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Overt propositional speech in chronic nonfluent aphasia studied with the dynamic susceptibility contrast fMRI method

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This study examined activation levels in the left (L) supplementary motor area (SMA) and the right (R) SMA (separately), and activation in nine R perisylvian language homologues during overt, propositional speech in chronic nonfluent aphasia patients. Previous functional imaging studies with a *variety* of chronic aphasia patients have reported activation in these regions during different language tasks, however, overt propositional speech has not been examined. In the present research, four nonfluent aphasia patients were studied during overt elicited propositional speech at 4–9 years post-single L hemisphere stroke, which spared the SMA. The dynamic susceptibility contrast (DSC) method of functional MRI was used to calculate relative cerebral blood volume (relCBV) for cortical regions of interest (ROIs) during the first-pass bolus of gadolinium during two conditions: (1) pattern (silent viewing of checkerboard patterns) and (2) story (overt, elicited propositional speech describing sequential pictures, which formed a story). During the story condition, controls had significantly higher relCBV in L SMA than in R SMA; aphasics, however, had significantly higher relCBV in R SMA than in L SMA. During the pattern condition, no significant differences were observed between the L SMA and the R SMA for either controls or aphasics. In addition, aphasics had significantly higher relCBV in the R sensorimotor mouth during story than pattern. This R sensorimotor mouth relCBV was also significantly higher in aphasics than controls during story, and the two groups did not differ during pattern. The overall mean relCBV for the nine R perisylvian ROIs was significantly higher for aphasics than controls during both story and pattern. These results suggest that poor modulation, including possible over-activation of R sensorimotor mouth and other R perisylvian language homologues may underlie in part, the hesitant, poorly articulated, agrammatic speech associated with nonfluent aphasia.
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Introduction

Some functional imaging studies with aphasia patients have observed activation in remaining left (L) hemisphere cortical regions of interest (ROIs) to have a primary role in aphasia recovery (Heiss et al., 1997, 1999; Karbe et al., 1998; Metter, 1987; Miura et al., 1999; Warburton et al., 1999). Other studies have observed activation in non-damaged right (R) hemisphere ROIs to have a primary role (Cappa et al., 1997; Musso et al., 1999; Rosen et al., 2000; Thulborn et al., 1999). A possible role for the R hemisphere had been suggested as early as the 1970s by Kinsbourne (1971) and Czopf (1972). They had observed that in most aphasia patients with unilateral L hemisphere stroke, injection of intracarotid amobarbitol into the R carotid produced the customary speech arrest, whereas injection into the left side produced almost no alteration on aphasic speech. Many studies have suggested each hemisphere to be important, depending on the type of language behavior and when it was examined (Ansaldo et al., 2002; Basso et al., 1998; Belin et al., 1996; Cao et al., 1999; Hund-Georgiadis et al., 1999; Mimura et al., 1998; Weiller et al., 1995). Thus, in spite of theoretical and clinical importance, the cortical regions associated with language recovery in aphasic stroke patients are largely unknown.

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Functional imaging studies where *only nonfluent* aphasia patients were examined have observed unusually high activation levels in R perisylvian language homologues. For example, Belin et al. (1996) reported in PET studies performed at 4–41 months poststroke onset (MPO), significant increases in the R sensorimotor mouth region, R prefrontal, R Wernicke's, and R anterior superior temporal gyrus during overt, nonfluent bisyllabic single word repetition (versus hearing words) in seven nonfluent aphasia patients. A significant decrease in L Broca's area was also observed.

Rosen et al. (2000) reported a stronger-than-normal response in the R inferior frontal gyrus region during overt (PET) and covert (fMRI) word stem completion tasks with six stroke patients who had L inferior frontal gyrus lesions who were studied at least six MPO. In addition, Thulborn et al. (1999) observed a shift of activation to R Broca's area within 3 days poststroke (and continued rightward lateralization over 6 months) in one nonfluent aphasia patient with lesion in L Broca's area. The patient was tested with fMRI BOLD on a silent reading task of simple sentences, where true/false decisions were made using a yes/no button box. Van Lancker and Grafton (1999) also observed significantly greater activation in R inferior motor area in chronic, severe aphasia patients versus normal controls utilizing a non-language paradigm of overt, repetitive vocalizations (e.g., /ba/ba/ba/, /da/da/da/, /ga/ga/ga/) during PET.

Whether R hemisphere activation observed during functional imaging in nonfluent aphasia patients is beneficial or maladaptive remains to be clarified. Belin et al. (1996) have suggested that increased, abnormal activation patterns in the lesioned brain may not necessarily be related to recovery. In fact, the increased activation may be a marker of failed or faulty recovery attempts in the sense of maladaptive plasticity or the breakdown of normal inter-hemispheric control within a distributed neural network for a language task. Rosen et al. (2000) concluded that "...the anomalous R frontal response after L frontal damage may reflect the loss of active inhibition or competitive interaction from the homologous L frontal area, or an inefficient 'dead-end' strategy."

Heiss et al., (1997, 1999) and Karbe et al. (1998) have studied the L SMA and the R SMA, separately, across a wide variety of aphasia types including Broca's, anomic, Wernicke's, conduction, transcortical sensory, and residual aphasia. They reported higher activation in the R SMA (and poor activation in the L SMA and L superior temporal gyrus area) in patients with poor overall language recovery (as measured with auditory comprehension on the Token Test) after 1 year, during overt, single word repetition using PET. However, those with better overall recovery had higher activation in the L SMA (and the L superior temporal gyrus area).

The present study is based on the theoretical notion that transcallosal disinhibition and poor modulation of R hemisphere language homologues may be underlying factors associated with chronic nonfluent aphasia. To date, no studies have conducted functional imaging with nonfluent patients during overt propositional speech, which is the purpose of this study. We chose to evaluate *overt propositional speech* at the discourse level because it is an ecologically valid test for these patients who produce hesitant, poorly articulated agrammatic speech. Results from the above-mentioned functional imaging studies suggest two main regions to examine in nonfluent patients: (1) the L and R SMA (separately) and (2) the R perisylvian language homologues. The following two primary hypotheses were tested:

1. Chronic nonfluent aphasia patients will have significantly higher activation in R SMA than L SMA during overt, elicited propositional speech.
2. Chronic nonfluent aphasia patients will have significantly higher activation in R perisylvian language homologues than controls, during overt, elicited propositional speech.

Materials and methods

Participants

According to the declaration of Helsinki, before participation in this study each participant signed a consent form which had been approved by the Institutional Review Boards of the V.A. Boston Healthcare System and McLean Hospital. The age of all participants was kept below 65 years to avoid the possibility of any age-related decrease in blood flow (Rempp et al., 1994; Wenz et al., 1996).

Normal controls

The four controls included three males and one female (mean, 47 years; SD, 10.1). They had no neurological disorders, were generally healthy, and were all right-handed.

Aphasia patients

Six aphasia patients were initially run: one was excluded because of poor signal on the dynamic susceptibility contrast (DSC) fMRI scan and the second was excluded from these analyses because he was left-handed. The four remaining right-handed aphasia patients were male, ages 47 to 63 years (mean, 52 years; SD, 4.5) when DSC fMRI was performed, ranging from 4 to 9 years poststroke.

