



## Variability in blood oxygen level dependent (BOLD) signal in patients with stroke-induced and primary progressive aphasia



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### ABSTRACT

Although fMRI is increasingly used to assess language-related brain activation in patients with aphasia, few studies have examined the hemodynamic response function (HRF) in perilesional, and contralesional areas of the brain. In addition, the relationship between HRF abnormalities and other variables such as lesion size and severity of aphasia has not been explored. The objective of this study was to investigate changes in HRF signal during language-related neural activation in patients with stroke-induced aphasia (SA). We also examined the status of the HRF in patients with aphasia due to nonvascular etiology, namely, primary progressive aphasia (PPA). Five right handed SA patients, three PPA patients, and five healthy individuals participated in the study. Structural damage was quantified with T1-weighted MR images. Functional MR imaging was performed with long trial event-related design and an overt naming task to measure BOLD signal time to peak (TTP) and percent signal change ( $\Delta S$ ). In SA patients, the average HRF TTP was significantly delayed in the left hemisphere regions involved in naming compared to healthy participants and PPA patients. However,  $\Delta S$  was not different in SA patients compared to the other two groups. Delay in HRF TTP in the left hemisphere naming network of SA patients was correlated with lesion size and showed a negative correlation with global language function. There were no significant differences in the HRF TTP and  $\Delta S$  in the right hemisphere homologues of the naming network or in the left and the right occipital control regions across the three groups. In PPA patients, HRF had a normal pattern. Our results indicate that abnormal task-related HRF is primarily found in the left hemisphere language network of SA patients and raise the possibility that abnormal physiology superimposed on structural damage may contribute to the clinical deficit. Follow-up investigations in a larger sample of age-matched healthy individuals, SA, and PPA patients will be needed to further confirm and extend our findings.

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### 1. Introduction

Task-based functional MRI (fMRI) is based on changes in oxygenated hemoglobin in the vascular bed surrounding the neural tissue and has been a widely used tool to investigate neural activity during different cognitive tasks including language processing (Huettel et al., 2008). Hemodynamic response function (HRF) is the basis for fMRI statistical computations. In healthy participants canonical HRF peaks on average at about 6–8 s after a short dip and then has an undershoot that lasts for as long as 15 s post-onset before returning to baseline. The shape of the HRF curve can deviate from the canonical form due to different causes including relatively small age related changes and more dramatic changes observed in brain disease, such as stroke (D'Esposito et al., 2003). Consideration of HRF changes is important for two reasons. First,

HRF abnormalities, if not accounted for can potentially affect blood oxygen level dependent (BOLD) signal maps and bias results of an fMRI study. This is particularly important when analyzing patient data (Bonakdarpour et al., 2007; Carusone et al., 2002; Meinzer et al., 2013; van Oers et al., 2010). Second, characterization of changes in BOLD signal can reflect brain pathophysiologic changes that contribute to clinical symptoms and their evolution over time (Peck et al., 2004).

Several neurologic diseases are associated with changes in micro-circulatory hemodynamics (D'Esposito et al., 2003). Stroke is of particular interest amongst these, as brain hemodynamics, the major determinant of fMRI measurements, can be affected. Although initial studies of HRF investigated sensory or motor performance (Aguirre et al., 1998; Handwerker et al., 2004), subsequent studies also looked at these changes using more complex experimental tasks such as language processing (Altamura et al., 2009; Bonakdarpour et al., 2007; Peck et al., 2004; Thompson et al., 2010). Dependent measures included changes in the HRF amplitude (i.e. percent change

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in BOLD signal, or  $\Delta S$ ), as well as BOLD signal time to peak (TTP) (Carusone et al., 2002; Peck et al., 2004).

Carusone et al. (2002), in a study of patients with baseline vasculopathy and carotid artery stenosis showed both a decrease in amplitude and increased TTP in the primary motor cortex of the affected side. Also, Fridriksson et al. (2006), in a case study of an aphasic patient with right hemiparesis due to a left middle cerebral artery (MCA) infarction, reported HRF changes associated with chronic ischemia in a motor task (Fridriksson et al., 2006). The patient in their case had a prolonged HRF negative dip and a late time to peak (TTP). Similar findings were also reported by Rother et al. (2002).

In another study of patients with stroke induced aphasia (SA), Peck et al. (2004) reported a similar delay in the HRF time to peak with a shift to normal HRF TTP after aphasia treatment. This study was the first to suggest that BOLD signal could be used as a biomarker for recovery from aphasia. Hillis et al. (2004) used hemodynamic variables, as measured by perfusion MRI, to demonstrate and predict recovery from acute aphasia. In this study hemodynamic changes were not associated with any task performance within the scanner. Perfusion MRI also has been used as a marker of pathophysiology in chronic aphasic patients (Brumm et al., 2010; Love et al., 2002). Although relationship between regional brain perfusion and aphasic symptoms has been demonstrated in the latter two studies, correlations between task-based BOLD signal and language performance have not been reported.

Change in vascular reactivity after stroke and aging have been cited as a source of BOLD signal under-detection (D'Esposito et al., 2003). D'Esposito and colleagues recommended several approaches in both experimental design and statistical analysis of fMRI data to address the potential confound of changes in BOLD signal. These included testing for differences in the relative performance (e.g. using a control task), correlating changes in BOLD signal with changes in behavioral measures, and using event-related fMRI designs and quantification of differences in vascular reactivity and the hemodynamic response for all subjects to establish a baseline for each subject. Following these recommendations, Bonakdarpour et al. (2007) reported hemodynamic changes in a series of 5 patients with chronic stroke-induced aphasia and 5 healthy participants, using a lexical decision task. A long trial event related experiment revealed that when compared to healthy participants, in three out of five patients, BOLD signal TTP was significantly delayed around the lesion and in two cases even in areas remote from the lesion in the contra-lesional hemisphere. The previous study, however, did not investigate whether the severity of TTP prolongation was related to lesion size and whether changes in HRF were correlated with language performance. The Bonakdarpour et al. (2007) study also did not focus on changes in the amplitude of the BOLD signal ( $\Delta S$ ) and the long trial experiment took 25.5 min. Although powerful, that design was difficult for aphasic patients and it was yet to be determined whether a shorter experiment would have the ability to measure BOLD signal reliably.

