# Overt naming in aphasia studied with a functional MRI hemodynamic delay design

Paula I. Martin,[a,*] Margaret A. Naeser,[a] Karl W. Doron,[a] Andrew Bogdan,[a] Errol H. Baker,[a] Jacquie Kurland,[a] Perry Renshaw,[b,c] and Deborah Yurgelun-Todd[b,c]

[a]Harold Goodglass Boston University Aphasia Research Center, Department of Neurology,
 Boston University School of Medicine and the Veterans Affairs Boston Healthcare System, 150 So. Huntington Avenue, Boston, MA 02130, USA
[b]Brain Imaging Center, McLean Hospital, Belmont, MA 02478, USA
[c]Harvard Medical School, Boston, MA 02115, USA

The purpose of this study was to develop a functional MRI method to examine overt speech in stroke patients with aphasia. An fMRI block design for overt picture naming was utilized which took advantage of the hemodynamic response delay where increased blood flow remains for 4–8 s after the task [Friston, K.J., Jezzard, P., Turner, R., 1994. Analysis of functional MRI time-series. *Hum. Brain Mapp.* **1**, 153–171]. This allowed task-related information to be obtained after the task, minimizing motion artifact from overt speech [Eden, G.F., Joseph, J., Brown, H.E., Brown, C.P., Zeffiro, T.A., 1999. Utilizing hemodynamic delay and dispersion to detect fMRI signal change without auditory interference: the behavior interleaved gradients technique. *Magn. Reson. Med.* **41**, 13–20; Birn, RM., Bandettini, P.A., Cox, R.W., Shaker, R., 1999. Event-related fMRI of tasks involving brief motion. *Hum. Brain Mapp.* **7**, 106–114; Birn, R.M., Cox, R.W., Bandettini, P.A., 2004. Experimental designs and processing strategies for fMRI studies involving overt verbal responses. *NeuroImage* **23**, 1046–1058]. Five chronic aphasia patients participated (4 mild–moderate and 1 severe nonfluent/global). The four mild–moderate patients who correctly named 88–100% of the pictures during fMRI, had a greater number of suprathreshold voxels in L supplementary motor area (SMA) than R SMA ($P < 0.07$). Three of these four mild–moderate patients showed activation in R BA 45 and/or 44; along with L temporal and/or parietal regions. The severe patient, who named no pictures, activated almost twice as many voxels in R SMA than L SMA. He also showed activation in R BA 44, but had remarkably extensive L and R temporal activation. His poor naming and widespread temporal activation may reflect poor modulation of the bi-hemispheric neural network for naming. Results indicate that this fMRI block design utilizing hemodynamic response delay can be used to study overt naming in aphasia patients, including those with mild–moderate or severe aphasia. This method permitted verification that the patients were cooperating with the task during fMRI. It has application for future fMRI studies of overt speech in aphasia. Published by Elsevier Inc.

*Keywords:* Aphasia; fMRI; Overt speech

## Introduction

Despite a number of functional neuroimaging studies that have examined language, our understanding of language recovery poststroke is incomplete. Debate continues as to whether the left hemisphere (LH), right hemisphere (RH), or both play a role. Some studies have suggested that the RH is important in language recovery after stroke (Thulborn et al., 1999; Peck et al., 2004). Others have posited, however, that RH activity may be 'maladaptive' or 'an inefficient dead-end strategy' (Belin et al., 1996; Rosen et al., 2000; Naeser et al., 2004). Some studies have suggested that the LH perilesional areas are of greater significance in recovery (Perani et al., 2003; Warburton et al., 1999; Heiss et al., 1999; Demeurisse and Capon, 1987). Others have suggested that the LH, RH, or both may be recruited in recovery (Thompson, 2000; Gold and Kertesz, 2000).

Salmelin et al. (1994) has used MEG to study picture naming in normals. Language processing was observed to advance sequentially from the posterior visual (occipital) to language (temporal), and finally to vocalization (premotor, frontal) areas. Left-sided activation was present earlier and was stronger, although both hemispheres were involved.

PET studies have also suggested that naming in normals involves a distributed neural network. Damasio et al. (1996, 2004), for example, have observed specific regions to be relatively more activated during picture naming for specific categories—i.e., L temporal pole (people); L middle infero-temporal and bilateral mesial occipital (animals); and L posterior, infero-temporal and

 * Corresponding author. Fax: +1 617 739 8926.
   *E-mail address:* paulak@bu.edu (P.I. Martin).
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supramarginal gyrus (tools). Martin et al. (1996) also observed separate areas to be associated with naming of animals versus tools. Murtha et al. (1999) have observed animal naming to be associated with L and R Brodmann areas (BA) 18, 19, and 37; L BA 21, 38, 22, insula, BA 24, 32, BA 4, L thalamus and R BA 22, 42.

Early functional magnetic resonance imaging (fMRI) studies used only covert or silent paradigms to investigate speech in normals (Rueckert et al., 1994; Shaywitz et al., 1995). Moore and Price (1999) used covert fMRI with normals, while naming pictures of objects. Activation was observed in L anterior medial fusiform, posterior fusiform, lateral posterior, inferior temporal, and posterior occipito-temporal areas.