Patients were recruited for the study if they met the criterion of nonfluent speech, that is, the longest phrase length was four meaningful words or less, for the Cookie Theft picture description in the Boston Diagnostic Aphasia Exam (BDAE) (Goodglass and Kaplan, 1983), see Table 1. All patients had adequate auditory comprehension to cooperate fully with the fMRI-scanning procedures.

Each patient was aphasic from a single, unilateral, L middle cerebral artery stroke. No lesion was present in the SMA, as evidenced from visual inspection of their chronic, structural MRI scans shown in Figs. 1a–d. Anatomical description of the lesion sites for each patient is provided in the figure legend. Each patient had lesion in one or both of the two deep white matter areas near ventricle, which were observed in our previous structural imaging research to be compatible with nonfluent speech (Naeser and Palumbo, 1994; Naeser et al., 1989).

Fig. 2 shows the location of these two white matter areas near ventricle, for example, (1) the medial subcallosal fasciculus (M Sc F) which is located adjacent to the frontal horn deep to Broca's area; and (2) the middle 1/3 periventricular white matter area (M 1/3 PVWM) which is located adjacent to the body of the lateral ventricle deep to the sensorimotor cortex, mouth level. The M Sc F contains pathways from SMA and anterior cingulate (BA 24) to head of caudate (Barnes et al., 1980). The M 1/3 PVWM area contains pathways from SMA to the body of caudate; motor and

Table 1
Boston diagnostic aphasia exam (BDAE) test scores for aphasia patients

Patient	Age at stroke onset (years)	Time poststroke when tested with BDAE	Longest Number of Words per Phrase Length(Cookie Theft Picture)	Auditory Comprehension					Repetition			Naming
					Overall auditory comprehension percentile	Word discrimination	Body part identification	Commands	Complex ideational material	Repetition of single words	High probability sentences	Low probability sentences	Visual confrontation naming
			Max. = 7	Max. Score	90	72	20	15	12	10	8	8	114
1	48	10 months	2		35.3	46	8.5	9	3	8	1	0	28
		4 years[a]	4		44.3	62.5	8	8	9	8	1	0	59
2	42	3 years	1		59	50	14	12	9	3	–	–	18
		5 years[a]	1		–	–	–	14	–	1	–	–	13
		7 years	1		72.3	59	18	13	9	3	–	–	19
3	51	9 years[a]	1		52.5	68.5	7.5	8	6	2	–	–	14
		11 years	1		40.8	59	9	9	3	3	0	0	17
4	58	5 years[a]	1		75.5	66	18.5	14	6	–	–	–	–
		7 years	1		72.0	68	18	11	7	1	–	–	8

[a] Time poststroke when DSC-fMRI scan was performed in this study.

