction who often show altered cerebral blood flow or lack of vascular tone in response to autoregulation to preserve cerebral blood flow. Carusone et al. (2002), for example, showed that patients with intra and extracranial vascular obstruction had a non-canonical HRF with a delayed peak response and a blunted magnitude (Fig. 1). Roc et al. (2006) also reported a prolonged BOLD hemodynamic response in patients with significant stenosis of the anterior circulation. They observed a larger early negative BOLD, response or dip in patients, which was followed by a delayed hyperemic response.

Unusual HRF curves also have been found as a result of stroke. For example, Fridriksson and colleagues (2006) reported a stroke survivor with an unusual HRF curve that was persistently negative during the task. However, the effect of vascular disease on the hemodynamic response has been studied primarily in sensory motor areas of the brain. That is, investigators concerned with mapping cognitive behaviors in brain-damaged individuals have not completely considered this issue. In our previous work with stroke-induced aphasic patients, many showed little or a complete lack of activation under conditions in which activation in control participants was present, even when the behavioral data showed that the patients were accurately and promptly responding to the

* Corresponding author. Fax: +1 847 467 7377.
E-mail address: borna@northwestern.edu (B. Bonakdarpour).
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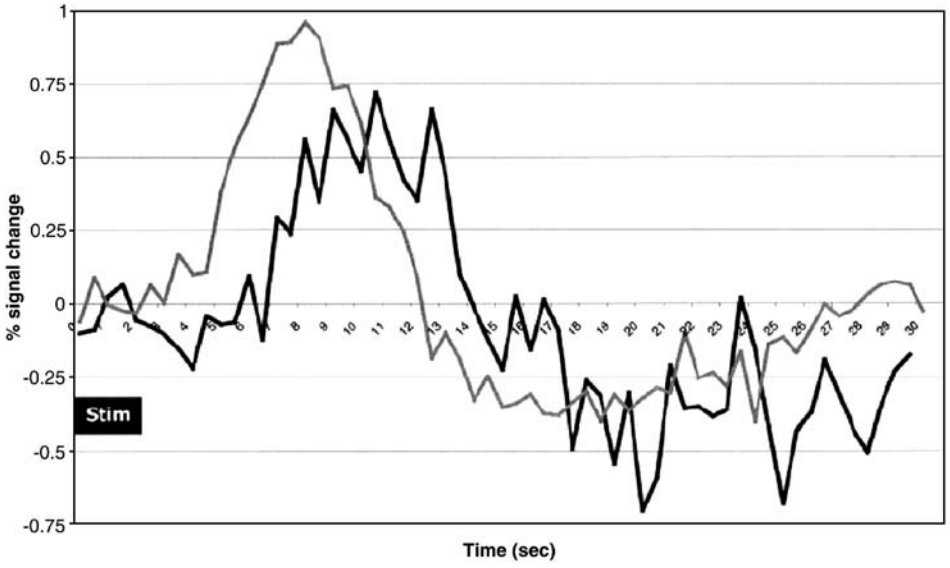

Fig. 1. The BOLD signal time courses for a patient with right internal carotid artery occlusion. Event-related paradigm curves show the HRFs for the right (black curve) and left motor cortex (gray curve). The black box denotes the timing of the stimulus (Stim). A decrease in amplitude and delay in onset of the hemodynamic response function exists in the hemisphere ipsilateral to the occlusion (black curve). (source: Carusone et al., 2002; used with the permission from the *American Journal of Neuroradiology*).

task. We therefore queried whether this putative underactivation could be accounted for by aspects of hemodynamic regulation in our stroke patients.

We first considered the temporal signal to noise ratio (tSNR) in our data acquisition. Because cerebral blood flow is altered in patients with stroke this can lead to a decreased BOLD signal response. Therefore, to verify adequate detection a higher temporal signal to noise (tSNR) is required. The tSNR is measured as the mean signal over time divided by the standard deviation of the fluctuations. Parrish et al. (2000) used computer simulations and empirical measures to determine the minimum tSNR required to detect a BOLD signal change. The following relationship of tSNR, statistical threshold (t), expected BOLD signal change (ΔS) and total number of volumes (N) was determined:

$$\mathrm{tSNR} \propto \frac{2t}{\Delta S\sqrt{N}} \quad (1)$$

The initial parameters of this relationship were determined by computer simulation and then could be modified to fit specific experimental designs (Parrish et al., 2000).

Results of our pilot data showed that indeed the lack of signal detection in some patients was due to low SNR values. In other patients, however, a desirable SNR value was found. We therefore sought to investigate other potential reasons for lack of signal detection in these patients, namely, the BOLD signal pattern. The issue of undetectable BOLD response in the presence of functioning neural network has been addressed by Rossini et al. (2004) who studied the primary sensory-motor cortex. They showed that in the presence of a detectable stimulus-locked MEG signal, fMRI activation could be missing. The authors considered changes in cerebral vasomotor reactivity as the contributing factor. The details of changes in vascular response, however, was yet to be investigated.

The purpose of this study was to extend our previous work, examining both SNR and HRF in language-related areas of the brain in a group of individuals with aphasia caused by stroke and a group of normal control participants. Time to peak (TTP) in each region and the tSNR required for signal detection was estimated. We predicted that the HRF in patients would be blunted and delayed compared to normal subjects and that accounting for these changes in fMRI analyses would improve detection of activation. Furthermore, measurements of BOLD signal change, accounting for the delay in the HRF, would enable us to determine whether the tSNR was adequate for detecting signal change using a general linear model analysis.