Recent fMRI experiments have studied overt speech across a variety of language tasks in normals (Barch et al., 1999; Abrahams et al., 2003; Bookheimer et al., 1995; Burton et al., 2001; Palmer et al., 2001; Price et al., 2001). A number of these functional imaging paradigms utilized sparse temporal sampling, clustered volume acquisition, and behavior interleaved gradients or similar techniques that allow for stimulus presentation and response generation during a period of silence, between image acquisitions (Edmister et al., 1999; Hall et al., 1999; Elliott et al., 1999; Eden et al., 1999). These investigators have shown that it is possible to overcome problems associated with overt speech while in the scanner including (1) increases in head movement artifact due to speaking; (2) artifacts from articulation-related movements of the jaw and tongue which result from volume changes in the sinus cavities during speaking; and (3) scanner noise which makes hearing and recording responses difficult. Huang et al. (2001) used event-related fMRI to investigate naming of letters and animals in normals with both silent and overt speech. In this study, regions activated during silent and overt speech included: SMA, lateral premotor area, anterior and posterior cingulate, supramarginal gyrus, angular gyrus, superior parietal lobule, posterior superior temporal gyrus, middle temporal gyrus, insula, and occipital lobe.

There is still a need, however, to utilize fMRI paradigms to examine overt speech in aphasia patients. It is necessary to utilize overt speech paradigms with aphasia patients to verify that they are cooperating with the task and to what level, which covert speech studies do not permit. Head movement artifact due to speaking aloud has been one complication, particularly within a patient population. Training is especially important with these patients to avoid excessive head movement and to get them into set to perform the task. Additionally, examining overt speech in nonfluent aphasia patients can be difficult due to their hesitant, poorly articulated, agrammatic speech. Their poor articulation can make responses difficult to transcribe. Distortions in the fMRI data, particularly around the lesion, and the ventricles can also be an issue when studying stroke patients.

The purpose of this study was twofold: (1) to develop an fMRI method to examine overt speech in stroke patients with aphasia and (2) to apply this method across a spectrum of aphasia patients (mild to severe). An fMRI block design for overt picture naming was utilized and found suitable for use with aphasia patients for the following reasons: (1) it permitted use of the temporal dynamics of the hemodynamic response delay where increased blood flow remains 4 to 8 s after the response (Friston et al., 1994). This technique is similar to the techniques of sparse temporal sampling and clustered volume acquisition. It allows task-related information to be obtained after the task, during the silent period of no speech, minimizing motion artifact from overt speech (Eden et al., 1999; Birn et al., 1999, 2004); (2) A block design permitted examination

of overt speech in the aphasia patients despite the false-starts and hesitations present in their speech. An event-related paradigm may allow analysis of overt speech responses in greater depth; however, the variation in timing of response output in aphasia patients is great because of their false-starts and many hesitations.

A region of interest (ROI) method of analysis was chosen. The following a priori cortical ROIs based on previous functional neuroimaging studies with naming (reviewed above) were investigated in both the LH and RH: SMA; BA 24 (anterior cingulate); prefrontal, BA 45 and 44; premotor, BA 6; motor, 4; temporal, BA 22, 21, 37, and 20; parietal, BA 40 and 39; and BA 13 (insula).

## Methods

### Participants

Participants included five chronic aphasia patients: two anomic/recovered Broca's, one anomic, one mild–moderate nonfluent, and one severe nonfluent (see Table 1 for patient demographics and language test scores). All patients had a single left middle cerebral artery stroke and they were studied 1–10 years poststroke. Their language was evaluated with the Boston Diagnostic Aphasia Exam (BDAE) 3rd Edition (Goodglass et al., 2001). The milder patients (P1–P3) had some recovery of speech with longer phrase lengths (6–7 words); however, word-finding difficulties and hesitations in spontaneous speech still remained. The severe patient had only a 1-word phrase length; therefore, language testing for this patient was completed with the Boston Assessment of Severe Aphasia (BASA) (Helm-Estabrooks et al., 1989). Only patient P4 had a right-sided paralysis. Fig. 1 shows a structural MRI scan for each patient. Signed informed consent was obtained, and the Institutional Review Board at the VA Boston Healthcare System approved the study.

### Acquisition parameters for fMRI

Functional, T2*-weighted gradient echo, echo-planar images were acquired in the axial plane parallel to the anterior commissure and posterior commissure line, using a 1.5-T GE Signa scanner at the Brain Imaging Center, McLean Hospital, Belmont, MA. Functional runs began with a set of 4 dummy scans to establish longitudinal magnetization. Two functional runs were acquired, each with 104 images per slice, 30 contiguous 5-mm slices, TE = 14 ms, TR = 3 s, FOV = 24 × 24 cm, 64 × 64 matrix, and an in-plane resolution of 3.75 mm. These parameters enabled coverage of the whole brain. Matched T1-weighted axial images were also acquired. A 3D spoiled gradient echo (SPGR) high-resolution anatomical scan was also acquired, TR = 35 ms, TE = 5 ms, FOV = 24 × 24 cm, 256 × 256 matrix, and an in-plane resolution of 0.94 mm with contiguous 1.5-mm slice thickness.