In this study, we tried to improve on the methodology used in Bonakdarpour et al. (2007) and take the first steps towards exploring the relationship between HRF changes, lesion size, and language performance. Specifically, we studied chronic stroke aphasic patients using a 6 minute long trial event related fMRI and an overt naming task. HRF

components (TTP and  $\Delta S$ ) were measured in regions of interest known to be involved in picture naming (Baldo et al., 2013; Price et al., 2005). These areas include: the left fusiform gyrus (l-FG), the left posterior middle temporal gyrus (l-MTG) and Broca's area. HRF abnormalities were determined by comparing HRF measures in patients with those of the healthy participants. Within the patient group internal control was established by comparing naming network regions with their contralateral homologous areas in the right hemisphere and with the occipital control regions.

While most research on changes in language network BOLD signal has focused on SA patients, changes due to other etiologies such as degenerative disorders, traumatic brain injury, tumors, and epilepsy, remain to be investigated. In this study, in addition to SA patients, we also investigated changes in brain hemodynamics in patients with aphasia due to neurodegeneration, also known as Primary progressive aphasia (PPA). Although changes in cerebral blood perfusion have been shown in PPA (Caso et al., 2013), language induced BOLD signal changes have not been studied. This study gave us an opportunity to investigate the BOLD signal in both SA and PPA patients and compare both with the healthy participants.

## 2. Methods

### 2.1. Subjects

Five patients with chronic SA (4 men and 1 woman, mean age = 59.6), three patients with PPA (2 men and 1 woman, mean age = 72), and five healthy participants (3 women and 2 men, mean age = 41) participated in the study. Western Aphasia Battery Aphasia Quotient (WAB-AQ) ranged from 29.3 to 96.3 for the post-stroke patients and from 78.2 to 97.5 for the PPA patients. Stroke etiology was thromboembolic in four patients and hemorrhagic in one. See [Tables 1 and 2](#) for more demographic and clinical information.

### 2.2. MRI data acquisition

#### 2.2.1. Structural (T1) MR images

A 3 T GE scanner was used to obtain the anatomical MR images. Images were acquired using a TR of 7.4 ms, TE of 3.0 ms, FOV of  $26 \times 26 \times 9 \text{ cm}^3$ , matrix size of  $256 \times 256 \times 24$ , voxel size of  $1 \times 1 \times 1.5 \text{ mm}^3$  with 160 slices per volume.

#### 2.2.2. Functional (T2) MR images

Functional MR imaging was performed using a long trial event-related design and an overt picture naming task. Participants named aloud 12 color pictures (Rossion and Pourtois, 2004) during the long trial run. Each picture stayed on a screen for 2.5 s, after which a fixation cross appeared for 27.5 s for an inter-trial interval (ITI) of 30 s. The total time for the naming run was therefore 360 s (6 min). Participants received no training on the pictures before scanning. They were instructed to name the stimuli immediately after the pictures appeared on the screen. Images were acquired using spiral imaging sequence with a TR of 2 s, TE of 35 ms, FOV of 24 cm, matrix size of  $64 \times 64$ , voxel size of  $3.75 \times 3.75 \times 4 \text{ mm}^3$  with 30 slices per volume.

**Table 1**  
Demographic and clinical information for patients with stroke-induced aphasia.

	Age (yrs)	Gender	TPO (yrs)	Handedness	WAB AQ	Aphasia Type	Etiology	Total lesion volume ( $\text{cm}^3$ )
SA1	67	Male	2.5	Right	41	Broca's	L-MCA stroke	117.654
SA2	65	Male	4.5	Right	29.3	Broca's	L-MCA stroke	138.706
SA3	51	Male	0.5	Right	82.2	Anomic	L-MCA stroke	71.276
SA4	78	Male	8	Right	96.3	Anomic	L-MCA stroke	45.920
SA5	37	Female	1.5	Right	80	Anomic	L-temporo-occipital hemorrhage	11.000

TPO = Time post-onset of stroke; WAB-AQ = Western Aphasia Battery Aphasia Quotient; L-MCA = left middle cerebral artery.

**Table 2**  
Demographic and clinical information for patients with primary progressive aphasia.

	Age	Gender	TPO (yrs)	Handedness	WAB-AQ	Type	Total volume of atrophy (cm <sup>3</sup> )
PPA1	70	Female	3	Right	89.9	Logopenic	44.384
PPA2	75	Male	2	Right	78.2	Logopenic	9.812
PPA3	71	Male	5	Ambidextrous	97.5	Progressive alexia	2.532

TPO = Time post-onset of stroke; WAB-AQ = Western Aphasia Battery Aphasia Quotient.

### 2.3. Data analysis

#### 2.3.1. Structural data analysis

In stroke patients, lesions were manually mapped in the native space and on a slice-by-slice basis using MRICron (Rorden and Brett, 2000) and a Wacom tablet. Following the creation of binary lesion images, each brain was normalized in SPM5 by unified segmentation and medium regularization using precise, unsmoothed lesion masks. This method has been shown to yield the most accurate estimation of the lesion volume (Andersen et al., 2010).