Method

Participants

Aphasic participants

Five aphasic patients (one female), recruited from the subject pool at Northwestern University, Aphasia and Neurolinguistics Research Laboratory, volunteered to participate in the study. Age

Table 1
Demographic data and Western Aphasia Battery (WAB) scores for the aphasic participants

	A1	A2	A3	A4	A5
Age	48	59	60	65	36
Gender	Male	Female	Male	Male	Male
Handedness	Right	Right	Right	Right	Right
Education	Masters degree	Bachelors degree	Some college	Masters degree	Bachelors degree
Years post-stroke	3	9	4	10	2
Language profile					
Naming	9	6.8	6.3	8.8	9.2
Fluency	6	6	4	5	5
Comprehension	9.4	8.35	8.25	8.6	9.2
Repetition	9.8	2.9	5	7.5	8.8
Aphasia Quotient (AQ)	82.4	66	64.2	77.8	82.4

range for the patients was 36–65 years; four were monolingual English speakers and one (A1) was a bilingual English/Spanish speaker. Aphasia in all patients resulted from a cerebral infarction due to thromboembolic stroke with the exception of participant A5 who suffered a cerebral hemorrhage. Also of note, in patient A4, stroke was preceded by a head trauma; however, based on the patient's medical records, vascular occlusion was determined to be the major cause of brain damage. Patients were at least 2 years post-onset of stroke and all were right handed. All were diagnosed with agrammatic aphasia based on results of the Western Aphasia Battery (WAB, Kertesz, 1982), with WAB aphasia quotients (AQs) ranging from 66.0 to 82.4. All patients showed relatively spared auditory comprehension ability, but production was impaired. They produced primarily short, ungrammatical sentences, with more nouns than verbs, and deletion or substitution of grammatical A2 morphemes (see Table 1).

MRI scans showed differences in lesion size and localization in the left hemisphere across patients. Patients A1, A2, A3 and A4 presented with thromboembolic, middle cerebral artery (MCA) territory infarctions, affecting cortical regions. Whereas, patient A5 suffered an intracranial hemorrhage, involving only subcortical tissue. Selected slices from patient T1 images are shown in Fig. 2. The following provides lesion specifications for each patient.

Patient A1. The posterior lateral aspect of frontal lobe, including the motor cortex and part of the pars opercularis of Broca's area, was affected. Wernicke's area, the prefrontal cortex and the insula were undamaged and the lesion did not extend to the periventricular white matter.

Patient A2. Damage involved almost the entire superior and middle temporal gyri, and part of the inferior temporal gyrus, but

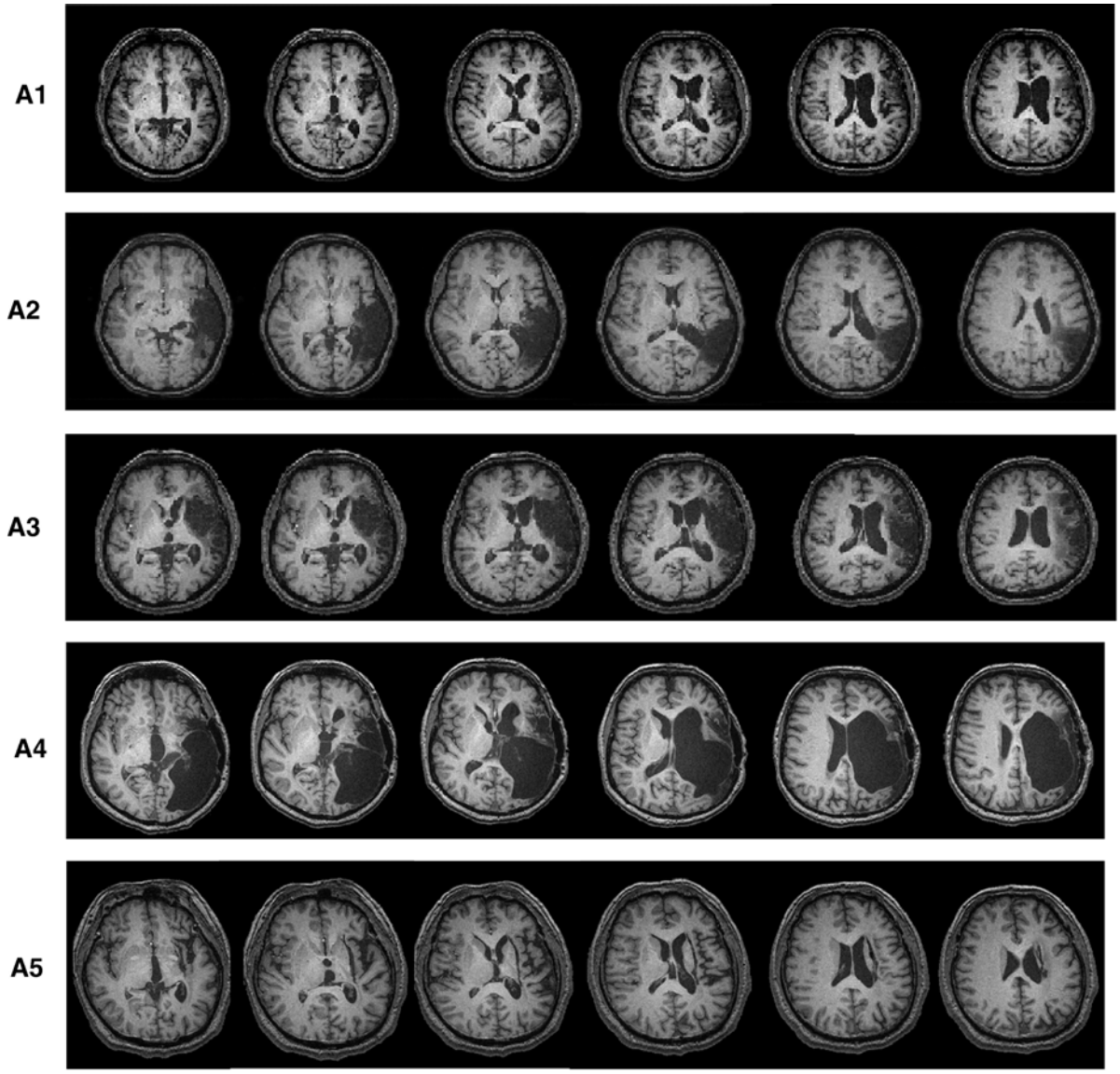

Fig. 2. Axial anatomical T1 MRI scans from selected perisylvian slices in five patients who participated in the study. See text for details regarding lesion boundaries.