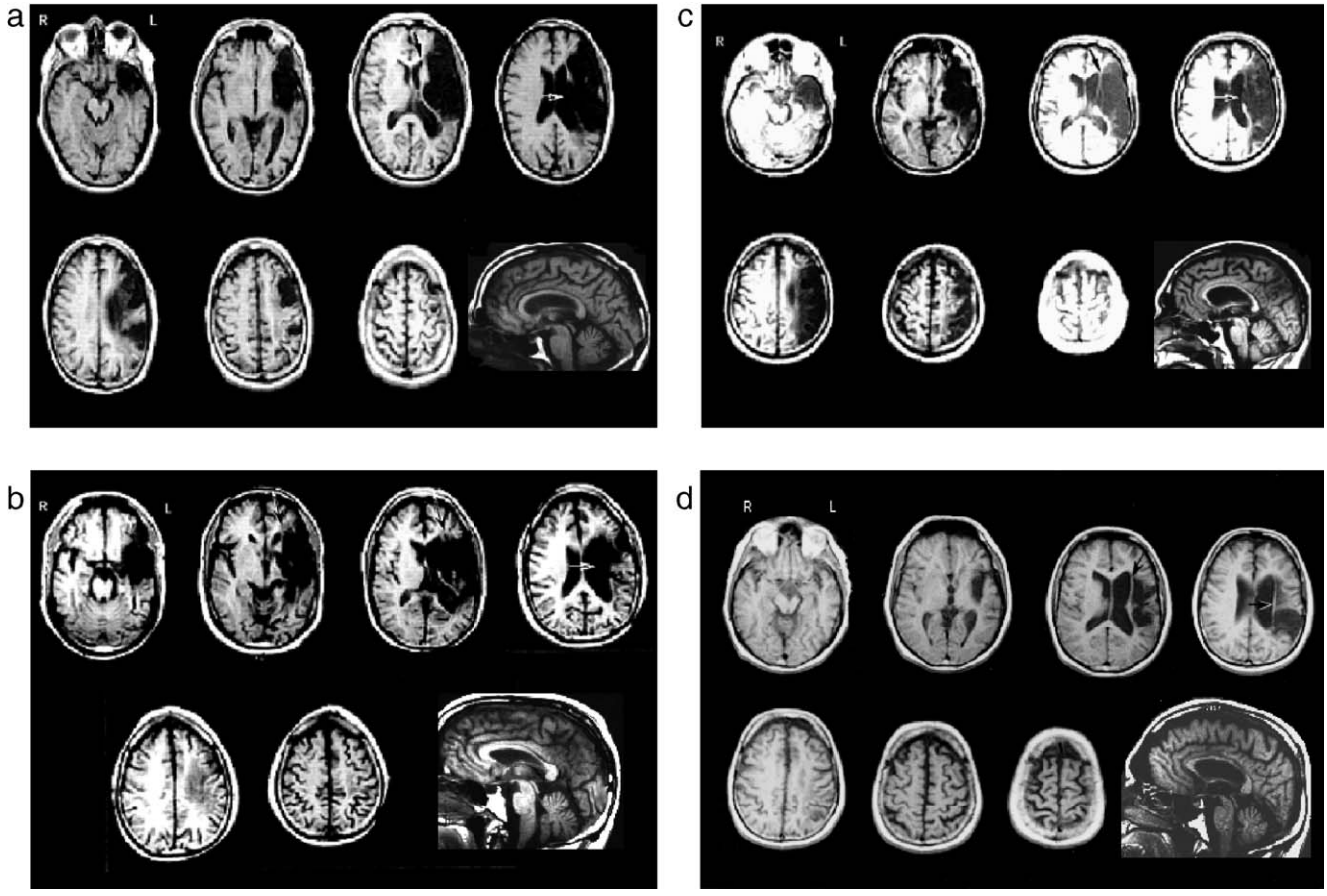

Fig. 1. Anatomical T1-weighted MRI scans showing left hemisphere lesions for the four nonfluent aphasia patients (a–d). Included within each lesion site description is information on the two white matter areas near ventricle relevant to presence and severity of nonfluent speech: (1) medial subcallosal fasciculus area, adjacent to left frontal horn; and (2) middle 1/3 periventricular white matter area, adjacent to body of left lateral ventricle. (See also Fig. 2) For each patient, a mid-sagittal slice showing atrophy in the corpus callosum is also included. (a) Nonfluent aphasia patient 1 (53 years old, M, 4 years poststroke). Lesion was present in only one of the two white matter areas near ventricle: (1) medial subcallosal fasciculus area was largely spared (black arrow near frontal horn); (2) middle 1/3 periventricular white matter area had extensive lesion (horizontal white and black arrow). Lesion was also present in Broca's area; frontal operculum; sensorimotor mouth region; anterior and posterior supramarginal gyrus; angular gyrus; and portions of Wernicke's area and posterior middle temporal gyrus (BA 37). (b) Nonfluent aphasia patient 2 (47 years old M, 5 years poststroke). Extensive lesion was present in both of the white matter areas near ventricle: (1) medial subcallosal fasciculus area (black arrows near frontal horn); (2) middle 1/3 periventricular white matter area (horizontal white and black arrow). Lesion was also present in Broca's area; frontal operculum; sensorimotor mouth region; portions of anterior and posterior supramarginal gyrus; and angular gyrus (some lesion was patchy and deep to these areas). Extensive lesion was present in Wernicke's area, and partial lesion, in the posterior middle temporal gyrus (BA 37). (c) Nonfluent aphasia patient 3 (60 years old, M, 9 years poststroke). Extensive lesion was present in both of the white matter areas near ventricle: (1) medial subcallosal fasciculus area (black arrow near frontal horn on lower slice, and black arrow near frontal horn on next slice); (2) middle 1/3 periventricular white matter area (horizontal white and black arrow). Lesion was also present in Broca's area; frontal operculum; sensorimotor mouth region; anterior and posterior supramarginal gyrus; angular gyrus; Wernicke's area; most of the posterior middle temporal gyrus (BA 37); anterior temporal lobe; high parietal and frontal lobe. (d) Nonfluent aphasia patient 4 (63 years old M, 5 years poststroke). Extensive lesion was present in both of the white matter areas near ventricle: (1) medial subcallosal fasciculus area (black arrow near frontal horn); (2) middle 1/3 periventricular white matter area (horizontal white and black arrow at body of lateral ventricle slice). This was primarily a subcortical lesion centered over the putamen with the white matter lesion extension into (1) and (2), compatible with severe nonfluent speech. There was no lesion in Broca's or Wernicke's cortical areas. Some cortical lesion was present in the supramarginal and angular gyrus areas.

sensory pathways; thalamo-cortical pathways (motor and limbic) and interhemispheric callosal connections (reviewed in Naeser and Palumbo, 1994). Patients with more extensive lesion in *both* of these deep white matter areas have been observed to have a more severe form of nonfluent speech, for example, a phrase length of only one word or less (Naeser et al., 1989). In the present study, the three patients with more severe nonfluent speech (patients 2, 3, and 4) had extensive lesion in these two white matter areas. See arrows pointing to lesion in these areas on each patient's structural MRI scan in Figs. 1a–d.

Description of the DSC fMRI technique

A common technique used in functional imaging today is blood oxygen level-dependent (BOLD) fMRI. However, it is unclear whether this technique may be used successfully during overt imaging tasks such as speech, where face, jaw, and tongue movements may produce a high degree of motion artifact. Therefore, the dynamic susceptibility contrast (DSC) fMRI method was chosen because it permits acquisition of functional images during overt behavior (e.g., speech) similar to PET or SPECT studies, however,

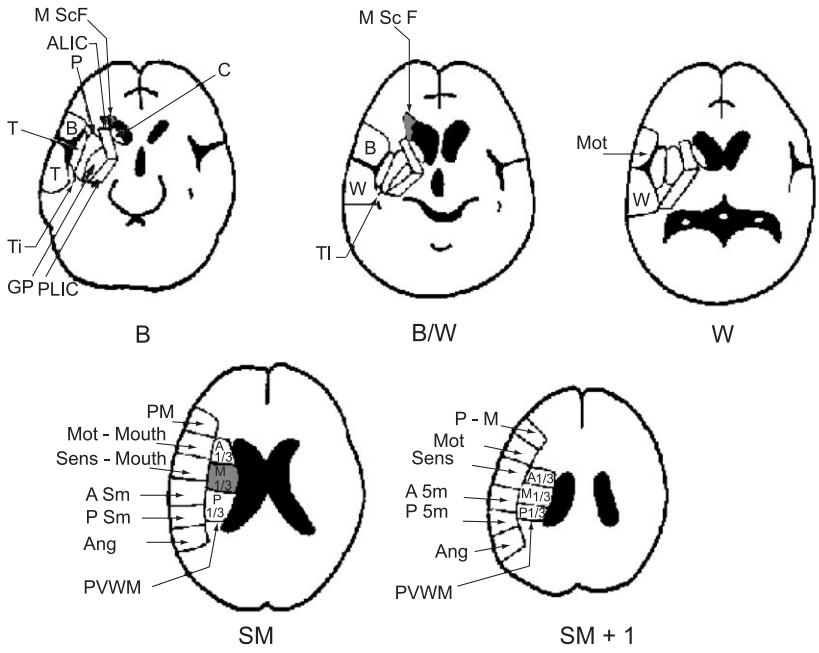

Fig. 2. Diagram of axial slices showing location of the two deep, white matter areas near ventricle (shaded areas), which are relevant to presence and severity of nonfluent speech: (1) M Sc F = medial subcallosal fasciculus area (located deep to Broca's area on slices B and B/W); and (2) M 1/3 PVWM = middle 1/3 periventricular white matter area (located deep to sensorimotor mouth area on slice SM). Slices in this figure are labeled with reference to cortical language areas present on each slice, for example, B = Broca's; B/W = Broca's and Wernicke's; W = Wernicke's; SM = supramarginal gyrus (Naeser et al., 1989).

no radioactive isotopes are necessary and the resolution is superior. Thus, DSC fMRI is less likely to be confounded by motion artifact than BOLD fMRI.

DSC fMRI uses injected gadolinium as a contrast agent to provide enhanced MRI information for mapping of cerebral blood volume (CBV) (Belliveau et al., 1990; Rosen et al., 1989, 1991; Villringer et al., 1988). This method takes advantage of the paramagnetic property of gadolinium as a magnetic tracer, which disturbs the homogeneity of a uniform magnetic field. As a bolus of the contrast agent passes through the vasculature, its susceptibility effects cause a transient magnetic field disruption around these vessels and a reduction in signal intensity of T2 (spin echo) or T2* (gradient echo) weighted images. This transient signal loss, proportional to the amount of tracer in a region, is monitored by rapid imaging of the first pass of the contrast agent. The decrease in image signal intensity at each time point may be used to determine relative CBV (relCBV) either regionally or on a pixel by pixel basis (Belliveau et al., 1990). High-resolution maps of relCBV are produced by integration of these data over the time course of the first pass of contrast agent through the cerebral vasculature.

The DSC fMRI method allows construction of relCBV maps with high contrast to noise ratios (CNR). Because cerebral blood flow (CBF) and relCBV are correlated, at steady state, relCBV maps are sensitive to changes in brain activity that occur over a short period of time (5–10 s). Thus, the temporal resolution of DSC fMRI is much greater than that typically obtained in BOLD fMRI studies, which usually employ signal averaging strategies over multiple trials to increase CNR. DSC fMRI does require the intravenous injection of paramagnetic contrast agents and is more "invasive" than BOLD fMRI. However, contrast administration is generally well tolerated and is a standard practice in most diagnostic imaging centers.

Parameters for structural MRI and fMRI scan acquisition

All MRI scans were obtained at the Brain Imaging Center, McLean Hospital, Belmont, MA. Scans were performed with a General Electric (Milwaukee, WI) 1.5 Tesla Signa Scanner, retrofit with an Advanced NMR (Wilmington, MA) Instascan system for echo-planar acquisition. Before any activation DSC imaging, structural MR imaging was performed on all subjects with eyes closed. Axial T1 images (TR = 100 ms, TE = 60 ms), proton density and T2-weighted images (TR = 2 s, TE = 30 and 80 ms) were obtained. Sagittal T1-weighted images over the middle region were obtained. Ten axial images were obtained with the most inferior slice positioned through the middle of the cerebellum and the most superior slice positioned over the vertex to insure acquisition of images which would include the superior, mesial aspect of the SMA. Most axial images were obtained parallel to the AC-PC line.