Voxel based morphometry (VBM) was used to determine the presence, location, and extent of atrophy in the patients with PPA (Wilson et al., 2010). High resolution T1 anatomical images were segmented using SPM5's automatic segmentation (Ashburner and Friston, 2005). Modulated gray and white matter probability maps were scaled by their Jacobians and smoothed with a 10 mm FWHM Gaussian kernel and added together. Each of the three participants was compared to a group of 18 age matched individuals using voxel-wise two-sample *t*-test with independent variance, thresholded at voxel-wise  $p < 10^{-5}$  with a minimum cluster size of 1000 mm<sup>3</sup>. Age, sex, and total intracranial volume were included as covariates of no interest.

#### 2.3.2. Functional data analysis

The functional data were analyzed using Brain Voyager (QX, Maastricht, The Netherlands) running in a Windows 7 environment (Landini et al., 2005).

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 (2 TR periods). To avoid post-normalization distortions, anatomical scans were kept in the subject's native space and the HRF analyses were performed similar to a previously published methodology (Bonakdarpour et al., 2007; Carusone et al., 2002). Three regions of interest (ROIs) recruited during overt picture naming based on a meta-analysis of functional imaging studies (Price et al., 2005) and associated with naming impairment in lesion-deficit correlation studies (Baldo et al., 2013), were examined for BOLD signal measurements (Fig. 1). These regions included Broca's area (pars opercularis and pars triangularis of the inferior frontal gyrus), posterior half of the middle temporal gyrus (MTG), the fusiform gyrus (FG), and their homologous areas in the right hemisphere.

ROI boundaries were based on sulci and gyri as defined by two sources (Parent and Carpenter, 1996; Talairach and Tournoux, 1988). In patients with lesions affecting the regions of interest, BOLD signal was extracted from the perilesional regions not more than 5 mm from the lesion in three axes. In addition, three occipital gyri (lingual, calcarine, and cuneus) were chosen as control regions for the language areas. 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  $r = 0.15$ – $0.25$ , depending on signal to noise, was applied to the HRF lag map to form local clusters for further analysis. Within a suprathresholded cluster, which had a volume of 500–1000 mm<sup>3</sup>, a stimulus-locked average of all voxels formed the HRF curve for that particular cluster.

#### 2.3.3. Statistical analysis

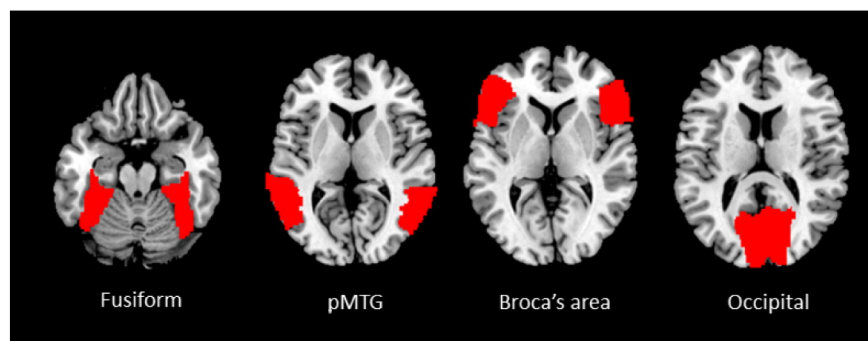
SPSS software was used for statistical comparisons across subject groups and for examining the relationship between structural and functional MRI measures and patients' language performance. First, the average HRF TTPs were statistically compared across the three participant groups in the left hemisphere naming network (FG, MTG, and IFG) using the Kruskal–Wallis test. The same analysis was performed for the right hemisphere homologous areas of the naming network. Similar comparisons were also computed for these left and right hemisphere ROIs investigating changes in  $\Delta S$ . We also examined HRF changes across the three groups for the left and right occipital ROIs which served as control regions. Finally, the relationship between abnormal HRF measures, lesion size, and aphasia severity was explored using the *Spearman* correlation test.

## 3. Results

### 3.1. Structural MRI

T1 images for stroke aphasic (SA) patients are demonstrated in Fig. 2. In three SA patients, lesion involved both the anterior and posterior left perisylvian language areas. Patient SA4 had a lesion restricted to the posterior perisylvian areas and patient SA5's lesion affected the white matter underlying the left fusiform gyrus. Lesion size in stroke patients ranged from 11–138 cm<sup>3</sup>. Table 1 demonstrates quantitative lesion measures in SA patients.

T1 images for PPA patients are demonstrated in Fig. 3. In the PPA patients atrophy volume (as compared to age-matched control individuals)



**Fig. 1.** Regions of interest (ROIs) used for BOLD signal measurements: fusiform gyri, posterior middle temporal gyri (pMTG), Broca's area and its right homologue, and occipital (lingual, cuneus and calcarine) gyri.