Table 2
Stimuli used for the long trial lexical decision task

Pseudowords	Verbs	Nouns
Zim	Stir	Rabbit
Framp	Meet	Whale
Cuplum	Keep	Shark
Elt	Spend	Eagle
Shub	Consume	Lizard
Lill	Erase	Cow
Nolk	Join	Pig
Crenise	Injure	Mouse
Pader	Become	Chicken
Loperb	Slay	Lion
Barign	Pursue	Spider
Hydked	Cut	Horse
Hif	Destroy	Fish
Consken	Eat	Camel
Krobe	Resist	Leopard
Inclop	Collect	Dog
Sinloy	Achieve	Panda

Fifty-one stimuli were used including 17 verbs, 17 nouns and 17 pseudowords.

spared the occipitotemporal junction. The lesion also extended medially to the posterior horn of the left lateral ventricle.

Patient A3. Most of Broca's area, the middle frontal gyrus, part of the inferior parietal lobule and superior temporal gyrus were involved. The lesion extended to the anterior horn of the left lateral ventricle and affected part of the anterior internal capsule.

Patient A4. Damage extended to the temporal lobe, inferior parietal lobule and posterolateral part of frontal lobe, including the opercular part of Broca's area.

Patient A5. A subcortical lesion deep to the insula damaged the left basal ganglia and anterior limb of internal capsule.

Unimpaired control participants

Four normal control participants (all females) also were recruited for the study. These subjects were undergraduate students at Northwestern University and aged 18–21 years. All were right handed, monolingual English speakers with no history of neurological, psychiatric, speech, language or learning problems.

Stimuli and fMRI design

A set of 34 real words (17 nouns and 17 verbs) and 17 pseudowords were used as stimuli for the experiment. Verbs were all transitive with an average frequency of 27.2. Nouns included animal names with an average frequency of 26.17. There was no statistically significant difference between the frequencies of the two groups of words ($p=0.23$).

Pseudowords were created by breaking one- and two-syllable words into two pronounceable segments and randomly recombining these segments. For a list of stimuli see Table 2.

A long trial event-related (ER) design was used for presentation of the stimuli. Words and pseudowords were randomized and visually displayed using SuperLab (Cedrus Corp., version 2.00 for PC, Phoenix, AZ). SuperLab was run on a Compaq Pentium 4 computer with visual stimuli projected by an ELP link IV, Epson projector onto a custom-designed, non-magnetic rear screen.

Each stimulus was presented for 1200 ms followed by a 500-ms blank screen. After each stimulus trial, patients were presented with a large fixation cross for 26000 ms followed by a small cross that prepared them for the next stimulus. The small cross was displayed for 2300 ms. The total time for each stimulus trial was 30 s.

Participants performed a lexical decision to each visually presented stimulus. Accuracy and response time were measured using two fiber optic buttons held in their left hand, one for words and the other for pseudowords. The subject's head was immobilized using a vacuum pillow (Vac-Fix, Bionix, Toledo, OH) and restraint calipers built into the head coil.

Aphasic patients participated in two to five pre-experimental training sessions in a simulated scanner in the Aphasia and Neurolinguistics Research Laboratory. This was done to acclimatize participants to the scanner environment. Participants performed a lexical decision task using stimuli similar, but not identical, to the experimental stimuli. An accuracy of 90% or higher was required for cessation of training.

Scanner parameters

A 3-T Siemens scanner was used to obtain both anatomical (T1-weighted) and functional scans (T2*-weighted) obtained in the trans-axial plane parallel to the AC-PC line using a transmit/receive head coil. T1-weighted 3D volumes were acquired using MP-RAGE with a TR/TE of 2100 ms/2.4 ms, flip angle of 8°, TI of 1100 ms, matrix size of 256×256; FOV of 22 cm and 160 slices with a slice thickness of 1 mm. This orientation was identical for the functional scans. T2*-weighted volumes were acquired using a single-shot gradient echo, echo-planar sequence with a TR of 2 s, TE of 30 ms, flip angle of 80°, FOV of 22 cm, matrix size of 64×64 and 32 slices with a slice thickness of 3 mm with a zero gap. Total number of volumes was 771 including 6 dummy scans. Stimuli were presented in one run that lasted for 25 min and 30 s.

Data analysis

The functional data were analyzed using Brain Voyager (QX 1.4, Maastricht, The Netherlands) running in Windows XP environment.

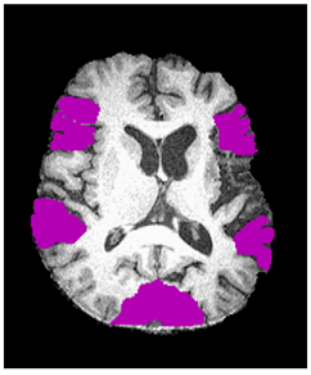

Fig. 3. Regions of interest for patient A1. In the anterior region remaining tissue in Broca's area was examined. The posterior region included spared pSTG, pMTG, left angular gyrus and left supramarginal gyrus. Homologues of the same areas were used as ROIs in the right hemisphere. Also shown is primary visual cortex which was used as a control region.

