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Task-Evoked BOLD Responses Are Normal in Areas of Diaschisis After Stroke

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Introduction

For more than 100 years it has been known that changes in blood flow and metabolism in the brain are closely linked to neural activity[1]. Increases in neural activity are followed by an increased blood flow and glucose metabolism but not a proportional change in oxygen consumption[2]. Mismatch between blood flow change and oxygen consumption leads to an increase in the T2*-weighted magnetic resonance (MR) signal, an effect known as blood oxygen level dependent (BOLD) contrast.

Neuroimaging techniques have been widely used to study the neurological mechanisms of poststroke recovery[3, 4]. However, the use of BOLD response to measure neuronal activity in patients with abnormal brain vessels and ischemia is attended by uncertainties[5, 6]. Among other concerns (eg, penumbral BOLD responses), the question arises whether functional magnetic resonance imaging (fMRI) responses are affected by diaschisis. Diaschisis refers to decreased metabolism and blood flow in anatomically intact brain regions remote from a lesion. The primary mechanism underlying diaschisis is believed to be functional deafferentation, that is, withdrawal of excitatory influences from anatomically connected regions of the brain[7].

The preceding considerations raise questions regarding the interpretation of fMRI responses in areas of diaschisis. We therefore investigated whether chronic diaschisis affects the dynamics of the BOLD response to task performance. Altered BOLD effects have been described in penumbral tissue[8]. However, there have been very few studies of physiological responses to behavioral paradigms specifically in areas of diaschisis remote from the lesion, and, to our knowledge, there are no previous reports relating fMRI responses to diaschisis as measured by positron emission tomography (PET).

Methods

Subjects

A total of 3 right-handed native English-speaking subjects with left frontal infarcts and 3 age-matched controls were studied. Stroke patients were recruited after reviewing the radiology files and hospital admissions at Washington University Medical Center in St Louis, Missouri, during 1995 and 1997. Control participants were recruited from Washington University and the metro area. All stroke patients had a single left-hemisphere lesion that included the left inferior frontal gyrus and operculum and were studied at least 6 months after the stroke. Inclusion criteria included 1 cerebral cortical lesion, as revealed by computed tomography (CT) or MRI. Exclusion criteria included stenosis greater than 50% of the lumen of the internal carotid artery as shown by Doppler ultrasonography or cerebral angiography, dementia, and any other significant illness (eg, cancer, congestive heart failure class IV). A board-certified neurologist interviewed and examined each participant. All patients were able to follow task instructions, but at the time of the experiment a standardized language examination revealed variable levels of recovery (for details see study by Rosen et al [9]). Participants practiced the word-stem completion task (see below) prior to the MRI session. The study was approved by the Washington University Human Studies Committee.

MRI Data Acquisition

The fMRI data were acquired with a Siemens 1.5 Tesla MAGNETOM Vision system (Erlangen, Germany) and the standard circularly polarized head coil. High-resolution structural images were obtained using a sagittal T1-weighted MPRAGE sequence (echo time [TE] = 4 milliseconds, repetition time [TR] = 9 milliseconds, inversion time [TI] = 300 milliseconds, flip angle = 12°, 160 slices, 1 × 1 × 1 mm voxels). T2-weighted images were also collected (TE = 80 milliseconds, TR = 2500 milliseconds, flip angle = 90°, 12 slices 1.2 × 0.9 × 5 mm voxels). fMRI series were collected using an asymmetric spin-echo (ASE) echoplanar (EPI) sequence (TR = 2364 milliseconds, TE = 50 milliseconds, flip angle = 90°, 8-mm slices, in-plane resolution 3.75 × 3.75 mm) sensitive to BOLD contrast. Each fMRI run included 128 whole-brain volumes (frames). Stimuli were projected with a Sharp LCD projector (640 × 480 pixel resolution) onto a translucent screen at the end of the magnet bore. The subject viewed the screen through a mirror placed on the head coil. Anatomical imaging for atlas transformation and lesion segmentation included T1-weighted and T2-weighted scans.

The fMRI activation paradigm was acquired during covert performance of the word-stem completion task administered in block design (30 seconds ON, 30 seconds OFF). As described previously, 1 subjects generated 1 word to complete a wordstem presented as a visual cue. For example, a possible correct response to “DRA” would be “drama.” Each 3-letter cue could be used to complete at least 5 words with a frequency greater than 1 per million. Stimuli were presented with a Macintosh (Apple Computers, Cupertino, California) computer in capital letters in black 24-point Geneva font on a white background. Stimuli were presented for 4.25 seconds, at a rate of 1 every 5 seconds. Each scan began with a 19-second period of visual fixation followed by alternating 30-second periods of wordstem completion and visual fixation. Each fMRI run included about 30 word-stem completions. Each participant completed between 6 and 8 runs.