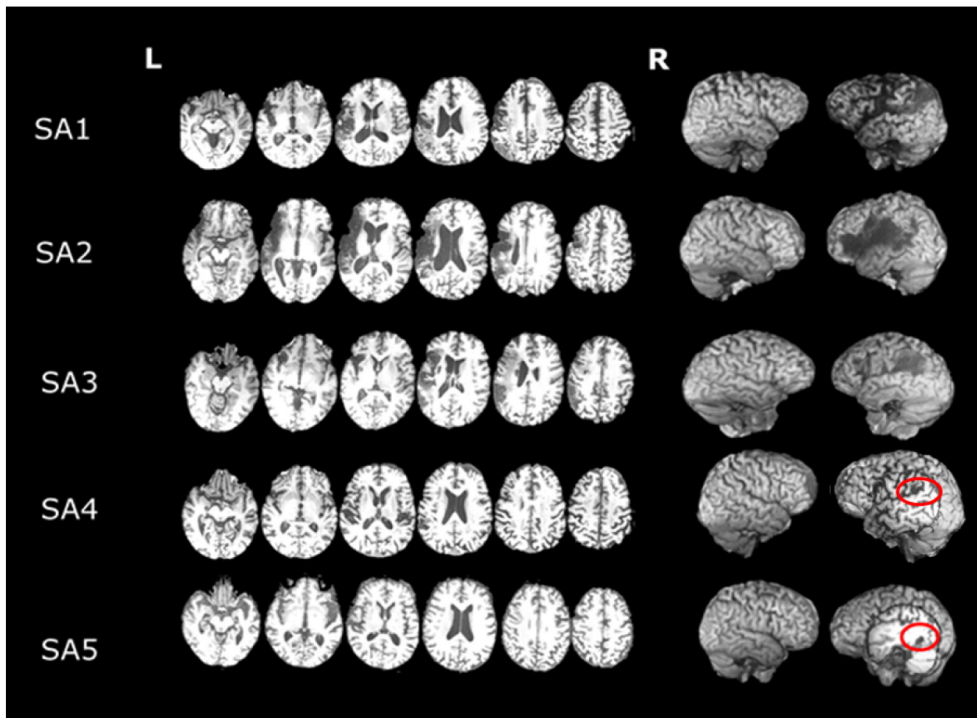


Fig. 2. Axial and three dimensional reconstructed T1 MRI images for the five stroke-induced aphasic patients (SA). See the text for a detailed description of location and extent of lesions.

ranged from 2–44 cm<sup>3</sup> and was moderately advanced in patient PPA1 and mild in the other two patients (PPA2 and PPA3). Degree of atrophy based on VBM is displayed in Table 2. In PPA1, peak atrophy was located within the left posterior inferior temporal gyrus (ITG), the left posterior MTG and the left FG. PPA2 had peak volume loss within the left ITG, the left MTG, and the left FG, but to a lesser extent compared to PPA1. In PPA3 peak atrophy was within the left posterior ITG and the left IFG. This patient had the least amount of atrophy.

### 3.2. HRF findings

What follows is a detailed report of BOLD signal characteristics in the healthy participants, SA, and PPA patients. Fig. 4 demonstrates the fMRI *r* map in one of the healthy volunteers. As shown in the

figure, in the healthy participants, HRF time course showed a robust stimulus-locked response for each naming trial in all regions of interest. It should be noted that an *r* map is different from the conventional *t* map used in task-based fMRI studies, which demonstrates significance of BOLD signal amplitude change when “active” and “rest” conditions are compared. The average TTP and  $\Delta S$  values for all ROIs across hemispheres for the healthy participants are displayed in Table 3.

The SA patients, similar to the healthy participants, showed the same robust response for each stimulus. An example of time courses for normal and abnormal HRF responses for a SA patient is demonstrated in Fig. 5. TTP and  $\Delta S$  values for all SA patients are summarized in Table 4.

The TTP and  $\Delta S$  values for all PPA patients are summarized in Table 5.

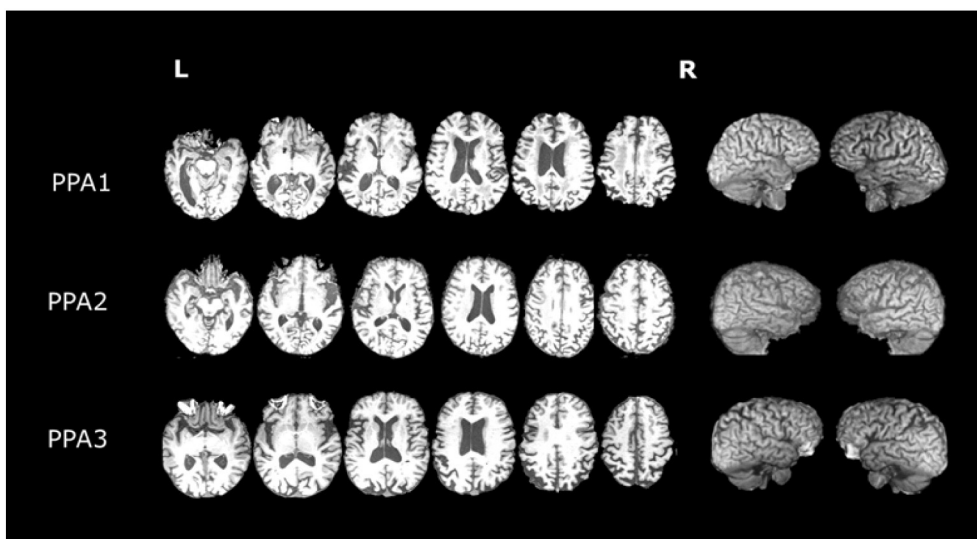
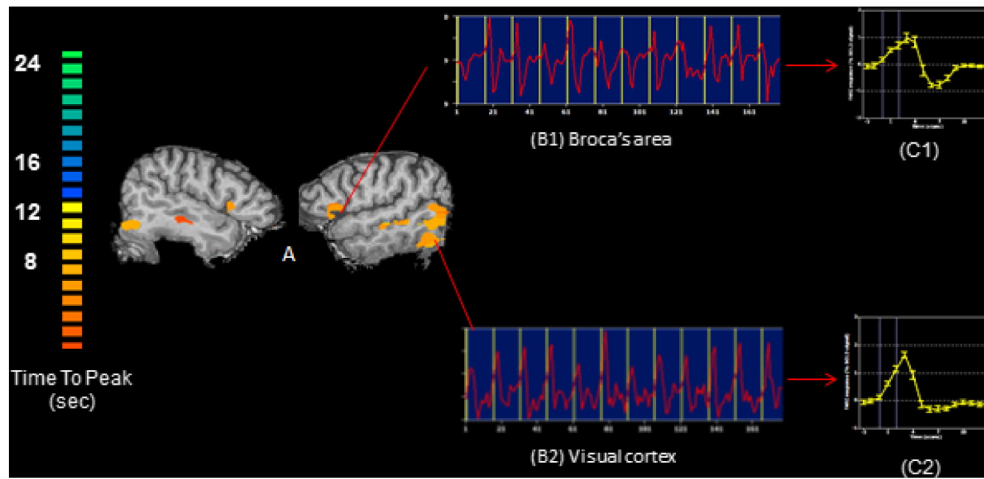


Fig. 3. Axial and three dimensional reconstructed images for the three primary progressive aphasic (PPA) patients. See the text for a detailed description of atrophy pattern.