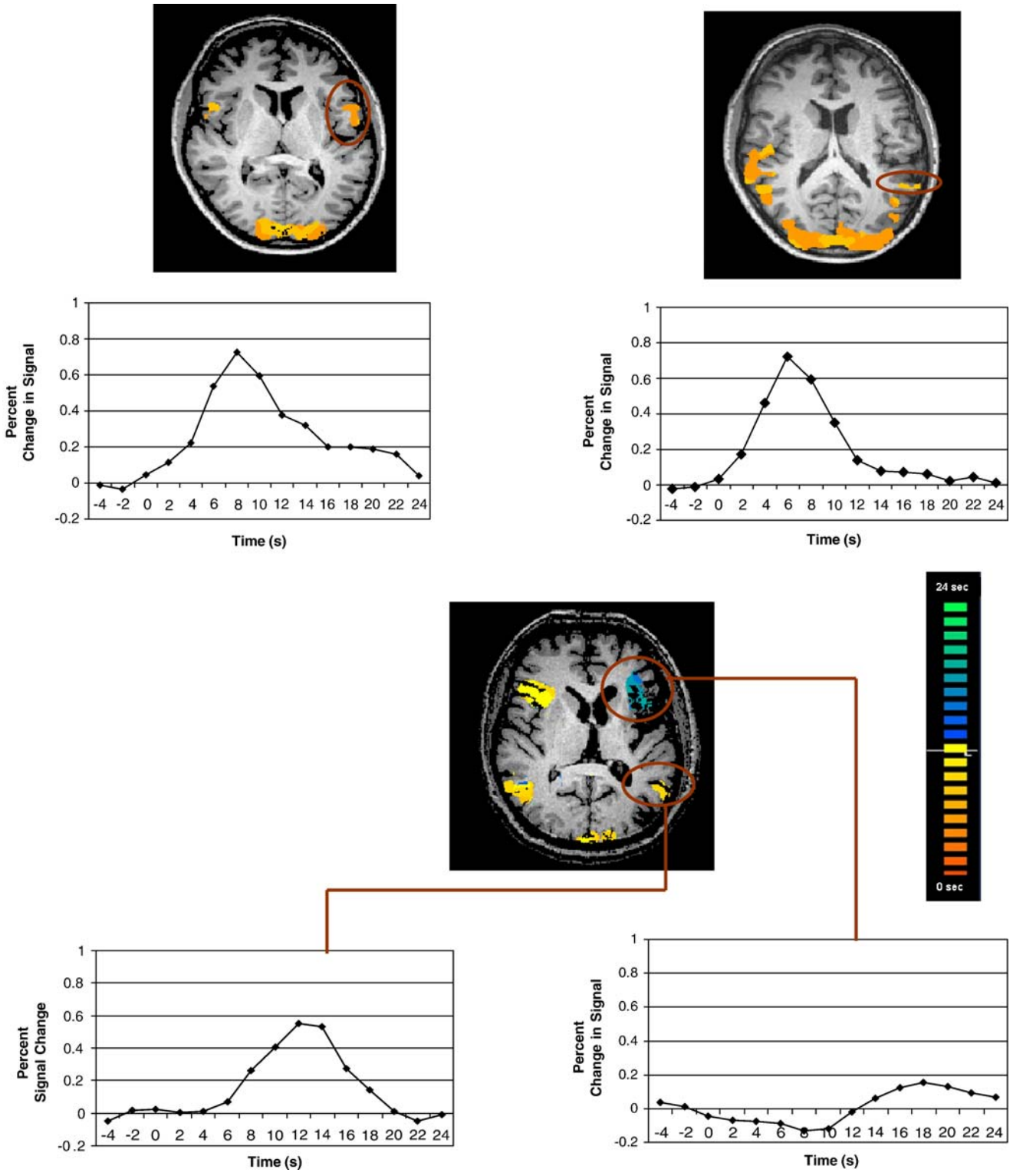

Fig. 4. Linear correlation lag maps at a threshold of $r=0.12$ in patient A1 (left side of figure) and a normal participant (right side of figure). Plots show BOLD signal peaks at 18 s post-stimulus onset in Broca's Area and 12 s post-stimulus onset in the PPN for the patient, as compared to the normal subject, who showed a peak at 6–8 s in both regions. The color bar shows the lag time, with red being zero delay and green being a 24-s delay.

Functional scans were corrected for slice-acquisition timing and 3D motion. Next, the data were spatially smoothed using a Gaussian kernel with an FWHM of 5 mm and temporally smoothed using a Gaussian kernel of 4 s (two TR periods). For normal individuals, the anatomical and functional volumes were normalized into Talairach space. In patients, the data were kept in the subject's native space.

Anatomical regions of interest were first identified in normal participants' perisylvian language regions. These areas included

Table 3
Minimum SNR values required to detect associated BOLD signal change

Change in BOLD signal (ΔS) (%)	SNR_{min}
1	67.36
0.75	89.8
0.5	134.72
0.25	269.4
0.1	673.6

ΔS=change in BOLD signal; SNR_{min}=minimum SNR required to detect a given change in signal. SNR_{min} was scaled using equation 1 (see text) with fixed parameters of number for volumes (N)=352, α=0.05 and β=0.05.

Broca's area (pars opercularis and pars triangularis in the inferior frontal gyrus) and what we refer to as the posterior perisylvian network (PPN). The PPN for our purposes included the following areas in the left hemisphere: Wernicke's area (the posterior third of the superior temporal gyrus or pSTG), the posterior third of the Middle Temporal Gyrus (pMTG), the Angular Gyrus and the Supramarginal Gyrus. Homologous areas on the right side were chosen as ROIs in the right hemisphere. Various research groups have reported differing locations for these brain regions (see Amunts et al., 1999); thus, we defined the ROIs based on sulci and gyri boundaries using definitions provided by Parent (1996) and Mesulam (1990). In patients with lesions affecting the regions of interest, we developed HRF maps from the perilesional regions not more than 5 mm from the lesion in three axes. Fig. 3 displays ROIs for a patient with a lesion in the perisylvian regions. As a control for the language task, we examined the HRF in the primary visual cortex (area 17).