During the DSC fMRI portion of the imaging session, $T2^*$-weighted echo-planar images were collected over a period of 100 s, with 10 axial slices aligned as mentioned above (TR = 2 s; TE = 100 ms; 50 sets of 10 image planes over 100 s; 128 × 256 matrix, FOV = 20 × 40 cm, 1.5 × 1.5 mm pixels, in-plane spatial resolution on the order of one pixel [1.5 mm]; 7-mm slice thickness with a 5-mm gap, acquisition window = 64 ms).

Thirty seconds into the 100-s scanning period (after 15 sets of baseline images were acquired) subjects were injected with 0.10 mEq/kg intravenous gadoteridol (ProHance, Bracco Diagnostics Inc., Princeton, NJ) as a bolus over 6 s through an 18-G angiocath inserted into a vein overlying the left antecubital fossa. Subjects received a total of 0.30 mEq/kg of gadoteridol (GD) during the three sets of DSC fMRI scans acquired (explained below). Following each injection, the IV catheter and line was flushed with saline.

All studies were performed with subjects lying quietly, eyes open so they could see the stimulus materials, which were reflected onto a mirror above their eyes. The stimulus materials were reflected onto the mirror from a back-lit screen located toward the end of the scanning table.

Echo-planar images were registered for each slice over time with a motion correction algorithm to reduce patient motion artifact (Maas et al., 1997). This motion correction algorithm is an automated, one-pass method for estimating and correcting in-plane rotational and translational motion. It is computationally efficient; it decouples the estimation of translation and rotation, allowing the application of rapid cross-correlation and cross-spectrum techniques for the determination of displacement parameters. The accuracy of the algorithm, assessed using phantom data, is $\pm 0.17^{\circ}$ (standard deviation) for rotational error and ± 0.054 pixels for translational error. This performance compares favorably with published motion correction algorithms.

RelCBV images were created by the method described by Belliveau et al. (1990) using a post-processing program (FAT) developed by L. Maas at the Brain Imaging Center, McLean Hospital. The images obtained after the injection are compared to the baseline echo-planar images before injection, thus creating a functional image of CBV.

Activation paradigms

The design of activation paradigms used with DSC fMRI differs from the design commonly used with BOLD fMRI. For example, with BOLD fMRI a repeated box-car design is used where the two conditions are repeatedly alternated during a specific imaging run. With DSC fMRI, however, because a high signal-to-noise ratio is obtained with the injection of gadolinium, the repeated box-car design is not necessary, and stimuli for only one condition are used during a specific imaging run. In the present DSC fMRI study, three conditions were presented during three separate imaging runs: (1) silent viewing of geometric shapes; (2) silent viewing of patterns; and (3) overt speaking for pictures in a story. There were 10 stimulus images per activation condition and all stimuli were presented in a fixed sequence for all participants. All three runs were obtained on the same day, with a 10-min break between each (the participant remained in the scanner).

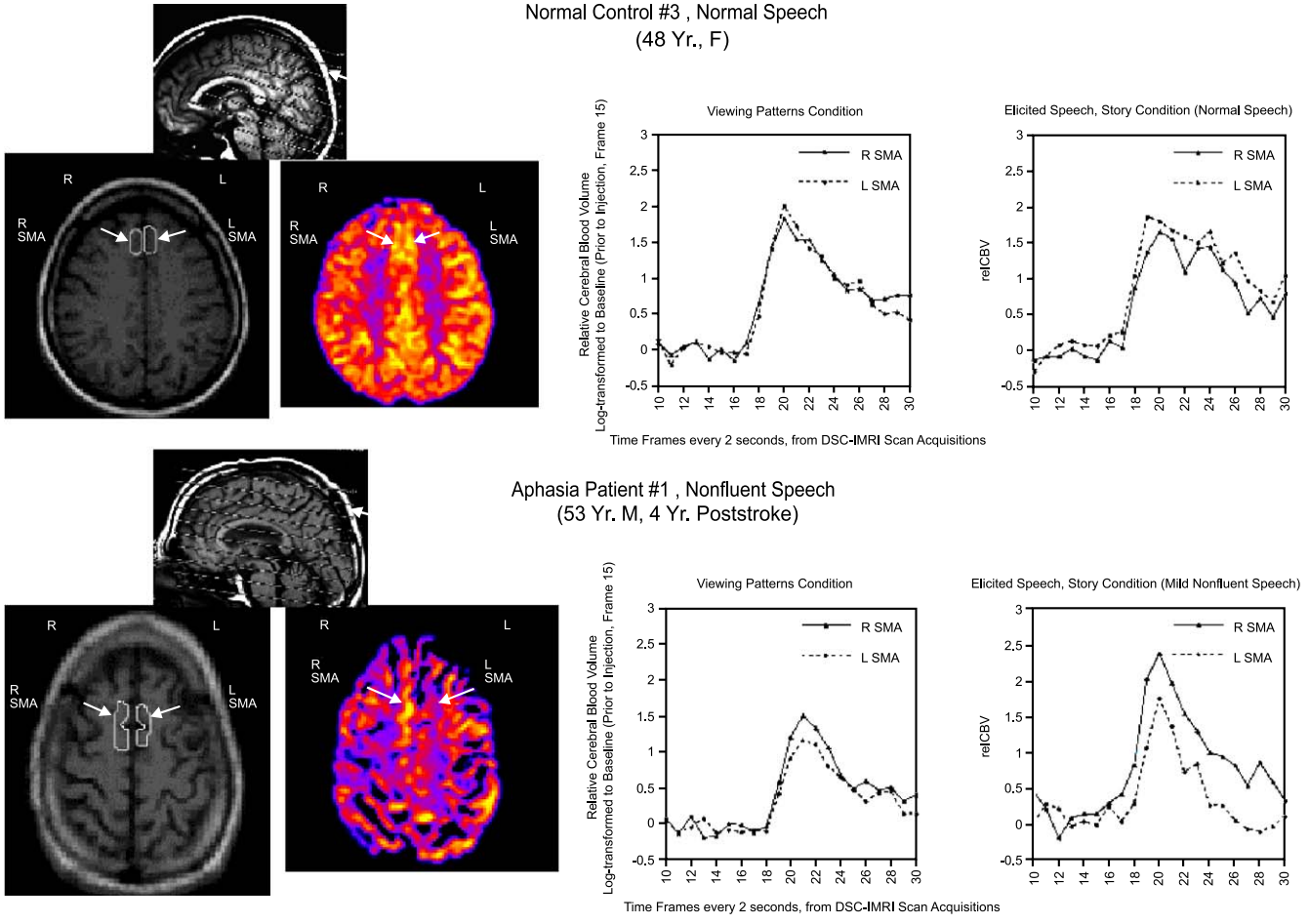

Fig. 3. Location of ROI samples for L SMA and R SMA, and concentration–time curves for these ROIs for one normal control (top), and one aphasia patient (bottom). The color-scale images reflect relCBV, with yellow indicating higher relative CBV. The ROIs were drawn on the T1-weighted structural images, based on sulcal and gyral boundaries (see text). The mid-sagittal scout is also shown for each subject to show location of the slice level where these SMA samples were taken (arrow). This control was scanned at a steeper angle than the aphasia patient, hence, the SMA samples are located more rostral on the transaxial slice for this control, than the aphasia patient.