**Fig. 4.** (A) fMRI *r* maps for a healthy participant generated using correlation lag analysis. The scale depicts colors assigned to different TTPs. Clusters within the selected ROIs (Broca's area, MTG, and visual) are seen in orange (time to peak of 6–8 s). (B) Plots demonstrate functional MRI time-course for clusters in (A). (B1): Left Broca's area, (B2): left occipital cortex. (C) In this individual both Broca's area (C1), and the visual cortex (C2) BOLD signals peak at 6 s post-stimulus onset.

3.2.1. HRF TTP comparisons across three groups

3.2.1.1. *Left hemisphere naming network.* The average TTP for the left hemisphere naming network ROIs (FG, MTG, and IFG) was 6.27 ( $\pm 1.67$ ) for the healthy participants, 10.67 ( $\pm 5.34$ ) for the SA patients, and 7.11 ( $\pm 1.72$ ) for the PPA patients. The Kruskal–Wallis test showed an effect of group ( $H = 9.230, p = 0.010, df = 2$ ). A follow-up Wilcoxon rank-sum test revealed a significant delay in SA aphasic patients' left hemisphere naming network when compared to the same network in the healthy participants ( $W = 40.00, p = 0.008$ ) and PPA patients ( $W = 6.00, p = 0.036$ ). There was no statistically significant difference between the PPA patients' and healthy participants' left naming networks ( $W = 17.00, p = 0.393$ ).

Further inspection of individual data revealed that in four SA patients (SA1–SA4), TTPs were delayed in the perilesional left MTG ( $>2$  standard deviation from the average left MTG TTP in healthy participants). In addition to the left MTG, SA3 also had delayed TTP in perilesional left IFG, while TTP abnormalities in SA5 were confined to the left FG.

3.2.1.2. *Right hemisphere naming network homologues.* The average TTP for the right hemisphere ROIs homologous to the naming network (rIFG, rMTG, and rIFG) was 6.67 ( $\pm 1.95$ ) for the healthy participants,

7.73 ( $\pm 0.92$ ) for the SA patients, and 6.67 ( $\pm 1.44$ ) for the PPA patients. The Kruskal–Wallis test indicated no difference across the groups ( $H = 2.926, p = 0.232, df = 2$ ).

3.2.1.3. *Left occipital ROIs.* The average TTP for the left hemisphere occipital control ROI was 6.8 ( $\pm 0.98$ ) for the healthy participants, 7.2 ( $\pm 1.60$ ) for the SA patients, and 7.33 ( $\pm 0.94$ ) for the PPA patients. The Kruskal–Wallis test showed no effect of group ( $H = 0.400, p = 0.819, df = 2$ ).

3.2.1.4. *Right occipital ROIs.* The average TTP for the right hemisphere occipital control ROI was 6.4 ( $\pm 0.80$ ) for the healthy participants, 8.00 ( $\pm 2.19$ ) for the SA patients, and 6.67 ( $\pm 1.89$ ) for the PPA patients. The Kruskal–Wallis test revealed no differences across groups ( $H = 1.522, p = 0.467, df = 2$ ).

3.2.2. HRF  $\Delta S$  comparisons across the three groups

3.2.2.1. *Left hemisphere naming network.* The average  $\Delta S$  for the left hemisphere naming network ROIs was 0.45 ( $\pm 0.28$ ) for the healthy participants, 0.53 ( $\pm 0.37$ ) for the SA patients, and 0.57 ( $\pm 0.12$ ) for the PPA patients. The Kruskal–Wallis test showed no effect of group ( $H = 0.780, p = 0.677, df = 2$ ).

3.2.2.2. *Right hemisphere naming network homologue.* The average  $\Delta S$  for the right hemisphere ROIs homologous to the naming network was 0.43 ( $\pm 0.26$ ) for the healthy participants, 0.59 ( $\pm 0.12$ ) for the SA patients, and 0.47 ( $\pm 0.18$ ) for the PPA patients. The Kruskal–Wallis test showed no group differences ( $H = 0.326, p = 0.850, df = 2$ ).

3.2.2.3. *Left occipital ROIs.* The average  $\Delta S$  for the left hemisphere occipital ROI was 1.00 ( $\pm 0.23$ ) for the healthy participants, 0.84 ( $\pm 0.51$ ) for the SA patients, and 0.57 ( $\pm 0.19$ ) for the PPA patients. The Kruskal–Wallis test revealed no effect of group ( $H = 2.594, p = 0.273, df = 2$ ).