HRF latency maps were formed using linear correlation lag analysis of the stimulation onsets and the time series on a voxel by voxel basis. A threshold of r=0.11 to 0.20, depending on signal to noise, was applied to the HRF lag map to form local clusters for further analysis. Within a suprathresholded region of interest, a stimulus-locked average formed the HRF curve for that particular cluster. The volume of each cluster within a region of interest ranged from 500 to 1000 mm^3. If more than one cluster was detected, the stimulus-locked average time courses for different clusters were averaged. Fig. 4 demonstrates the average HRF curves for clusters within each ROI in an aphasic and a normal subject.

In addition, temporal SNR maps were created for each subject in the same ROIs described above using MRIcro (Rorden, 2005). The minimum tSNR required to detect changes in the BOLD signal was calculated based on the SNR equation shown above, based on Parrish et al. (2000) (see Table 3).

Results

Behavioral data

Response accuracy for the normal control participants and the patients was 99.5% and 92.6% correct, respectively. The reaction time (RT) data, however, showed a significant difference between normal and aphasic participants, with average RTs of 594.31 (range=530.67–675.48) and 1352.41 (range=818.88–2130), respectively (p=0.036, Wilcoxon signed rank test) (see Table 4). These data indicated that the patient RTs were significantly slower than that of the normal control participants.

Table 4
Reaction times and accuracy for aphasic and control participants

Patients	Reaction time	Accuracy (%)	Control subjects	Reaction time	Accuracy (%)
A1	818.88	98	N1	548.77	100
A2	1348.5	96	N2	530.67	98
A3	1112.26	92	N3	622.33	100
A4	2130	84.3	N4	675.48	100
A5	967.5	92.6			
Average	1352.41	92.6	Average	594.31	99.5

SNR data and HRF curves

Control participants

For the normal control participants SNR values ranged from 114 to 491 across all ROIs and were well above the estimated values required to detect the BOLD signal changes measured (see Table 5). The only exception was participant N3 who showed a low SNR in the right PPN. The average post-stimulus onset BOLD signal time to peak (TTP) was 8±0.81 in the left hemisphere and 8.05±0.41 in the right, with no significant difference found between these values (see HRF information for control participants in Table 5 and Figs. 5 and 6). In the left and right occipital regions, average TTP was 9±0.20 in the left and 9.5±1.91 in the right with no significant difference between the two hemispheres. Also there was no significant difference between the perisylvian and occipital TTPs in each hemisphere.

Table 5
Measured HRF parameters and SNR values for normal control participants

Patient code	Anatomical localization	Percent change in BOLD signal (ΔS)	Required SNR	Measured SNR	TTP (s)
N1	L Broca's	0.72	93.5	205.2–284.7	8
	L PPN	0.72	93.5	181.5–369	6
	L Occipital	1.9	35.45	134–243	8
	R Broca's	0.50	134.7	181–260	8
	R PPN	0.50	134.7	177–260	8
	R Occipital	1.10	61.24	173–237	8
N2	L Broca's	0.28	240.6	162.7–269.5	8
	L PPN	0.29	232.3	271–400	8
	L Occipital	0.40	168.4	172–219	10
	R Broca's	0.31	217.3	166–217	8
	R PPN	0.30	224.5	215–275	6
	R Occipital	0.50	134.7	169–339	12
N3	L Broca's	0.36	187.1	175–349	12
	L PPN	0.2	336.8	260–491	6
	L Occipital	0.3	224.53	321–491	8
	R Broca's	0.43	156.6	255–407	10
	R PPN	0.16	421	209.7–299.7	6
	R Occipital	0.28	240.57	234–437	8
N4	L Broca's	0.34	198.2	114–325	8
	L PPN	0.47	143.3	189.9–350.7	8
	L Occipital	0.61	110.42	229–400	10
	R Broca's	0.36	187.1	129.6–286.	8
	R PPN	0.47	143.3	156.9–365.8	8
	R Occipital	0.61	110.42	165–467	10

Percent change in the BOLD signal (ΔS) and HRF time to peak (TTP) were measured in perisylvian and occipital areas of the left and right hemispheres. Note that the measured SNR values fall within the required SNR range in all cases except for participant N3 in the right posterior perisylvian region.