During Activation 1 (*geometric shapes*), the participant was shown a series of 10 black and white images of geometric shapes. A different image was shown every 10 s, for a total of 100 s (there was no pause between presentation of each geometric shape). The participant was instructed to only look at each shape, and say nothing. During Activation 2 (*pattern condition*), the participant was shown a series of 10 black and white images of checkerboard patterns. A different pattern was shown every 10 s, for a total of 100 s (no pause between each pattern). The participant was instructed to only look at each pattern, and say nothing. During Activation 3 (*story condition*), the participant was shown a series of 10 black and white, line-drawn, cartoon-strip pictures (no writing). The pictures depicted persons performing sequential activities, which formed a story, with a different picture every 10 s, for a total of 100 s (no pause between each picture). There were three stories, for example, a burglar stealing jewelry who is then caught by a policeman; a man and woman who are on a picnic where a dog has stolen the food; a man who sleeps through his alarm clock is awakened by his angry wife, and he is later shown asleep at his desk. Each story had four pictures (total of 40 s per story). However, for the third story, only the first two pictures could be shown due to termination of the 100-s imaging run.

An overt (versus covert) speech activation paradigm was chosen because it was important to know what level of speech was actually produced by each subject during the functional imaging. Each subject's speech was tape recorded, and later transcribed.

The normal controls produced normal speech. Patient 1 with a milder form of nonfluent speech produced meaningful utterances relevant to the stories such as, "...the window, take money, cop'er (policeman); picnic, eat meat, what happened; get up, bed, clock..." Patients 2, 3, and 4 with a more severe form of nonfluent speech produced less meaningful utterances such as, "...uh, nope, ah, gone, dog, trick them, um, trick, one, why, mmm, there's um, it's um, I don't know, wait, what, hey, epp, ey a boy, eh, it, I don't..."

Only imaging data from the pattern and story conditions were analyzed because studies on the effect of sequential gadolinium injections (with a minimum of 10 min between each injection) have shown that a relative steady state is achieved only between the second and subsequent injections. Thus, after the first injection, the later injections provide reliable measurements of relCBV during activation (Levin et al., 1995).

ROI method of analysis

In most BOLD fMRI studies, a voxel-wise analysis with statistical parametric mapping (SPM) is performed. However, this voxel-wise SPM method has not been applied in DSC fMRI analysis and instead, the hand-drawn region of interest (ROI) method is used. This ROI method has been successfully used in DSC studies with a variety of other disorders, for example, schizophrenia, Alzheimer's disease, alcoholism (Cohen et al., 1995; Harris et al., 1996; Streeter et al., 1998), and thus it was also used in the present study.

The placement of each ROI was made from gyral boundaries and structural landmarks that were visible on an axial set of high-resolution T1-weighted structural MRI slices for each subject (Damasio and Damasio, 1989). The depth of the ROI was determined by the depth of the deepest sulcus for that specific ROI. The scanning angulation was determined for each subject and a template was established for each set of MRI slices based on the axial templates provided in Damasio and Damasio (1989). ROIs were drawn onto each patient's set of images based on these templates. The person performing the ROI analysis (AB) was blinded regarding the level of speech production for each subject. Only the structural MRIs were used for the online ROI drawings which were then transferred automatically to the matched functional DSC fMRI slices using the post-processing program FAT (L. Maas, Brain Imaging Center, McLean Hospital).

Cortical ROIs were examined in the R and L hemispheres (except where L hemisphere lesion was present in the aphasia patients) in 11 regions: SMA (mesial sample, BA 6, located at least two slices above the bodies of the lateral ventricles, in a mid-to-superior level of BA 6 but not at the vertex); prefrontal (BA 46); Broca's area (BA 45); frontal operculum (BA 44 and lower portion of BA 6); premotor at mouth level (BA 6); sensorimotor mouth region; anterior supramarginal gyrus (BA 40); posterior supramarginal gyrus (BA 40); angular gyrus (BA 39); Wernicke's area (BA 22); and posterior middle temporal gyrus (BA 37).

A concentration–time curve was generated for each ROI where the pre-injection frames (before frame 15, first 30 s) were used as a baseline to compute the relCBV and *inverse*, log-transformed signal curve for that ROI for each patient for each condition (Belliveau et al., 1990). Thus, a higher signal curve reflected greater relCBV, even though there was actually a lower signal due to the susceptibility effects of increased gadolinium in the blood vasculature within a specific ROI, at a specific time frame. Sample concentration–time curves for the first-pass bolus of gadolinium for the L SMA and the R SMA (separately) are shown during the pattern condition, and the story condition for one normal control and one aphasia patient in Fig. 3.

Results

Primary analyses

RelCBV in L SMA versus R SMA

The relCBV levels for the L SMA and the R SMA during each condition for each group were submitted to a mixed-design (1 Between, 2 Within) 2 × 2 × 2 Analysis of Variance [group

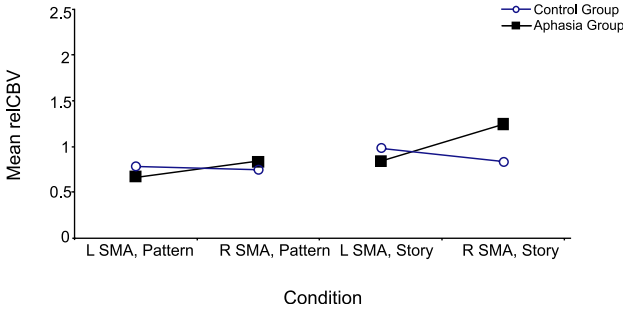

Fig. 4. Mean relCBV levels for the L SMA and the R SMA during the pattern condition and story condition for the control group and for the aphasia group. There were no significant differences during pattern. During story, the L SMA was significantly higher than the R SMA for the control group ($P < 0.01$); for the aphasia group, however, the R SMA was significantly higher than L SMA ($P < 0.01$). For controls, there was significantly higher relCBV in L SMA during story than during pattern ($P < 0.01$). For aphasics, there was significantly higher relCBV in the R SMA during story than during pattern ($P < 0.01$). During story, the R SMA was significantly higher for the aphasia group than the control group ($P < 0.05$).

(aphasics, controls); condition (pattern, story); and ROI Side (L SMA, R SMA)]. The ANOVA established a group × condition × ROI Side interaction [$F(1,6) = 11.30$, $P = 0.015$].

All pairwise comparisons were carried out using a Newman–Keuls procedure (Myers, 1967). During pattern, neither group demonstrated a significant ROI side effect, nor did they differ significantly from one another either on the left or on the right side. During story, the controls had significantly higher relCBV ($P < 0.01$) in L SMA than in R SMA. Also for the controls, there was significantly higher relCBV ($P < 0.01$) in L SMA during story than during pattern. See Fig. 4.

The aphasics, however, exhibited a pattern of results that was the mirror image to that observed for the controls. During story, the aphasics had significantly higher relCBV ($P < 0.01$) in R SMA than in L SMA. See Fig. 4. Also for the aphasics, there was significantly higher relCBV ($P < 0.01$) in the R SMA during story than during pattern. During story, the aphasics had significantly higher relCBV ($P < 0.05$) in R SMA than the controls. Moreover, unlike the results for the pattern condition, there was a significant group × side interaction for the story condition ($P = 0.05$).