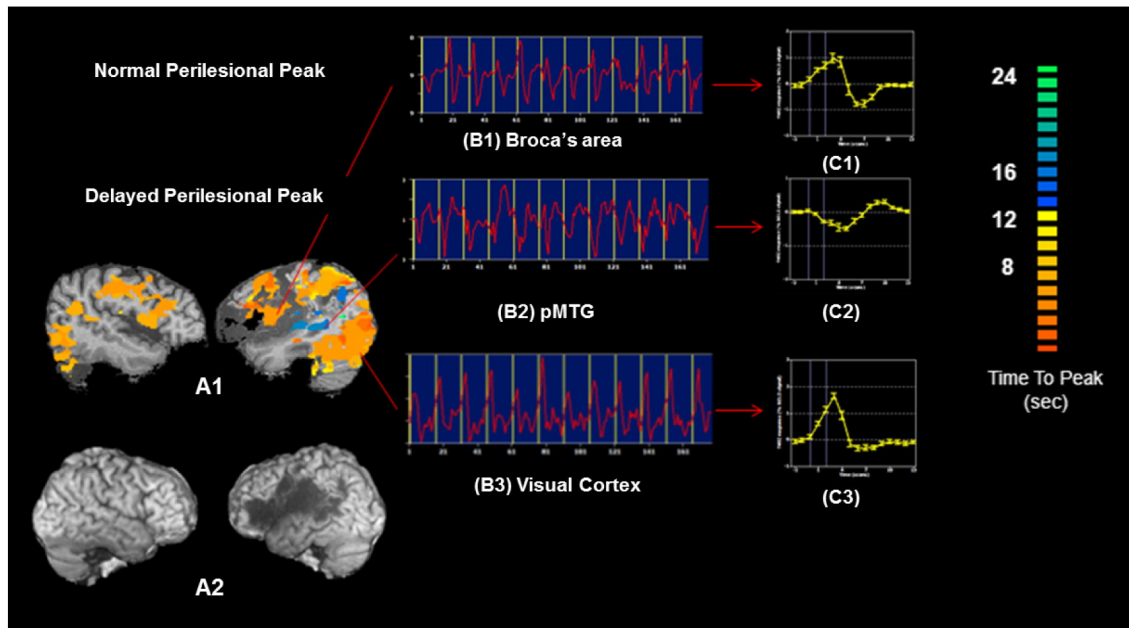
3.2.2.4. *Right occipital ROIs.* The average  $\Delta S$  for the right hemisphere occipital ROI was 0.91 ( $\pm 0.32$ ) for the healthy participants, 0.68 ( $\pm 0.33$ ) for the SA patients, and 0.90 ( $\pm 0.65$ ) for the PPA patients. The Kruskal–Wallis test showed no group differences ( $H = 0.538, p = 0.764, df = 2$ ).

3.2.3. HRF correlation with language function

HRF TTP was shown to be significantly delayed in the left hemisphere naming network of the SA patients when compared to both the healthy individuals and the PPA group. We further investigated

**Table 3**  
Time to peak (TTP) in seconds, and percent signal change ( $\Delta S$ ) in four regions of interest (ROIs) in the five healthy participants.

	Occip		FG		MTG		IFG	
	TTP	$\Delta S$	TTP	$\Delta S$	TTP	$\Delta S$	TTP	$\Delta S$
<i>Left</i>								
N1	6	1.2	6	1.1	6	0.4	6	0.6
N2	6	0.7	6	0.3	8	0.3	8	0.9
N3	8	1	4	0.4	4	-0.4	6	0.7
N4	8	1.3	6	0.3	6	0.5	10	0.7
N5	6	0.8	4	0.3	8	0.2	6	0.7
Avg.	<b>6.8</b>	1	<b>5.2</b>	0.48	<b>6.4</b>	0.2	<b>7.2</b>	0.68
SD	0.98	0.23	0.98	0.31	1.50	0.32	1.60	0.13
<i>Right</i>								
N1	6	1	6	0.5	6	0.3	6	-0.4
N2	6	0.7	6	0.3	8	0.4	8	0.4
N3	6	0.7	4	0.5	8	0.4	6	0.3
N4	6	0.65	6	0.5	8	0.8	6	0.7
N5	8	1.5	4	0.5	12	0.3	6	0.9
Avg.	<b>6.4</b>	0.91	<b>5.2</b>	0.46	<b>8.4</b>	0.44	<b>6.4</b>	0.38
SD	0.80	0.32	0.98	0.08	1.96	0.19	0.80	0.44



**Fig. 5.** (A1) fMRI *r* maps for a SA patient generated using correlation lag analysis. The scale depicts colors assigned to different TTPs. Clusters within the selected Broca's area and visual cortex are seen in orange (time to peak of 6 s), and the MTG cluster is delayed at 16 s post-stimulus onset. (A2) Structural T1 image is displayed below the fMRI image. (B) Plots demonstrate functional MRI time-course for clusters in Fig. 1A: (B1) Left Broca's area, (B2) left posterior middle temporal gyrus (pMTG). (C) Average HRF plot for fMRI time-courses. C1 and C3 show a canonical HRF pattern, while C2 demonstrates a non-canonical (delayed) HRF pattern.

the correlation between HRF TTP, stroke lesion size, and language function to look for the pathophysiologic and functional significance of this finding. Statistical analysis showed that the average TTP for the naming network was positively correlated (Fig. 6A) with lesion size (*Spearman*  $\rho = 0.872, p = 0.027$ , one-tailed). By contrast, WAB-AQ was negatively correlated (Fig. 6B) with the naming network TTP (*Spearman*  $\rho = -0.821, p = 0.04$ , one-tailed). No significant correlation was found (Fig. 6C) between the WAB-AQ and stroke lesion size (*Spearman*  $\rho = -0.70, p = 0.094$  one-tailed).

3.2.4. Effect of age

It should be noted that although the age range of the three groups was not perfectly matched, *Spearman* correlation analysis across all groups did not show a significant correlation between age and the left hemisphere language network HRF TTP ( $\rho = 0.282, p = 0.175$ ). Correlation between age and the left hemisphere naming network TTP was similarly not significant when tested in each of the three groups

**Table 4**  
Time to peak (TTP) and percent signal change ( $\Delta S$ ) in four regions of interest (ROIs) in five stroke aphasic patients.