### Stimuli

The design consisted of two alternating conditions: silently viewing patterns (control condition) and overt picture naming. The control condition consisted of six different black and white checkerboard patterns presented in random order, which the participants passively viewed. Pictures presented in the overt picture naming condition were from the Snodgrass and Vanderwart (1980) database of black and white line drawings (120 most

Table 1
Demographic and language data for aphasia patients

| Patient | Gender | Years poststroke at time of fMRI | Age at time of fMRI | Years poststroke at time of language testing | Aphasia type | Boston Diagnostic Aphasia Examination (3rd ed., Goodglass et al., 2001) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Percent correctly named (two fMRI runs) | Boston naming test first 20 items (max = 20) | BDAE longest number of words per phrase length (max = 7) | Articulatory agility (max = 7) | Repetition of single words (max = 10) | Repetition of sentences (max = 10) | Comprehension of single words (max = 37) | Commands (max = 15) |
| P1 | M | 10 | 56 | 9 | Anomic/ recovered Broca's | 100 | 55[a] | 7 | 6 | 9 | 6 | 36 | 15 |
| P2 | M | 3 | 59 | 3 | Anomic | 98.3 | 20 | 6 | 6 | 10 | 10 | 35 | 15 |
| P3 | M | 1 | 57 | 1 | Anomic/ recovered Broca's | 96.3 | 19 | 7 | 3 | 9 | 7 | 36 | 15 |
| P4 | F | 8.5 | 61 | 8.5 | Mild– moderate nonfluent | 88 | 54[a] | 3 | 3 | 8 | 3 | 34.5 | 8 |
| | | | | | | Percent correctly named (two fMRI runs) | BASA auditory comprehension raw score (max = 16) | BASA oral/gestural raw score (max = 21) | BASA overall score (max = 61) | | | | |
| P5 | M | 3 | 70 | 3 | Severe | 0 | 8 | 4 | 39 | | | | |

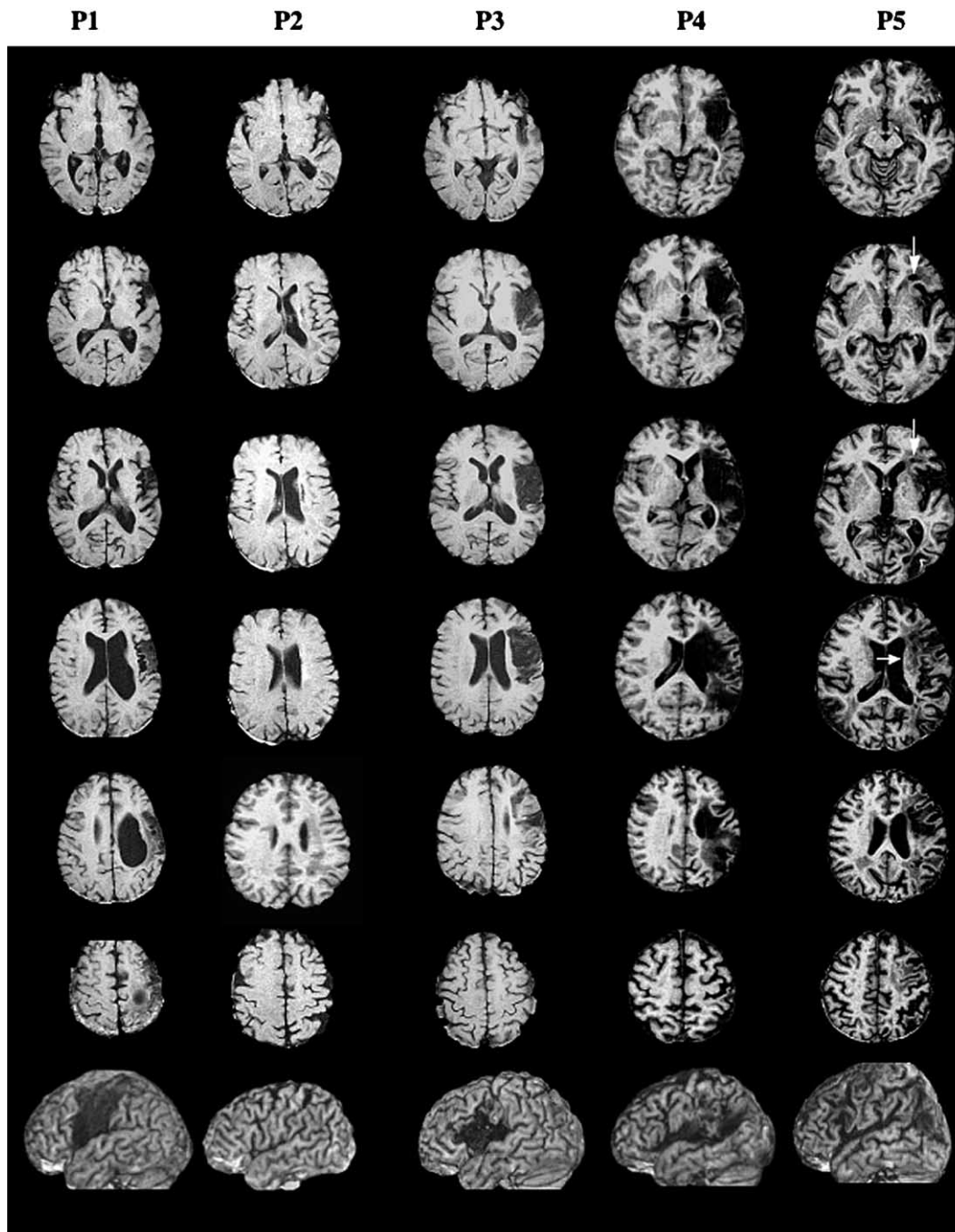[a] Patient tested with all 60 pictures on BNT due to ceiling at first 20 pictures.