PET Data Acquisition

PET scanning was performed on a Siemens 961 EXACT HR scanner operating in 3D mode. During the scan, subjects maintained fixation on a visual crosshair. For each scan, 12 to 16 mCi of [15O]H₂O was administered as an intravenous bolus. Brain radioactivity was

measured over a 40-second period to estimate relative (nonquantitative) blood flow. Images were reconstructed and smoothed (Butterworth filter) with a full-width at half maximum of 14 mm. For each patient, the PET images were registered using the vector gradient method² to the T1-weighted MPRAGE MRI data. The PET data were registered to the atlas via the MPRAGE using transform composition (PET MPRAGE atlas representative target). The PET data were intensity normalized to a whole brain mean of 1000 (PET units) and resampled in atlas space. PET data were not obtained in control participants.

Image and Statistical Analysis

The fMRI data were corrected for physical artifacts, realigned within and across fMRI runs, and normalized to a mode intensity value of 1000.³ After subtraction of linear trends on a voxel-by-voxel basis, voxels that were significantly activated during the word-stem completion task were identified using a Wilcoxon rank-sum statistic.⁴ Wilcoxon statistical images were then transformed into *z*-maps. For controls, voxels that were significantly active were identified based on the general linear model using a canonical hemodynamic response function of the gamma type.⁵ One-sample *t* tests were performed and then transformed into *z*-maps. These functional maps were transformed to atlas space using transform composition (EPI T2W MPRAGE atlas representative target). Thus, the fMRI and regional cerebral blood flow (rCBF) data were mutually coregistered via the MPRAGE. To avoid transformation inaccuracy owing to lesions, the damaged tissue was segmented and excluded from the MPRAGE atlas registration step.

Atlas-transformed single subject *z*-maps were multiple comparisons-corrected to an overall *P* value of $<.01$. Response foci above the threshold $z > 3.0$ were identified and regions of interest (ROI) were defined as spheres of radius 10 mm.

For quantitative analysis of the fMRI responses, BOLD modulation time series were extracted for each region by averaging over voxels. Each time series was made zero mean and linear trends were removed. Each time series then was subjected to Fourier analysis to extract modulations attributable to task performance versus rest.

BOLD modulation attributable to the task and rCBF were measured in homologous regions in both hemispheres. Regions were initially defined using a peak search algorithm to obtain the center of mass and cluster coordinates for statistically significant voxels. Peaks were identified after a 4-mm hard sphere preblur and a statistical threshold of $z > 3.0$. Peaks closer than 10 mm were consolidated into one averaged locus. Ten mm radius spherical regions then were defined around peaks. A region's homologue was defined as a mirror region in the opposite hemisphere separated by a vector distance of 15 mm or less. This distance was selected based on previous work on the individual variability of activation foci in functional neuroimaging data set[6].

Diaschisis was assessed by summing PET counts over voxels within regions in the coregistered data. Asymmetry of BOLD modulation and rCBF both were computed using the same formula.

Regions that were significantly modulated by the wordstem completion task were identified in both patients and controls. Homologous region pairs in intact tissue then were identified for the purpose of evaluating response symmetry. Summing over the 3 patients, a total of 182 regions of activation were identified. Patient 1 accounted for 69 regions (15 homologous), patient 2 accounted for 91 regions (22 homologous), and patient 3 accounted for 22 regions (1 homologous pair). The majority of region pairs were distributed throughout occipital, temporal, and parietal cortex remote from the lesion. Although the word-stem completion task does produce asymmetric BOLD responses, only bilaterally modulated ROI

pairs were included in the present analyses. In the patients, diaschisis was assessed in each region pair using the coregistered rCBF data and evaluated using the asymmetry index,

$$\frac{0.5*(R_{affected} + R_{non-affected})}{R_{affected}}$$

where R stands for rCBF averaged over a given ROI. The AI was similarly computed for quantitative measures of fMRI responses.

Quantitative measures of the fMRI response were obtained using Fourier analysis of the regional time series. Each fMRI run included 4 periods in which task and rest blocks alternated every 12 frames (30 seconds). Accordingly, the fundamental frequency corresponding to the block design was 1 cycle/60 seconds = 0.0167 Hz. The amplitude and phase of the modulation at the fundamental block design frequency provided measures of response strength and latency, respectively. The amplitude measure captures peak-to-peak BOLD modulation in a manner comparable to conventional measures of fMRI response magnitude (ie, percent signal change). In addition, to maximize the potential for objectively detecting asymmetries of response dynamics, the frequency domain data were divided into 3 bands. Root mean square (rms) power in the lowest (0.167 to 0.067 Hz) and middle bands (0.083 to 0.133 Hz) were identified as slow and fast modulation, respectively. The highest frequency band (0.133 to 0.2 Hz) was not used. This analysis thus yielded 4 quantitative measures of the BOLD response: (1) slow modulation, (2) fast modulation, (3) fundamental amplitude, and (4) fundamental phase (Figure 1A).