	Occip		FG		MTG		IFG	
	TTP	$\Delta S$	TTP	$\Delta S$	TTP	$\Delta S$	TTP	$\Delta S$
<i>Left</i>								
SA1	8	1.4	6	0.4	18	0.2	8	0.7
SA2	6	0.8	6	0.6	16	0.2	16	0.3
SA3	6	1.4	8	1.53	18	0.3	6	0.3
SA4	6	0.5	8	0.5	10	0.1	10	0.5
SA5	10	0.1	18	1.6	6	0.3	6	0.2
Avg.	<b>7.2</b>	0.84	<b>9.2</b>	0.926	<b>13.6</b>	0.22	<b>9.2</b>	0.4
SD	1.60	0.51	4.49	0.53	4.80	0.07	3.71	0.18
<i>Right</i>								
SA1	8	1.1	8	0.5	8	0.8	8	0.3
SA2	6	0.8	6	0.6	6	0.6	6	0.4
SA3	8	0.9	8	0.7	6	1.2	8	1.6
SA4	6	0.4	8	0.4	10	0.3	8	0.6
SA5	12	0.2	10	0.1	10	0.2	6	0.6
Avg.	<b>8</b>	0.68	<b>8</b>	0.46	<b>8</b>	0.62	<b>7.2</b>	0.7
SD	2.19	0.33	1.26	0.21	1.79	0.36	0.98	0.46

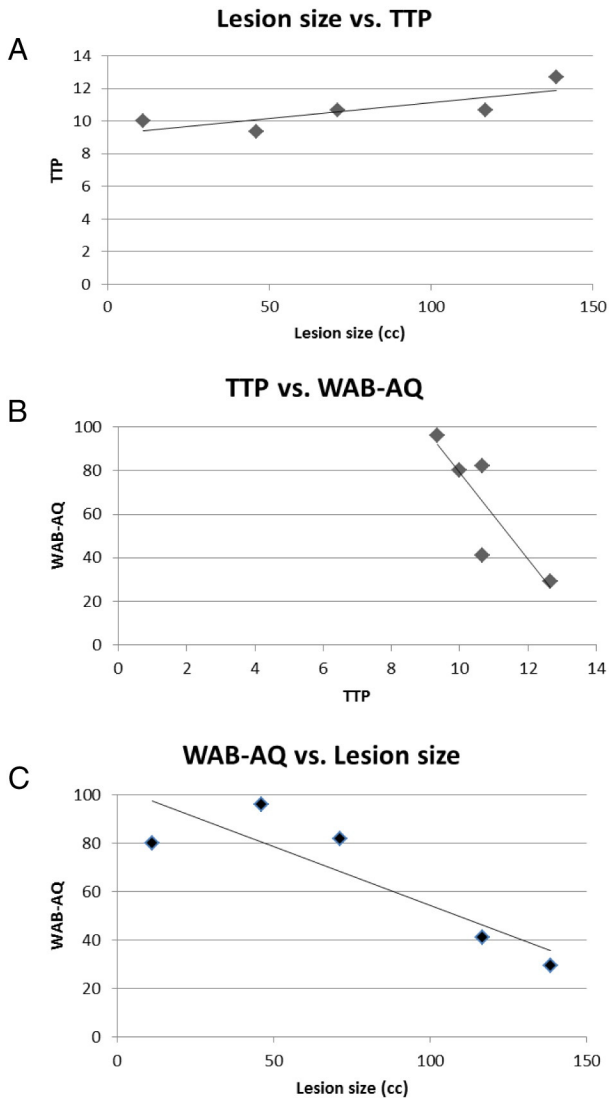
separately (healthy participants:  $\rho = 0.369, p = 0.541$ ; SA patients:  $\rho = -0.359, p = 0.553$ ; PPA patients:  $\rho = 0.500, p = 0.667$ ). Although age may change the morphology of the HRF curve, it affects the BOLD signal amplitude more than TTP (D'Esposito et al., 2003). In fact, TTP can become shorter with age (Richter and Richter, 2003). Therefore it is unlikely that the TTP prolongation in the left hemisphere naming network of the SA patients could be due to effect of age.

4. Discussion

In this study we used a long trial event related fMRI paradigm to measure hemodynamic reactivity within selected brain regions involved in overt naming. We found that, when compared with healthy participants and PPA patients, the SA patients showed evidence of increased HRF TTP in the left hemisphere naming network. Such changes were not observed in the homologous right hemisphere regions in the SA patients or in the control occipital ROIs. By contrast, signal amplitude was unaffected in SA patients compared to PPA patients and healthy

**Table 5**  
BOLD time to peak (TTP) and percent signal change ( $\Delta S$ ) in four regions of interest (ROIs) in the three PPA patients.

	Occip		FG		MTG		IFG	
	TTP	$\Delta S$	TTP	$\Delta S$	TTP	$\Delta S$	TTP	$\Delta S$
<i>Left</i>								
PPA1	6	0.3	4	-0.14	6	0.5	8	0.8
PPA2	8	0.7	8	0.9	8	0.7	6	0.6
PPA3	8	0.7	8	0.65	6	0.4	10	0.7
Avg.	<b>7.33</b>	0.57	<b>6.67</b>	0.47	<b>6.67</b>	0.53	<b>8.00</b>	0.70
SD	0.94	0.19	1.89	0.44	0.94	0.12	1.63	0.08
<i>Right</i>								
PPA1	4	0.3	6	0.5	4	0.1	8	-2.07
PPA2	8	1.8	6	0.8	8	0.4	6	0.09
PPA3	8	0.6	8	0.7	6	0.5	4	0.62
Avg.	<b>6.67</b>	0.90	<b>6.67</b>	0.67	<b>6.00</b>	0.33	<b>6.00</b>	-0.45
SD	1.89	0.65	0.94	0.12	1.63	0.17	1.63	1.16



**Fig. 6.** Plots demonstrating correlation between BOLD signal average hemispheric time to peak (TTP), lesion size, and WAB-AQ. Please refer to the text for more information.

controls. In the SA group, delay in HRF TTP was correlated with lesion size and language function, as measured by WAB-AQ.