Fig. 1. T1-weighted structural MRI scans for each chronic aphasia patient (P1–P5) showing L hemisphere lesion (axial and lateral view). The L lateral view is reconstructed from the 3D SPGR MRI scan. P2, a mild patient, and P5, the most severe, each had subcortical lesion only. P5 had extensive lesion in the two white matter areas near ventricle, compatible with severe nonfluent speech (Naeser et al., 1989): (1) the medial subcallosal fasciculus, deep to Broca's area adjacent to the L frontal horn (vertical arrow); plus (2) the periventricular white matter, deep to sensorimotor cortex, adjacent to the L body of the lateral ventricle (horizontal arrow). Patients P1–P4 had smaller lesion in one or both of these white matter areas.

frequent), 30 different pictures per run. Most words were monosyllabic and presentation was pseudo-randomized so that no two consecutive stimuli began with the same phoneme or belonged to the same semantic category (bow, church, tree). Each picture or pattern was presented for approximately 5 s and was preceded by a 120-ms beep and a 1-s fixation dot for a total trial time of 6 s.

Stimuli were projected onto a backlit screen and each participant viewed them through a mirror located over the head in the scanner. Subjects wore headphones with a microphone that transmitted the verbal responses to a speaker in the MRI control room. Overt responses were transcribed at the time of scanning, and simultaneously tape-recorded.[1] In addition to foam padding

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[1] Currently, participants wear a noise-reduction acoustical microphone and headset (FOMRI; Phone-Or Ltd., Or Yehuda, Israel) where the verbal responses are transmitted to a laptop computer, with sound filtering software.

around the head, adhesive tape was placed across the forehead and chin to further reduce head movement; this slightly restricted lower jaw movement. Prior to participation, subjects were trained on the task outside the scanner on an iMac G4 for up to 3 visits.

### fMRI experimental design

A block design was utilized that consisted of two alternating conditions: a control (pattern) condition and an overt picture naming condition. There were two runs of 104 image volumes, which lasted 5 min 12 s each. There was a short break between runs. In each run, there were 10 epochs of each condition (control and overt naming), for a total of 20 epochs of each condition. At the beginning of each run, there was an additional epoch of the control condition that was not included in the statistical analysis. The control epochs were 12 s each (4 image volumes), consisting of two patterns presented for approximately 6 s each. The naming epochs were 18 s each (6 image volumes), consisting of three pictures presented for approximately 6 s each. See Fig. 2.

### Data analysis

Analyses were completed using SPM99 (Wellcome Department of Cognitive Neurology, London, UK). Images were motion-corrected using a rigid body 6-parameter realignment algorithm using the first image after the dummy scans as a reference. The mean realigned image was coregistered to the 3D SPGR scan using mutual coregistration information. The resulting coregistration parameters were applied to all time series scans. The 3D SPGR anatomical scan was spatially normalized to the MNI T1 template image. The resulting spatial transformation parameters were then applied to the EPI time series. The spatially normalized EPI time series images were smoothed with a 6-mm FWHM Gaussian filter. The size of the voxels after normalization were $2 \times 2 \times 2$ mm$^3$.

The fMRI data were considered acceptable if the amount of motion after correction was within a range of less than 0.5 mm in any direction across a run of 104 images. Data outside this range of motion were removed from analysis if this occurred towards the beginning or end of a run. This occurred, for example, with patient P4, where 2 epochs of each condition were discarded from her first run, resulting in 36 image volumes each, for the hdN and pattern conditions.

Images were modeled using a box-car reference function for a block design. The block design allowed us to take advantage of the

hemodynamic response delay where increased blood flow remains present 4 to 8 s after the response (Friston et al., 1994; Barch et al., 1999; Eden et al., 1999; Birn et al., 1999, 2004). Images collected during the overt naming period, where motion from speaking occurs, were ignored in the statistical analysis. As depicted in Fig. 2, at the beginning of each silent 12-s pattern epoch, there continued to be approximately 6 s of hemodynamic response from overt naming (hemodynamic delay naming, hdN). The first 6 s of the pattern condition (hdN) could then be compared to the last 6 s of the pattern condition. A *t* contrast of overt naming (hdN) compared to pattern was set up to determine task-related functional activation.

Analysis was completed using different methods within SPM99. The initial and main approach to the analysis was an ROI method of analysis. However, a whole brain analysis method was also utilized. A threshold, for signal amplitude, $P < 0.01$, uncorrected was initially entered into the SPM analysis. Data were not grouped or averaged across patients due to their unique lesion patterns and the possibility of distortions of the data from the lesions.

Analysis was then completed by investigating the extent of activation within a priori ROIs using a toolbox within SPM99 (WFU PickAtlas, v1.02, Maldjian et al., 2003). This toolbox provided an atlas-based method of generating ROIs. Several atlases are available within the toolbox from which to create ROI masks. The analysis used the Brodmann area (cytoarchitectonic) atlas within WFU PickAtlas toolbox to define all ROIs with the exception of the SMA. The SMA was defined using the automated anatomical labeling atlas (aal) provided in this toolbox, which utilizes an anatomical parcellation of the MNI MRI single-subject brain, and sulcal boundaries to define each anatomical volume of interest (Tzourio-Mazoyer et al., 2002).