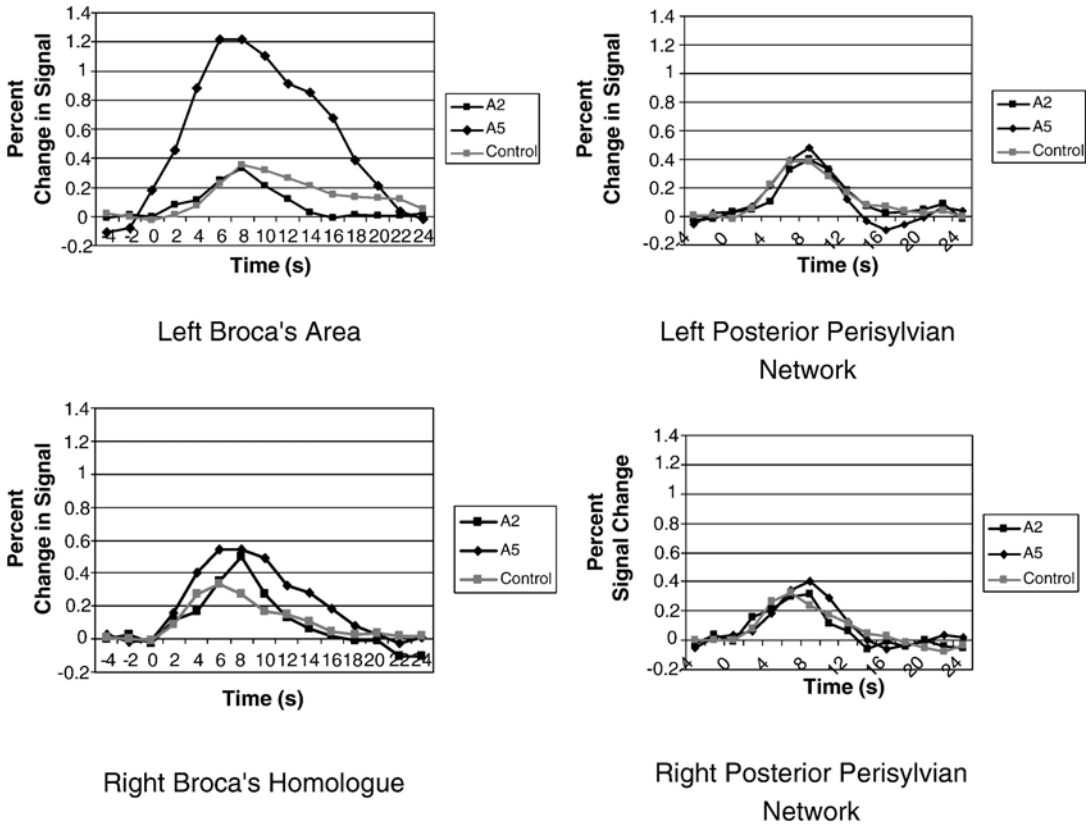

Fig. 5. Measured HRF data for two aphasic patients (A2, A5), who showed no delay compared to the normal subjects. In each plot above, the grey curve shows the average HRF plot from the four control participants. The PPN in this study included Wernicke's area, posterior middle temporal gyrus, angular gyrus and supramarginal gyrus. Note: TTP = time to peak.

Aphasic participants

The SNR and HRF data for the aphasic participants are shown in Table 6. The measured SNR ranged from 91 to 410 across all ROIs, which was greater than the required minimum SNR for BOLD signal detection for all but two patients. As shown in Table 6, the SNR values in the right PPN for participant A2 and left PPN for patient A3 were below that required.

The BOLD signal TTP showed two patterns across patients. Two patients, A2 and A5, showed an average perisylvian TTP of 8 and 7 s, respectively, which was not significantly different from control subjects (Wilcoxon signed rank test, $p=0.24$). Further, the TTP in the left and right hemispheres was identical for these patients. However, patients A1, A3 and A4 showed a delayed perisylvian TTP (mean = 16.5 s; range = 14–19.5 s), which was significantly delayed in the left hemisphere as compared to normal control participants (Wilcoxon signed rank test, $p=0.005$). These patients also showed unusual, complex HRF patterns in the left hemisphere as compared to patients A2 and A5, as well as the normal participants, with prolonged initial negative shifts followed by later peaks at 16–20 s post-stimulus. This pattern was seen in both anterior and posterior ROIs for patient A3 (see Fig. 6).

Participants A1 and A3 also showed greater delays in the left as compared to the right hemisphere, with a mean TTP in the right hemisphere of 11.75, which did not differ significantly from that in normal control participants (Wilcoxon signed rank test, $p=0.35$). However, patient A4 showed identical TTPs in the two hemispheres (i.e., 16 s).

Across patients the average TTP for the left primary visual cortex was 10 s, which was not significantly delayed compared to the same area in normal controls (Wilcoxon signed rank test, $p=0.16$). For the right occipital area, the average TTP was 11 s and again was not significant as compared to normal values (Wilcoxon test, $p=0.195$). Further, comparison of TTP for perisylvian and occipital areas in the left hemisphere showed a significant difference on the left side but not on the right side ($p=0.04$ and $p=0.25$, respectively).[1]

Discussion

The findings from this study showed differences in hemodynamic response functions across aphasic patients. While two patients (A2 and A5) did not show delays in perisylvian TTP as compared to normal participants, in three other patients the TTP was significantly slower than normal. In addition, these latter participants showed unusual response curves, with prolonged dips followed by a very late positive peak. This pattern was also found in recent studies by Roc et al. (2006) and Fridriksson et al. (2006) and suggests that oxidative metabolism was taking place without the typical increase in cerebral blood flow (CBF).

[1] Patient A4's data were not included in the right hemisphere group analysis because he showed bilaterally delayed TTP in the perisylvian region.