Previous study of BOLD signal in the language network in a group of stroke-induced aphasic patients showed abnormal microvascular reactivity in some but not all subjects (Bonakdarpour et al., 2007). In this study we used a different language task and altered the design in order to achieve better fMRI activations in a more efficient way. Our goal was to further examine the patterns of BOLD signal changes in aphasic patients with different etiologies. We also investigated how changes in microvascular reactivity were related to lesion size and the patient's language impairment.

In SA patients, compared with healthy participants, there was no drop in signal amplitude ( $\Delta S$ ) in the left hemisphere naming network. This finding is in line with other studies that looked at stimulus-bound signal change (e.g. van Oers et al., 2010). However, consistent with Bonakdarpour et al. (2007) and Peck et al. (2004), average BOLD signal TTP within the naming network ROIs was significantly delayed when the left hemisphere average was compared with both healthy participants and PPA patients. All patients had a lesion in the left hemisphere and therefore more vascular pathology on that side. This was further confirmed by the fact that BOLD TTP was not affected in the intact right hemisphere naming network homologous areas of the SA patients.

Also, BOLD TTP delay was only seen within the language related areas and not within the non-language related occipital ROIs.

In contrast to stroke patients, PPA patients showed no significant deviation from the canonical BOLD shape when TTP and  $\Delta S$  in the naming network and the occipital ROIs were compared to the healthy participants. Also, there was no change in the BOLD signal TTP and  $\Delta S$  in the unaffected right hemisphere naming network homologue and right occipital ROI. At the single subject level one patient (PPA3) had apparent prolongation in BOLD signal TTP in the left IFG when compared to the right IFG. However, the BOLD signal TTP of 10 s still remains within two standard deviation of the mean IFG TTP for normal individuals and may not be considered prolonged. A regional decline in CBF has been reported in patients with PPA and other degenerative dementias (Caso et al., 2013; Hu et al., 2010). Whether reported changes in CBF can cause deviation in BOLD response characteristics remains to be examined in future studies. However, based on our findings additional correction may not be needed to interpret the fMRI data for the reported PPA patients. The PPA patients in this study had mild aphasia and possibly minimal changes in regional CBF. It is yet to be determined whether progression of neurodegeneration and changes in regional perfusion would change the shape of the BOLD response.

Increased BOLD signal TTP in SA patients was positively correlated with lesion size in our study. Bonakdarpour et al. (2007) described SA patients with impaired vascular reactivity and prolonged BOLD signal TTP, however, it remained to be determined how this phenomenon was related to lesion variables. Patients with larger lesions have more vascular pathology in the perilesional areas and therefore more prone to have abnormal stimulus-induced BOLD signal changes during a naming task. As discussed before, knowledge of BOLD signal change is essential when analyzing SA fMRI data. Our findings suggest that HRF abnormalities may be more common in patients with larger lesions. It is important to note that at the single subject level, patient SA5 who had a hemorrhagic subcortical stroke had prolongation of BOLD signal TTP in the presence of a smaller lesion. This may be due to the fact that subcortical damage may affect a larger area of the cortex by "disconnection" mechanisms attributable to damage to white matter pathways. However, all other patients also had subcortical components to their lesions suggesting widespread disconnection of cortical areas. Since SA5 was the only patient with hemorrhagic stroke, it is possible that lesion etiology may have played a role. A larger study including both of hemorrhagic and ischemic stroke patients is needed to better understand potential differences in HRF changes related to stroke etiology.

The results of our study suggest that changes in BOLD signal and vascular reactivity may have clinical significance. Specifically, we obtained evidence of a negative correlation between BOLD signal TTP and SA patients' language function, as measured by WAB-AQ. These findings raise the possibility that part of the clinical impairment in SA patients may be due to abnormal physiology superimposed on structural damage. A correlation between perilesional hypoperfusion and aphasic symptoms in chronic stroke survivors has been shown in previous studies using MR perfusion (Brumm et al., 2010; Love et al., 2002). BOLD TTP is an even more sensitive measure of hemodynamic impairment and therefore information regarding the status of perilesional HRF TTP can be helpful in understanding brain function. Peck et al. (2004) were first to show that HRF TTP has clinical significance. They demonstrated that in patients with non-fluent aphasia who responded to treatment (improved word retrieval) TTP analysis was sensitive to functional changes and could be used to predict improvement in behavior, thus serving as a potential biomarker. Similar findings were reported in a group of agrammatic SA patients (Thompson et al., 2010). What has not been shown yet is whether knowledge of perilesional hemodynamic status using HRF TTP would have an implication for treatment responsiveness, or prognosis of aphasia recovery. This will be a goal for future research projects.

On a technical note, this study demonstrated that using overt naming, a larger network of brain regions can be recruited. This is an

improvement compared to Bonakdarpour et al. (2007), in which we used a lexical decision task. By using overt naming we were able to use fewer trials (12 trials compared to 51 in the previous study), which decreased the study time from 25.5 to 6 min and therefore avoiding subject fatigue and inattention.

Finally, it should be noted that the findings of this study are based on a small group of patients which limits our ability to make strong generalizations about abnormal BOLD response following stroke. Furthermore, in future studies, measurement of patients' online performance (including naming accuracy and reaction time), evaluation of other brain regions involved in naming, accounting for the effects of respiratory and heart rates on BOLD signal, and addition of MR perfusion/arteriograms, will provide a more comprehensive understanding of the hemodynamic changes associated with cerebrovascular diseases.

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