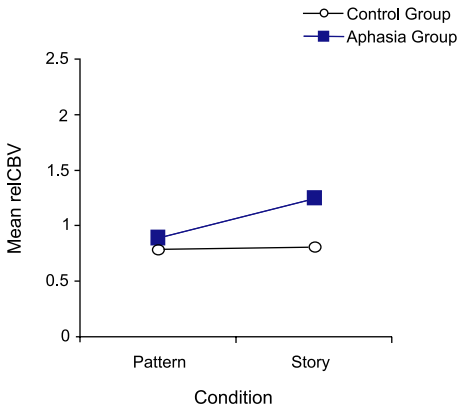

Fig. 6. Mean relCBV levels for the R sensorimotor mouth during the pattern condition and story condition for the control group and the aphasia group. There was no significant difference between the groups during pattern. For the aphasics, the R sensorimotor mouth was significantly higher ($P < 0.01$) during story, than pattern. In addition, the relCBV for R sensorimotor mouth was significantly higher for the aphasics versus controls during story ($P < 0.05$).

RelCBV in R perisylvian language homologues

To determine whether there was a significant difference in the *overall* relCBV in the nine R perisylvian language homologues between the two groups, the relCBV levels averaged across the nine R perisylvian ROIs were examined for the pattern condition and the story condition. A mixed design 2 × 2 ANOVA [group (aphasics, controls) and condition (pattern, story)] was performed. Results indicated a significant main effect for the variable group [$F(1,16) = 9.46$, $P < 0.01$], but no significant group × condition interaction [$F(1,16) = 2.83$, $P < 0.15$]. The overall mean relCBV

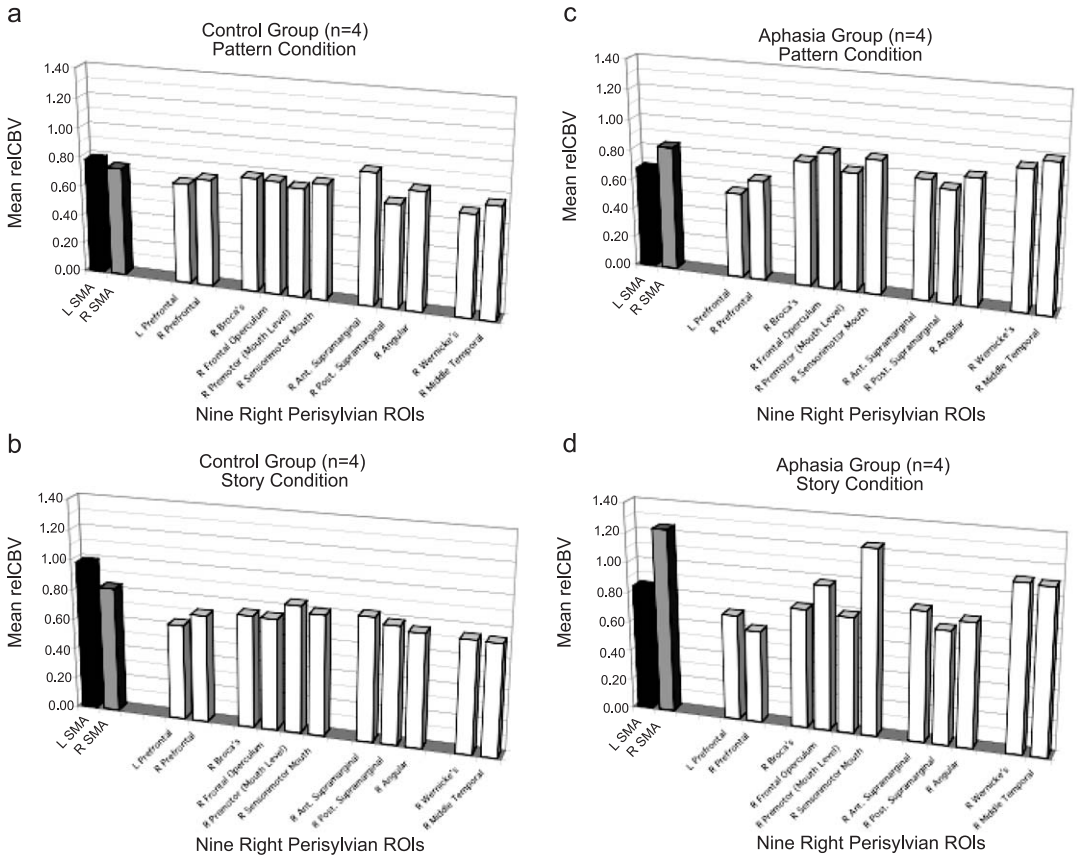

Fig. 5. Mean relCBV levels for each ROI during the pattern condition and the story condition for the control group and for the aphasia group. The overall mean relCBV level in the nine R perisylvian ROIs was significantly higher ($P < 0.01$) for the aphasia group than the control group, during both the pattern condition and the story condition.

level for the nine R perisylvian ROIs was significantly higher for the aphasia group than the control group in the pattern ($P < 0.01$) as well as in the story($P < 0.01$) (pattern: controls mean = 0.77, SD = 0.06; aphasics mean = 0.86, SD = 0.08; story: controls mean = 0.77, SD = 0.04; aphasics mean = 0.94, SD = 0.17). See Fig. 5. No other significant differences were found.

In addition, to determine whether there was any significant difference between the pattern and story conditions, for any of the nine *separate* R perisylvian ROIs, a series of nine univariate mixed-design 2 × 2 ANOVA's [group (aphasics, controls) and condition (pattern, story)] were performed. Alpha level was set at $P < 0.02$ to control for the multiple F-scores computed. Only the R sensorimotor mouth ROI showed significance and there was a significant group × condition interaction [$F(1,6) = 11.53$, $P = 0.01$]. The two groups did not differ on pattern, but did differ significantly on story ($P < 0.05$). See Fig. 6. Also, the aphasics had significantly higher ($P < 0.01$) relCBV in R sensorimotor mouth during the story than pattern; however, the controls did not differ on story versus pattern.

Number of target words spoken and relCBV levels

For the four nonfluent aphasia patients, correlational statistics were performed between the number of meaningful target words spoken by each patient during the story condition, and the relCBV for L SMA, R SMA and R sensorimotor mouth ROIs (see Table 2). Although the entire DSC fMRI run for the story condition lasted 100 s, the speech samples used in these correlational analyses were *only* taken from that portion of the run (18 s) which represented the concentration–time curve data for relCBV for each specific ROI, that is, only the target words spoken during 34 to 50 s of the 100-s run (time frames 17 to 25, see Fig. 3). Neither SMA correlated with the number of target words spoken. For the R sensorimotor mouth, the three patients (patients 2, 3, 4) who produced the *fewest* number of target words (0–1) had the *highest* relCBV scores ($r = -0.80$, but the sample size was too small to assign a P value). Note, patient 2, who had the highest relCBV for R sensorimotor mouth (1.41), produced zero target words. However, he was struggling to do so, and did vocalize automatic speech (e.g., . . .it's um. . .um. . .I don't know. . .). The other patients had also interspersed their meaningful target word production with word-searching and automatic speech behavior.