The following a priori cortical ROIs based on previous functional neuroimaging studies with naming were investigated in both the LH and RH: SMA (aal atlas); BA 24 (anterior cingulate); prefrontal, BA 45 and 44; premotor, BA 6; motor, 4; temporal, BA 22, 21, 37, and 20; parietal, BA 40 and 39; and BA 13 (insula) (latter 12 ROIs, Brodmann atlas).

A small volume correction, based on the size of each ROI, was computed within the WFU PickAtlas toolbox. (See Table 2 for number of suprathreshold voxels within each ROI for each patient and the associated *P* values after small volume correction.)

A second analysis (whole brain method) was also completed [$P < 0.05$, corrected at the cluster level using Family-Wise Error (FWE)] (Worsley et al., 1996). Statistical *t* maps showing functional
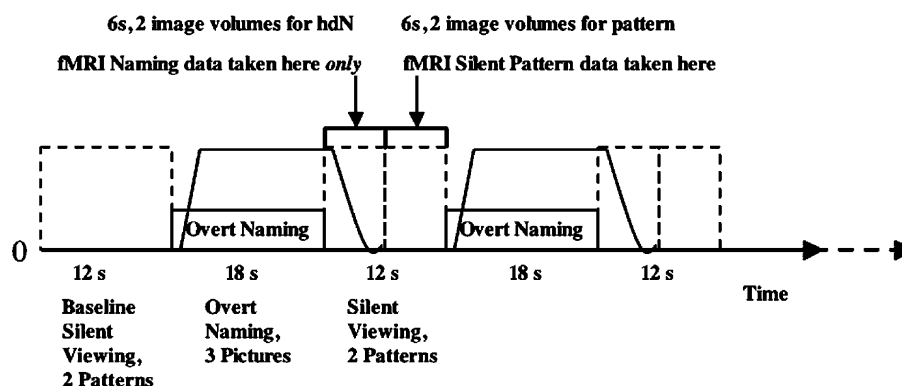


Fig. 2. Schematic showing block design utilizing hemodynamic response delay for overt naming fMRI (TR = 3).

Table 2
Number of suprathreshold voxels (WFU PickAtlas) and *P* levels within each LH and RH a priori ROI for each aphasia patient during overt naming fMRI

| Percent correctly named pictures (2 fMRI runs) | P1 | | P2 | | P3 | | P4 | | P5 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 100 | | 98.3 | | 96.3 | | 88.3 | | 0 | |
| Region of interest | L | R | L | R | L | R | L | R | L | R |
| SMA | 281*** | 231*** | 97** | 85** | 167*** | 111*** | 86** | 73** | 176**** | 333**** |
| BA 24 (ant. cingulate) | NS | NS | 38* | NS | NS | NS | NS | NS | 206*** | 210*** |
| Prefrontal | | | | | Small, partial lesion | | Small, partial lesion | | | |
| BA 45 | NS | NS | NS | 47* | 0 | 0 | 0 | NS | NS | NS |
| | Almost total lesion | | | | Some lesion | | Lesion, lowest opercular portion, only | | | |
| BA 44 | 0 | 100** | 46** | 101*** | 0 | NS | 0 | 95**** | NS | 45** |
| Premotor | Lesion, lower 2/3 | | | | Lesion, lower 1/3 | | Lesion, lowest opercular portion, only | | | |
| BA 6 | 233*** | 426**** | 159*** | 244*** | 98* | 149* | NS | 125* | 423**** | 636**** |
| Motor | Lesion, lower 2/3 | | | | Lesion, lower 1/3 | | Lesion, lowest opercular portion, only | | | |
| BA 4 | NS | NS | 115** | 115** | 82** | 57* | NS | 53* | 99** | 181*** |
| Temporal | | | | | | | Lesion, approximately 1/2 | | | |
| BA 22 | NS | NS | NS | NS | NS | NS | NS | 98* | 125** | 69* |
| BA 21 | 167** | 105* | NS | NS | NS | NS | NS | NS | 286**** | 194*** |
| BA 37 | 58* | 93** | 0 | 0 | 89** | 69* | NS | NS | NS | 68* |
| BA 20 | NS | NS | 0 | NS | NS | NS | NS | 119** | NS | NS |
| Parietal | | | | | | | Lesion, approximately 1/2 | | | |
| BA 40 | NS | NS | 79* | NS | NS | NS | NS | 0 | 0 | NS |
| | | | | | | | Lesion, approximately 1/2 | | | |
| BA 39 | 34* | NS | NS | 0 | NS | NS | NS | NS | 0 | NS |
| Total temporo-parietal suprathreshold voxels | 259 | 198 | 79 | 0 | 89 | 69 | 0 | 217 | 411 | 331 |

Numbers are significant at the following *P* values (corrected for multiple comparisons): ****$P < 0.001$; ***$P < 0.01$; **$P < 0.05$; *$P < 0.10$; NS = suprathreshold voxels not significant at the corrected level; 0 = no suprathreshold voxels.