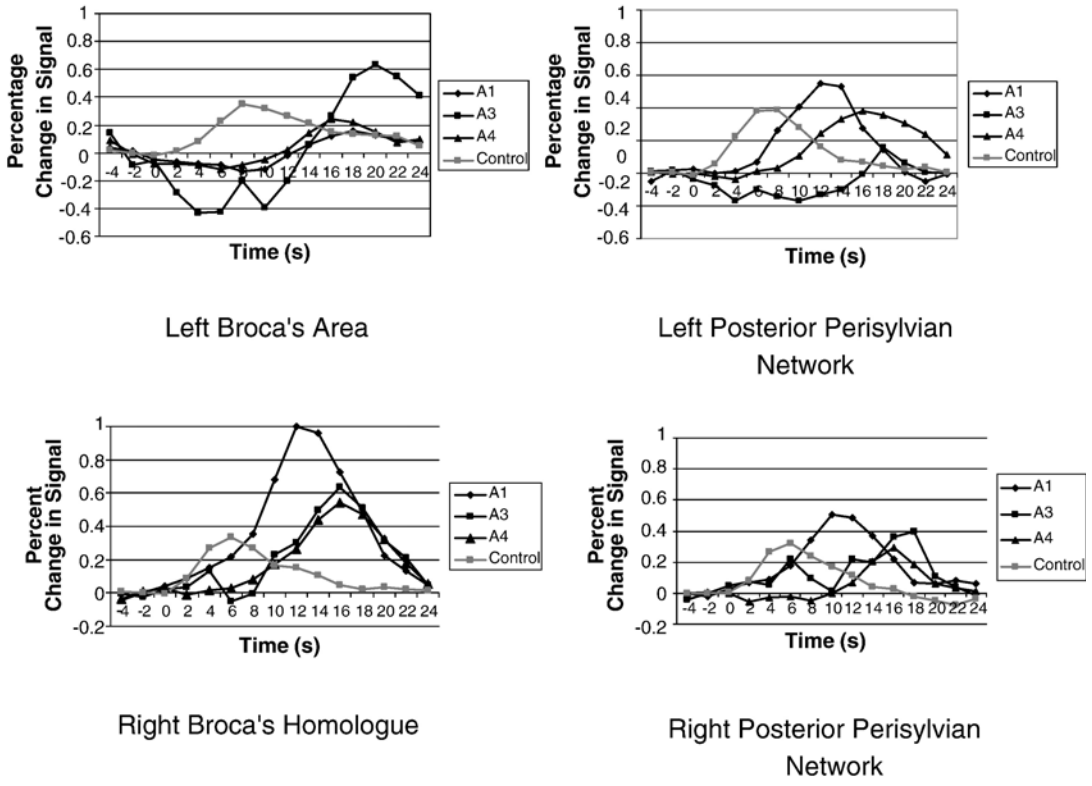

Fig. 6. Measured HRF data from three aphasic patients who showed a significant delay compared to normal control participants. In each plot above, the grey curve shows the average HRF plot from the four controls. The PPN included Wernicke's area, posterior middle temporal gyrus, angular gyrus and supramarginal gyrus. Note the prolonged dip in Broca's area in patients A1, A3, A5 and also in the PPN area in patient A3.

Interestingly, the TTP was significantly slower as compared to normal in the left hemisphere, but not in the right for two of these three participants (A1 and A3). That is, the HRFs derived from the right perisylvian ROIs were similar to those found in our normal participants; these patients showed delays only in the left perisylvian region. In addition, these patients did not show the same delay in the left occipital region: the perisylvian TTP was significantly slower than the occipital region TTP. Further, the TTP in both the left and right occipital region did not differ significantly from that in our normal controls. These findings indicate involvement of the vascular bed only in the left (infarcted) hemisphere within the distribution of the MCA, but not in the distribution of the posterior cerebral artery PCA.

Notably, a delayed HRF was noted in all ROIs, including occipital areas in both the left and right hemispheres for patient A4. The reason for this more global delay is unclear; however, this patient presented with the most extensive vascular lesion and in addition his neurological history was confounded by a closed head injury. Thus, it is possible that microvascular injuries secondary to head trauma contributed to this pattern.

In spite of A4s more extensive deficit, clearly three patients showed a left sided delayed BOLD signal as compared to normal participants. Notably, these delays can not be attributed to general processing delays, since reaction times (RTs) were similar across all patients, with no significant RT differences noted between patients who showed delays and those who did not. We therefore suggest that our findings can be attributed to delays in the vascular bed, as suggested by others (Roc et al., 2006; Fridriksson et al., 2006; Rossini et al., 2004; Hamzei et al., 2003; Carusone et al., 2002).

It also is possible that the delayed BOLD signal in our patients could be credited to age differences between the normal controls and the aphasic participants. Indeed, the latter were older. However, we point out that this factor alone is likely not responsible for our findings in that one of the older patients (60 years of age) showed a normal HRF pattern. Other studies directly examining the effects of age on the BOLD signal have found similar patterns. D'Esposito et al. (1999), for example, using a simple sensory motor task, found no significant differences between young and elderly subjects in the shape of the hemodynamic response or in its within-group variability. Similarly, Huettel et al. (2001) and Brodtmann et al. (2003) using simple visual paradigms found similar onset time, rate of rise and peak amplitudes, and Buckner et al. (2000) reported similar hemodynamic response summation in both groups, although reductions in amplitude were noted in the older participants. Finally, Nielson et al. (2004) found comparable hemodynamic responses in young and older subjects in an inhibitory control task (a higher cognitive task).

The finding that two participants showed a normal HRF (patients A2 and A5) indicates that, in some patients, blood flow dynamics may not be permanently impacted by stroke. While the reasons for the observed differences across patients are unknown, there are a number of variables to consider, among them the etiology of stoke and degree of recovery.

The etiology of stroke could explain the normal pattern of BOLD response in one of the aphasic participants (A5). He was a 36-year-old gentleman who evinced aphasia secondary to a subcortical infarction following intracerebral hemorrhage. Thus, he had little or no arterial occlusion. While regionally altered cerebrovascular

resistance has been reported in patients after stroke without occlusive arterial disease, these changes are most prominent in older patients and in those with lacunar infarcts (Kumar et al., 2005, Krainik et al., 2005). Thus, the normal HRF response in A5 may have been reflective of the non-occlusive nature of his stroke.

It is also possible that the degree of post-stroke language recovery is linked to the HRF. For example, Peck et al. (2004) suggested that treatment-induced recovery influenced the HRF, reporting that three aphasic patients who showed a delayed HRF demonstrated a faster TTP following successful language treatment. It could also be that language recovery takes place after the vascular physiology recovers to near normal levels. Since we did not obtain pre-recovery fMRI data from our participants, we can only speculate about this issue. We are presently investigating this question in aphasic patients by obtaining pre- and post-treatment blood flow measures and correlating them with the degree of language change. Normalization of the HRF after long-term recovery of stroke may be due to development of collateral circulation. In this case, follow-up study of patients with non-canonical HRF patterns may show normalization of the HRF in a few years.