Table 2
RelCBV for L SMA, R SMA and sensorimotor mouth ROIs and number of target words spoken (34–50 s) during the story condition

	L SMA	R SMA	L sensori-motor mouth	R sensori-motor mouth	Number of target words spoken (34 to 50 s)
Aphasia patients					
1	0.72	1.37	Lesion	0.84	4
2	1.23	1.47	Lesion	1.41	0
3	0.79	1.25	Lesion	1.36	1
4	0.63	0.87	0.89	1.36	1
Controls					
1	0.91	0.67	0.57	0.80	10
2	0.61	0.58	0.30	0.42	11
3	1.39	1.17	1.02	1.15	Not available
4	1.02	0.90	0.82	0.85	Not available

For each aphasia patient, the relCBV in the R sensorimotor mouth was higher than that in the L SMA (Table 2; and Fig. 5, group data). However, the opposite pattern was observed for the controls, where relCBV in the R sensorimotor mouth was lower than that in the L SMA (Table 2; and Fig. 5, group data).

Secondary analyses

RelCBV in L prefrontal versus R prefrontal

One analysis was performed on a second L and R ROI pair (prefrontal area, BA 46), a non-language area. Lesion in L BA 46 is not usually associated with aphasia, and it is considered to be outside the primary L perisylvian neural network for language. Activation in L BA 46, however, has been observed in nonfluent aphasia patients undergoing PET scanning, during the Melodic Intonation Therapy technique (Belin et al., 1996). A mixed-design (1 Between, 2 Within) 2 × 2 × 2 ANOVA was performed with relCBV data for the L and R BA 46, [group (aphasics, controls); condition (pattern, story); and ROI Side (L BA 46, R BA 46)]. Unlike the L SMA and R SMA, no significant interaction was observed in the L and R prefrontal regions.

RelCBV in R versus L perisylvian ROIs, controls only

A second set of analyses was also performed on relCBV data for the controls, only. To determine whether there was a significant difference in the *overall* relCBV level between the L and R perisylvian ROIs, the overall mean relCBV levels in across all nine R perisylvian ROIs and across all nine L perisylvian ROIs were examined for the pattern and story conditions. A 2 × 2 repeated measures ANOVA [Hemisphere (left, right) and condition (pattern, story)] was performed. No significant results were found.

In addition for the controls, to determine whether there was any significant difference between the pattern condition and the story condition for any of the nine *separate* L perisylvian ROIs and R ROIs, the relCBV for each L and R ROI was examined. A series of univariate 2 × 2 repeated measures ANOVAs [ROI side (left, right) and condition (pattern, story)] were performed for each of the perisylvian ROIs. Alpha level was set at $P < 0.02$ to control for the multiple comparisons performed. No significant differences were found.

Discussion

The first hypothesis of this study was confirmed, that is, chronic nonfluent aphasia patients have significantly higher activation in R SMA than in L SMA during overt, elicited propositional speech. These results are similar to the findings of Heiss et al., (1997, 1999) and Karbe et al. (1998) where higher activation in R SMA was associated with poor overall language recovery (as measured with auditory comprehension on the Token Test at 12–18 MPO). Recovery of propositional speech was not addressed in their studies. However, because our four aphasia patients were still producing mild-severe nonfluent speech at 4–9 years poststroke, it is likely our patients were more similar to their patients with poor overall language recovery, than those with good recovery.

Regarding the second hypothesis, when the *overall* relCBV levels were averaged across the nine R perisylvian language homologues, the aphasics were significantly higher than the controls during overt, elicited propositional speech, as predicted. However, unlike the SMA, there was no interaction between group

and condition. When each of the nine ROIs was investigated *separately*, the R sensorimotor mouth did demonstrate this interaction. The two groups were equivalent during pattern, but the relCBV in R sensorimotor mouth was significantly higher during story for the aphasics, than the controls. In addition, the aphasics had significantly higher relCBV in R sensorimotor mouth during the story, than pattern.

The increased relCBV in R sensorimotor mouth for the aphasics during nonfluent speech production may suggest over-activation and poor modulation in R hemisphere language homologues during overt propositional speech. The finding of over-activation in various R hemisphere language homologues has also been observed in previous functional imaging studies with nonfluent aphasia patients. Those studies, however, used different tasks from the present one. Belin et al. (1996) observed increased activation in R sensorimotor mouth region, R prefrontal, R Wernicke's, and R anterior superior temporal gyrus during overt, nonfluent bisyllabic single *word repetition* (versus hearing words) in a PET study. They also observed significant decrease in L Broca's area. (We could not examine L Broca's area in our aphasics because most of our patients had lesion there.)

Our results are also similar to those of Rosen et al. (2000) where they observed a stronger-than-normal response in the R inferior frontal gyrus region during overt (PET) and covert (fMRI) *word stem completion* tasks with stroke patients who had L inferior frontal gyrus lesions. They reported that the level of this R inferior frontal gyrus activation did not correlate with recovery of verbal performance. The two patients who had the best recovery showed peri-lesional activation in the L inferior frontal gyrus during the word-stem completion task, not R inferior frontal gyrus activation. These two patients had only small lesion in the L inferior frontal gyrus area, and small or no lesion in the two deep white matter areas near ventricle relevant to severity of nonfluent speech, for example, medial subcallosal fasciculus and middle 1/3 periventricular white matter area (Naeser et al., 1989). Hence, there was better potential for these two patients to utilize undamaged L inferior frontal gyrus and an L hemisphere language network for this task. It was only the nonfluent patients with poor recovery who utilized activation in the R inferior frontal gyrus to perform the word stem completion task.

In addition, our results are similar to those of a third study (Thulborn et al., 1999) where a shift of activation to R Broca's area was observed within 3 days poststroke (and continued rightward lateralization over 6 months) in a patient with lesion in L Broca's area who was tested with BOLD fMRI on a silent reading task of simple sentences. Van Lancker and Grafton (1999) also observed significantly greater activation in R inferior motor area in chronic, severe aphasia patients versus normal controls utilizing a non-language paradigm of overt, repetitive vocalizations (e.g., /ba/ba/ba/, /da/da/da/, /ga/ga/ga/) during PET.

In two of the four above-mentioned studies with nonfluent aphasia patients, an increase in the R motor cortex was observed during an *overt* speech task, that is, either overt bi-syllabic word repetition (Belin et al., 1996) or overt repetitive vocalizations (Van Lancker and Grafton, 1999). The significantly higher relCBV in the R sensorimotor mouth region in the nonfluent aphasia patients during overt propositional speech in the present study most closely resembles that observed in these latter two studies. Together, these studies and the present one, suggest that one factor which may be contributing to the hesitant, poorly articulated, agrammatic speech of nonfluent aphasia is activation (or over-activation) and poor modulation of the R sensorimotor mouth area.

In the present paper, we have interpreted an increase in relCBV for a specific ROI to reflect activation (excitation/facilitation) for that ROI, relative to another ROI, or another condition. An increase in relCBV could also reflect inhibition (activation of inhibitory neurons) for a specific ROI. This is unknown and open to future investigation. There are several potential mechanisms underlying the increased activation in R sensorimotor mouth and other R hemisphere language homologues in the aphasia patients observed in this study, as discussed below.

Role of dominant SMA during propositional speech

The dominant SMA has been suggested to have two roles during propositional speech.