activation at the corrected level for the whole brain and showing functional activation (small volume corrected) for the ROI analysis were superimposed on the anatomic images using MRIcro software.
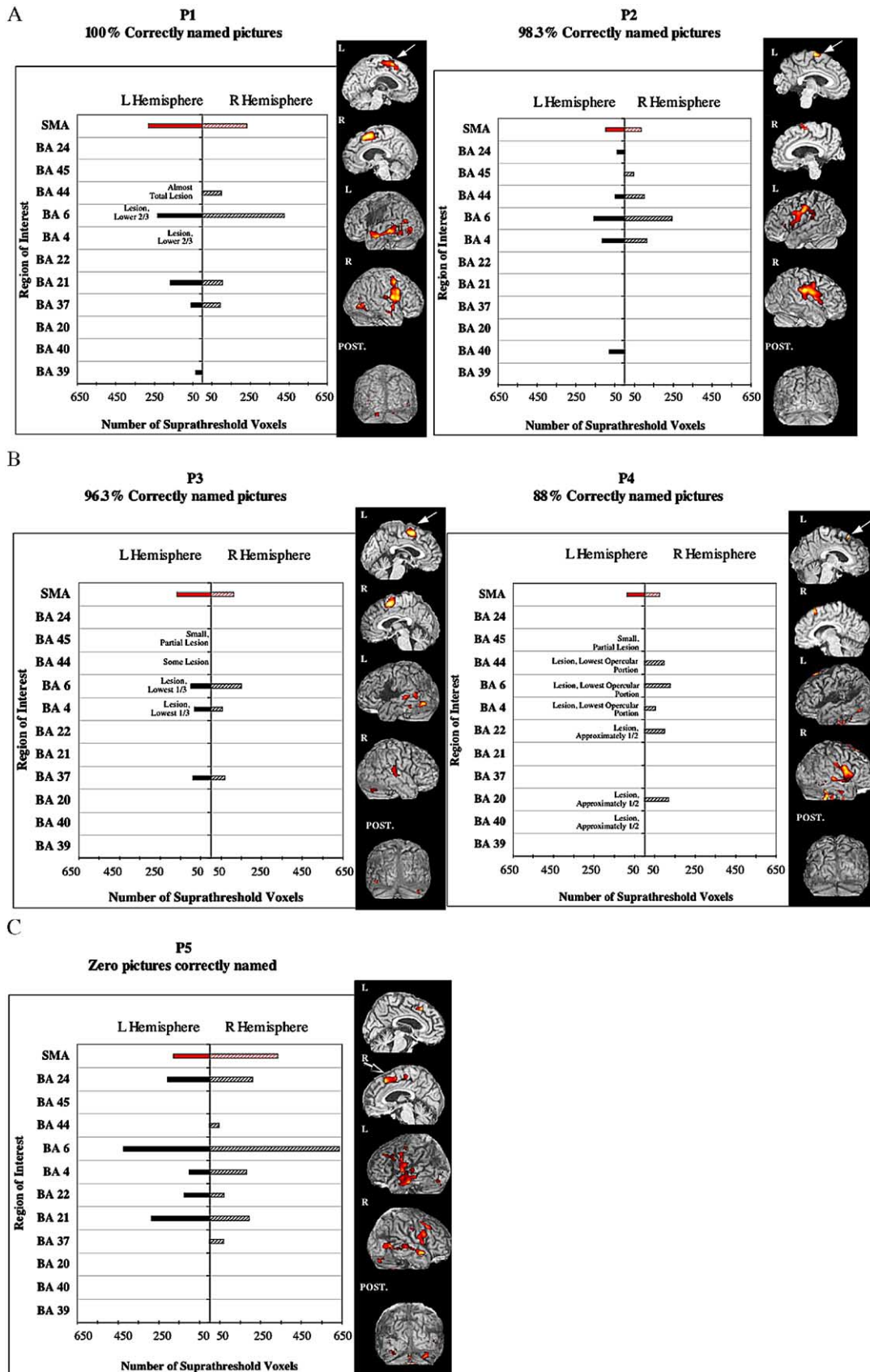
## Results

### Behavioral results

Accuracy in naming the 60 pictures during fMRI was 88–100%, for patients P1–P4. See Table 1. The severe nonfluent patient P5 did not correctly name any pictures. Typical output for this severe patient was 'yeah, yeah, yep, yep, yup, yeah'. All patients made an effort to name the pictures aloud, and they performed the task as instructed to the best of their ability.

### Functional MRI results

The numbers of suprathreshold voxels activated within the a priori ROIs in the LH and RH are listed in Table 2 (including *P* levels after small volume correction), and are presented in bar graph form in Fig. 3, for each patient. Fig. 3 also shows cortical areas of activation on each patient's reconstructed 3D SPGR image. The *medial* views show results of the a priori ROI analysis for the L SMA and the R SMA, only (small volume corrected; see Table 2 for *P* values). The *lateral* and *posterior*

views show results for significant activation in other areas [*P* < 0.05, corrected at the cluster level (FWE)] (Worsley et al., 1996). Although there were trends towards similar activation patterns across the aphasia patients (see Summary of ROIs activated), there were exceptions, and each patient showed a unique pattern of activation.

*Summary of ROIs activated*

Patients P1–P4 each had a greater number of suprathreshold voxels in L SMA than R SMA. These patients correctly named 88–100% of the pictures. *t* tests comparing the number of suprathreshold voxels in L SMA versus R SMA for these 4 patients showed a trend towards a significantly greater number in the L SMA (*t* = 2.79, *df* = 3, *P* = 0.07). The severe nonfluent patient P5, however, had the reverse, demonstrating almost twice as many suprathreshold voxels in R SMA than L SMA.