Table 6
Measured HRF parameters and SNR values for the aphasic subjects

Patient code	Anatomical localization	ΔS	Required SNR	Measured SNR	TTP (s)
A1	L Broca's	0.16	421.00	322–431.4	18
	L PPN	0.55	134.72	195.5–449.5	10
	L Occipital	0.41	164.30	322–376	10
	R Broca's	1.00	67.36	236–431.3	12
	R PPN	0.50	134.72	266.1–363.3	10
	R Occipital	0.82	82.10	311–400	12
A2	L Broca's	0.33	204.12	95–165	8
	L PPN	0.40	168.40	105–199	8
	L Occipital	0.60	112.30	154–323	8
	R Broca's	0.50	134.72	104–174	8
	R PPN	0.31	217.33	86–203	8
	R Occipital	0.50	134.72	154–233	8
A3	L Broca's	0.63	160.92	191–351	20
	L PPN	0.15	449.00	199–313	18
	L Occipital	1.00	67.40	238–350	10
	R Broca's	0.63	160.92	118–384	16
	R PPN	0.42	160.38	151–394	12
	R Occipital	1.20	56.10	221–360	10
A4	L Broca's	0.24	280.67	190.3–314.8	16
	L PPN	0.38	177.26	209.1–360.1	16
	L Occipital	0.40	168.40	234–271	18
	R Broca's	0.54	124.74	171.4–283.4	16
	R PPN	0.29	232.27	202–310.6	16
	R Occipital	0.70	96.22	191–239	14
A5	L Broca's	1.2	51.13	297–410	6
	L PPN	0.48	140.33	112–201	8
	L Occipital	0.60	112.30	184–265	8
	R Broca's	0.54	124.74	163–325	6
	R PPN	0.40	168.40	94–313	8
	R Occipital	0.50	134.72	138–211	8

Percent change in the BOLD signal (ΔS) and HRF time to peak (TTP) were measured in perisylvian and occipital areas of the left and right hemispheres. Patients A1, A3 and A4 had a delayed time to peak (TTP) compared to control individuals. In patients A2 and A5, the TTP was not delayed. Note that the required SNR value falls within measured SNR range in cases A1, A3, A4 and A5. In two cases (patient A2 in the rPPN and A3 in left PPN), the measured SNR was lower than required which may compromise signal detection.

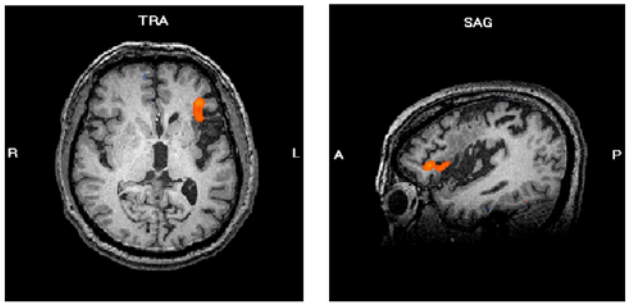

Fig. 7. An example of different activation patterns with and without consideration of the patient's HRF pattern. No significant activation was detected in Broca's area using a general linear model analysis modeled after the canonical HRF. However, activation was detected when the HRF was modeled after the patient's own hemodynamic pattern.

The finding that some stroke patients show a delayed HRF, however, emphasizes the importance of evaluating blood flow in patients who participate in fMRI experiments since an under-estimation of or complete lack of detection of activation may result when a canonical HRF is used for data analysis (see Thompson et al., 2006). Data from one of our aphasic participants attest to this. Patient A1s fMRI data were analyzed in two ways: first using a canonical HRF and second modeling the HRF after the patient's own hemodynamic curve. In the initial analysis, no significant activation was detected in Broca's area. However, using the patient's HRF, a significant cluster $p=0.0001$, corrected for multiple comparisons, was revealed in Broca's area (see Fig. 7). Given these findings, it is therefore recommended that in fMRI studies with stroke patients, each participant's HRF be measured using a long trial event-related study, conducted during each experimental fMRI session. Information about the hemodynamic parameters can then be used to optimize data analysis. Longitudinal alterations in the individual's HRF can also be used to determine if the underlying physiology has changed. We suggest that HRF curves from selected ROIs be assessed by evaluating the TTP as well as the overall BOLD signal change. The BOLD signal from these studies can also be used to determine if the lack of activation is due to insufficient SNR. As shown in this study in patients A2 and A3, the SNR value in some areas was not high enough to detect the small change in signal during the task. Therefore, one would not expect detection of the signal using a general linear model. A drop in SNR might be due to several factors, e.g., strength of vascular response and the performance of the scanner receiver. Our pilot data showed (see introduction) a decreased SNR in the perisylvian region in some aphasic participants, which interfered with signal detection. Therefore, monitoring SNR and HRF parameters is especially important for longitudinal studies of stroke subjects.

Conclusion

The goal of this paper was to evaluate individual HRF responses in selected regions (Broca's area and the PPN) within the language network in normal participants and those with aphasia secondary to stroke. In each subject the HRF in the primary visual cortex was measured for control purposes. The measured HRF in the left perisylvian area was significantly delayed in three out of five patients as compared to the measured HRF in the normal

individuals and to the left primary visual cortex. There was no significant delay in the TTP acquired from the right perisylvian region as compared to normal individuals except for delayed TTP in one patient with head trauma and possible right hemisphere micropathology. It was also demonstrated that in the face of altered hemodynamics using temporal information in the analysis of fMRI data improves detection of BOLD signal changes. Furthermore, one needs to verify that the regional tSNR is able to support detection of the BOLD signal change present in these patients. We recommend that these measures be incorporated into the data analysis in patient subjects in order to optimize detection of BOLD signal changes and minimize longitudinal variance in fMRI based studies of stroke and stroke recovery.

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