(a) The SMA plans for motor acts and instructs the primary motor cortex (M1) to put the plans into effect; and b) The SMA has an important inhibitory role in preventing entry into the M1 of influences that would disrupt an ongoing M1 program (Goldberg, 1985; Jonas, 1987).

In the cerebral blood flow studies by Roland et al. in the 1980s, normal controls were observed to have higher activation in L SMA than R SMA, during "fluent descriptive speech" while they overtly described furniture in their living rooms (reviewed in Roland, 1985). Similar results with the normal controls in the present study were observed, that is, significantly higher activation in L SMA than R SMA, during propositional speech. The results with the nonfluent aphasia patients in the present study, however, during elicited propositional speech showed significantly higher relCBV in the R SMA, than in the L SMA. Why this occurred is unknown, however, an impaired L SMA function is one possible mechanism, as discussed below.

There are direct connections between SMA and the motor cortex (Barbas and Pandya, 1987). All aphasia patients in the present study had lesion in the L motor cortex (mouth region) and/or in white matter deep to it (middle 1/3 periventricular white matter). (See Figs. 1 and 2) Thus, disconnections between the L SMA and L motor cortex (mouth region) were directly or indirectly present in all our nonfluent aphasia patients. These disconnections may have disrupted normal functioning of the L (dominant) SMA during propositional speech. Lesion in additional L perisylvian language areas with less direct connections to L SMA may also have adversely affected the function of L SMA during propositional speech.

This lower activation in L SMA during propositional speech production among the nonfluent aphasia patients, may be an example of "dynamic diaschisis" in stroke patients (Price et al., 2001). They studied four aphasia patients with lesion in L Broca's area, but without lesion in the L middle or inferior temporal gyrus areas, during a task involving discrimination of letter strings versus words. Normal controls activated L Broca's area as well as L posterior middle and inferior temporal gyrus areas during this task. However, the aphasia patients activated only the L posterior inferior temporal gyrus area, not the L posterior middle temporal gyrus area (despite absence of lesion in the latter). There appeared to be a network, which was active in normals, between activation of L Broca's area and L posterior middle and inferior temporal gyrus areas. In the aphasia patients, however, without activation in L Broca's area (due to lesion), there was also no activation in L posterior middle temporal gyrus,

despite absence of lesion there. Thus, this latter region showed a dynamic diaschisis effect for a specific cognitive task. In the present study, the lack of normal activation in the L SMA among our nonfluent aphasia patients (even with no lesion in L SMA) appears to be another example of ''dynamic diaschisis'' in aphasic stroke patients, however, here, it was observed during overt nonfluent speech production.

The increased activation in R sensorimotor mouth during nonfluent speech in the aphasia patients suggests a possible lack of adequate dominance and inhibition from the L SMA. Thus, this impaired function of the L SMA may be a factor, which results in poor modulation (possible over-activation) of R sensorimotor mouth during propositional speech. This notion was further supported by the negative correlation among the nonfluent aphasia patients between the relCBV level in R sensorimotor mouth and number of target words spoken during the story condition. The highest relCBV level was observed in the most severe nonfluent aphasia patient who produced no meaningful target words.

Possible transcallosal disinhibition, the right hemisphere, and aphasia recovery

The possible loss of active inhibition in the R sensorimotor mouth and other R hemisphere language homologues in nonfluent aphasia is indirectly supported by results from a recent study of corpus callosum size in chronic nonfluent aphasia patients where we observed an average loss of 40% in the corpus callosum (Martin et al., 2002). Meyer et al. (1998) has suggested that atrophy in the corpus callosum, especially in the posterior half of the body, may suggest a lack of transcallosal inhibitory input between motor cortices. Our strongest finding among the nine R perisylvian ROIs was in the R sensorimotor mouth area, where significantly higher relCBV was observed during the story condition for the nonfluent aphasia patients. While the size of the corpus callosum was not measured in the present study, obvious atrophy in the corpus callosum (including the posterior half of the body) was present on the MRI scans for each of the four nonfluent patients. See the mid-sagittal images provided for each patient in Figs. 1a–d.

Study limitations

These findings should be considered preliminary given the small sample size and the limitations of the imaging methods. In the current study, functional response was indexed using a derived relCBV measure for the area under the concentration–time curve in focal brain regions of interest. It was not feasible with our clinical sample of aphasia patients to complete any additional procedures such as carotid Doppler testing that would have allowed us to acquire more precise measures of blood flow.

Nevertheless, relCBV has been useful in describing regional brain changes within individuals, and the current findings are in agreement with other investigations that have applied complementary methods to study aphasia. This includes other studies with a *variety* of aphasia patients, where poor recovery was associated with poor activation of the L SMA (Heiss et al., 1997, 1999; Karbe et al., 1998) and poor activation of the L SMA was also observed in the nonfluent aphasia patients in the present study. In addition, this includes other studies with *nonfluent* aphasia patients where increased activation (possibly over-activation) in some R homologous language areas was observed (Belin et al., 1996; Rosen et al., 2000; Thulborn et al., 1999); this was also observed in the present study, for example, in the R sensorimotor mouth ROI during overt, propositional speech.

Conclusions

In summary, results from the present study suggest that nonfluent propositional speech may be associated in part, with transcallosal disinhibition. There is poor activation of L SMA and poor modulation of R SMA, R sensorimotor mouth, and other R perisylvian language homologues during propositional speech. The poor activation of L SMA may represent dynamic diaschisis associated with damage in the dominant L motor cortex mouth area and/or deep white matter near body of lateral ventricle (Naeser et al., 1989). There appears to be under-activation in the L SMA and perhaps over-activation in some R hemisphere language homologues. Hence, the language behavior observed during these unusually high levels of activation in R sensorimotor mouth and R hemisphere language homologues is the hesitant, poorly articulated agrammatic propositional speech characteristic of nonfluent aphasia. It is not that these patients have low activation of R hemisphere compensatory language areas, rather, it seems that they have over-activation and poor modulation of them. Whether this R hemisphere activation is beneficial or maladaptive remains to be clarified. However, the results from the present study tend to support the notion of ''maladaptive plasticity.'' Our nonfluent aphasics had significantly higher relCBV for R sensorimotor mouth than the controls, for example, during overt, propositional speech, yet their speech was not normal. These increased R hemisphere activation levels were thus abnormal and not compatible with recovery of good speech.

Based on our current understanding of over-activation in R hemisphere ROIs in nonfluent aphasia patients during propositional speech, we are developing a new language rehabilitation treatment approach for these patients. In a recent study, we have used repetitive transcranial magnetic stimulation (rTMS) with chronic nonfluent aphasia patients. Slow, 1 Hz rTMS reduces cortical excitability (Hilgetag et al., 2001; Kosslyn et al., 1999; Mottaghy et al., 2002; Robertson et al., 2001; Shapiro et al., 2001; Theoret et al., 2001). When 1 Hz rTMS was applied to R BA 45 in nonfluent patients, a significant improvement in single word naming ability was observed immediately following 10 min of rTMS treatment (Naeser et al., 2002). It is assumed that the 1-Hz rTMS promoted a decreased level of excitation in R BA 45 which in turn resulted in improved modulation at least in part, of R perisylvian homologues leading to an increased naming ability. Thus, while the abnormally high, increased R perisylvian activation during nonfluent speech has been suggested to be maladaptive, perhaps some modulated activation in the R hemisphere may be beneficial. The possible bilateral neural network for recovery of speech in nonfluent aphasia remains to be investigated with additional functional imaging studies.

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