In frontal regions, only patient P2 had suprathreshold voxels in R BA 45 (R pars triangularis, anterior portion of R Broca's homologue). All but one patient, P3, had suprathreshold voxels in R BA 44 (R pars opercularis, posterior portion of R Broca's homologue). Only P2 had suprathreshold voxels in L BA 44 (par opercularis, L Broca's area). All patients, except for P4, had suprathreshold voxels in L and R BA premotor 6; P4 had suprathreshold voxels in R BA premotor 6, only. Three patients had bilateral activation in BA 4 (P2, P3, P5); P4 had activation in R BA 4.

Activation in L temporal and/or parietal structures was associated with the best three naming scores (P1–P3). For example, P1 (100% correct) activated L BA 21, 37, and 39; P2 (98.3%) activated L BA 40; and P3 (96.3%) activated L BA 37. Note, P1 activated both L temporal and parietal regions; P2, only L parietal; and P3 only L temporal. Patient P4 (88.3%) had only R temporal activation (BA 22 and 20), and no parietal activation.

Patient P5, the severe nonfluent patient, demonstrated extensive bilateral temporal activation (L, 411 voxels and R, 331); this high number of suprathreshold voxels was not seen in the other patients, who all had much better performance in naming. For example, the second highest total number of suprathreshold temporo-parietal voxels in the mild–moderate patients was P1 (L, 259 voxels; R, 198).

Patient P5 also showed extensive bilateral activation in BA 24 (anterior cingulate), greater than that observed in any of the other patients (L, 206 voxels; and R, 210). Patient P2 activated the second highest number of voxels in this region (L, 38 voxels).

No activation of L or R BA 13 (insula) was found in any of the patients.

A secondary whole brain method of analysis showed that some occipital/visual regions outside those investigated in the ROI analysis were significantly activated in each patient (see Fig. 3, lateral and posterior views). However, there was no consistent pattern or region activated across the patients.

## Discussion

This study demonstrates that overt picture naming can be examined during fMRI with aphasia patients. The present method permitted verification that the patients were performing the task, and to what extent. A covert speech design, for example, would not have permitted monitoring of each patient's language behavior.

The most striking finding in the present study was the relatively greater extent of activation in L SMA versus R SMA, in the patients with better language recovery (P1–P4), who had the best overt naming scores (88–100% correct). The severe nonfluent patient P5, who named zero pictures during fMRI, activated almost twice as many voxels in R SMA than L SMA. The observation of more severe language impairment, and relatively more activation in R SMA than L SMA, is compatible with previously published aphasia recovery studies (Karbe et al., 1998; Naeser et al., 2004). It is posited that normal activation of L SMA provides the following: (1) initiation of motor programming for speech; and (2) prevention of interference from other brain regions during overt speech production (Goldberg, 1985; Jonas, 1987). Thus, increased L SMA (versus R SMA) activation during overt speech is likely compatible with improved speech and language in aphasia.

The SMA mask provided by the automated anatomical labeling atlas within WFU PickAtlas included the SMA and pre-SMA, as defined by Tzourio-Mazoyer et al. (2002): the posterior limit was the paracentral sulcus, the inferior limit was the cingulate sulcus and the anterior limit was 20 mm rostral to the Vertical Anterior Commissure (VAC) plane. The pre-SMA may contribute differently to language processes from that of the SMA due to differences in anatomic connectivity. Picard and Strick (2001) report that the SMA is directly connected to M1 and to the spinal cord, while the pre-SMA is connected with the prefrontal cortex, which suggests that its function may be more like a prefrontal area, providing cognitive, sensory, or motivational inputs for motor behavior. The functional differences between these two regions due to differences in anatomical connections and the effect of nearby lesion patterns is an area in need of further exploration in aphasia patients. New imaging techniques such as Diffusion Tensor Imaging may be useful in examining these differences in subjacent white matter connections for the SMA versus the pre-SMA.

Previous naming and semantic functional neuroimaging studies with normals have observed L inferior frontal gyrus BA 45/44 and L temporo-parietal structures to be active (Abrahams et al., 2003; Bookheimer et al., 1995; Price et al., 2001; Gold and Buckner, 2002; Poldrack et al., 1999). In the present study with aphasia patients, the three patients with the best naming scores had activation in R BA 45 and/or 44, along with L temporal and/or parietal regions. Only one patient (P2) activated L Broca's area, L BA 44.

Within the temporal lobes, there was variation in the areas of significant activation among the aphasia patients. For example, three of the four mild–moderate patients (P1–P3) had significant activation in L temporal and/or parietal regions. Patient P4 did not

Fig. 3. Bar graphs showing the number of suprathreshold voxels in LH and RH a priori ROIs for each aphasia patient (P1–P5) during overt naming fMRI. See Table 2 for *P* levels (after small volume correction). Cortical areas of activation are shown on each patient's reconstructed 3D SPGR image. The *medial* views, only, display results for the L SMA and R SMA from the ROI analysis (WFU PickAtlas). The *lateral* and *posterior* views show significant activation in other areas [*P* < 0.05, corrected at the cluster level (FWE)] (Worsley et al., 1996). Note, the mild–moderate patients (P1–P4) with high naming scores (88–100% correct) had a greater number of suprathreshold voxels in L SMA (white arrow) than R SMA. The severe patient (P5) who named zero pictures had a greater number of suprathreshold voxels in R SMA (black and white arrow) than L SMA.

significantly activate any L temporo-parietal area; she activated only R temporal. She also had a lower score, 88.3% correct, than any of the other milder patients. Thus, although there were some trends towards similar frontal, temporal, and parietal activation patterns across the aphasia patients, there were exceptions, and each patient showed a unique pattern of activation within these regions. Other researchers have also observed variability in activation among aphasia patients, indicating the need to examine individual, as well as group data, when studying cognitive processing in this patient population (Burton et al., 2001; Warburton et al., 1999).

For the severe patient (who named zero pictures during fMRI), in addition to having twice as many suprathreshold voxels in the R SMA than L SMA, large areas of bilateral activation were observed in the temporal lobes and BA 24 (anterior cingulate). The greater R SMA activation and other widespread bilateral activation may represent a maladaptive plasticity (Belin et al., 1996; Rosen et al., 2000; Naeser et al., 2004).

Task difficulty may also play a role in the large extent of bilateral temporal activation in the severe nonfluent patient P5. Studies by Fridriksson et al. (2004) and Just et al. (1996), for example, have suggested that task demand is an important factor in functional imaging contributing to the following: (1) intensity of activation; (2) extent of activation; and (3) recruitment of RH homologous regions. The fMRI results for the severe nonfluent patient P5 support this notion. Although P5 could name no pictures, he showed great effort when performing the task. Additionally, P5 showed extensive bilateral BA 24 (anterior cingulate) activation, not seen with any of the other mild–moderate patients. The greater extent of activation in the anterior cingulate (BA 24) during picture naming for P5 may have represented the greater amount of effort for him to cooperate with the task. Anterior cingulate activation has been associated with arousal responses, increased task difficulty, and monitoring of potential response errors (Fu et al., 2002; Barch et al., 2000). Price and Friston (1999) have suggested that it is difficult to separate abnormal processing from performance deficit; patient P5 may be a good example of this. Thus, task difficulty, on a per patient basis, is another factor to consider in designing and analyzing fMRI studies, particularly with aphasia patients who may vary greatly across performance ability.

Although, initially, an ROI method of analysis was chosen, it is possible that new areas outside the expected LH language and RH homologous language regions were recruited during the overt speech task. The whole brain method of analysis (SPM99) showed other regions to be active during overt naming, including some occipital/visual areas. (Shown on lateral and posterior views on Fig. 3.) No consistent trends or patterns in the regions outside those investigated with the ROI method emerged for these aphasia patients.

In the current study, with the present design, it was not possible to examine activation associated with responses in greater depth, for example, during correct versus incorrect responses or during responses involving specific categories. Future studies incorporating an event-related design would allow analysis in greater depth. However, the multiple hesitations and false-starts during overt speech in aphasia patients may make an event-related design difficult to use. Despite limitations of the current method, a strength of this design is that it did permit monitoring of overt speech during BOLD fMRI, thus providing a viable method applicable across a spectrum of aphasia patients, from mild to severe.

This block design relied on the assumption that the hemodynamic response in aphasia patients was similar to that in controls. However, it is possible that stroke patients may have a different hemodynamic response from that of controls. This is a topic beyond the scope of this study; however, further study of this is needed.

In this patient population, cooperation and training are important. Several training sessions on the task and mock fMRI scan sessions can help to minimize head motion associated with speaking. Additionally, training to reduce/limit hand gestures produced by these patients when trying to speak can help minimize head movement during fMRI.

Another issue unique to stroke patients is possible distortion of the data due to the lesion, particularly around the ventricles and surrounding the lesion itself. Therefore, patients in this study were not grouped, and data were not averaged. In Table 2, for each ROI, presence of lesion is noted for each patient; data obtained near these regions could have been affected. In the future, masking out the lesion in pre-processing, prior to spatial normalization of the data, although time consuming, may help to minimize distortions in the data.

## Conclusion

This study focused on establishing an fMRI design to examine areas of activation during overt picture naming in aphasia patients. The results suggest that the hemodynamic delay block design utilized in this study permitted acquisition of overt naming fMRI data in this patient population, across a variety of levels of severity (mild to severe). Previous naming and semantic functional neuro-imaging studies with normals observed activation in L inferior frontal gyrus BA 45/44 and L temporo-parietal structures. In the present study with aphasia patients, better performance in the three best patients was associated with activation in R BA 45 and/or 44; and L temporal and/or parietal regions. Activation in the L temporo-parietal regions has been associated with language improvement in several aphasia recovery studies (Knopman et al., 1984; Demeur-isse and Capon, 1987; Heiss et al., 1999; Warburton et al., 1999; Gold and Kertesz, 2000; Leger et al., 2002; Cornelissen et al., 2003; Perani et al., 2003).

In future studies, the hemodynamic delay block design as utilized here could be applied and might be helpful to predict potential for recovery of speech output in aphasia. It might also be useful as a measure of brain reorganization for speech and language, following therapeutic intervention with specific treatment programs in aphasia. The advantage of this design is the acquisition of actual, overt speech data without interference from motion artifact, while studying this patient population.

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