The AI was computed for each of these measures as described above for rCBF. Regression analyses were conducted over all regions and subjects, testing for systematic relationships between each BOLD response parameter and diaschisis. A direct comparison between the controls and patients was performed on these regression results using analysis of covariance.

Results

PET rCBF

PET measures demonstrated diaschisis in all 3 stroke patients (ie, a relative decrease in rCBF in structurally intact regions of the affected hemisphere as compared to homologous regions of the unaffected hemisphere; Table 1). A direct comparison of fMRI-derived regions in the affected and nonaffected hemispheres showed significant rCBF differences in 2 of 3 patients ($P < .0001$; Table 1). Significance could not be similarly assessed in patient 3 as only 1 homologous pair was identified. The corresponding mean intensity MRI values did not differ across hemispheres ($P = .385$, Table 1).

fMRI Responses

The BOLD data were analyzed separately in each participant. A total of 38 homologous pairs were identified and subsequently used for further analysis. All the homologous pairs showed qualitatively similar response time courses (Figure 1B).

Regression analysis (BOLD measure AI on rCBF AI) for all 4 quantitative measures showed no systematic relation between severity of diaschisis and the fMRI response (Figure 2). Analysis of covariance indicated that the fast component of BOLD modulation was more asymmetric (left hemisphere response greater) in patients compared with controls. Otherwise, measures of fMRI response symmetry in patients and control groups were not statistically different (Figure 2).

Discussion

Despite significant reductions in resting blood flow as measured by PET, task-evoked BOLD modulations in structurally intact regions of the brain were minimally affected in patients with left hemisphere infarcts. No systematic relation between diaschisis and any quantitative measure of the BOLD response was found. Thus, in this data set, the neurovascular mechanisms underlying the BOLD response to phasic changes in neuronal activity appear to be intact in areas of chronic diaschisis. (The distinction between acute and chronic diaschisis is discussed by Witte et al.¹⁰ Also see Weber et al.¹¹ for supporting evidence in a rat model.)

Of note, there are several limitations of this study that should be mentioned. The current study uses a limited data set (in which only 3 subjects were analyzed), and results are based on 1 task. The results in this article would benefit from a follow-up replication study with a larger number of subjects and tasks.

Another limitation is that patient 3 showed only 1 homologous pair. This raises the question that the BOLD signal was intact in only a subset of ROIs, and therefore, not in all areas of diaschisis. Although this is a possibility, the fact that patient 1 had more severe diaschisis, yet still a higher proportion of homologous region pairs makes this unlikely. Because we generated the regions using the same significance thresholds for all 3 patients, differences in signal to noise ratios for these single subjects likely contributed to the discrepancies in the number of regions obtained for each subject.

The difference identified in the fast modulations (Figure 1A) between controls and patients (Figure 2) may reflect a subtle variation in the underlying hemodynamic response to neuronal activity or possibly a remote functional effect of the lesion^[12]. We note that this difference was found in isolation and that fast modulation was not in any way related to diaschisis (Figure 2, row 1).

With the above limitations under consideration, an interpretation of the present results can be constructed within the following context. While the literature is limited, some investigators have argued that chronic diaschisis is characterized with the following hemodynamic and metabolic changes at *rest*: large decreases in cerebral blood flow (rCBF) accompanied by smaller decreases in oxygen metabolism and cerebral blood volume (CBV), and a corresponding increased oxygen extraction fraction.^{13,14}

Several groups have studied the effect of hypercapnea, hypocapnea, and acetazolamide infusion on blood flow in areas of diaschisis^[13–18], maneuvers assumed to alter cerebral blood flow and volume without changing neural activity.^{19,20} Although the results have been mixed^[15–18], the PET data suggest that, in areas of diaschisis, the blood flow response to acetazolamide is decreased absolutely but is normal if expressed as percent change relative to the baseline^[13, 14]. In contrast to rCBF in areas of diaschisis^[13, 14], our results suggest that the baseline BOLD signal is nearly the same in the affected and nonaffected hemispheres. Critically, the task-related BOLD response parallels the rCBF response to acetazolamide described above.

These findings can be understood in the light of previous work from 2 perspectives. First, we note that diaschisis is expected to manifest very differently in rCBF PET versus BOLD imaging. In PET, tracer uptake is approximately proportional to blood flow. Decreased blood flow therefore directly appears in rCBF images as reduced activity. In contradistinction, image intensity in T2*-weighted MRI primarily reflects anatomical contrast. Physiological changes in neuronal activity and blood flow indirectly lead to small (typically 1% or less) modulations of the MRI signal owing to the dephasing effects of

deoxyhemoglobin (HHb). These modulations can be usefully measured as signal change on a time scale of tens of seconds, which is the basis of fMRI. However, the BOLD effects of chronic diaschisis may be too small to be detected. Hence, the baseline BOLD signal intensity is not measurably affected by diaschisis, as seen here (Table 1).

Additional insight may be obtained by recognizing that the relation between the BOLD signal and rCBF is complicated. In diaschitic tissue, chronically decreased rCBF without a proportional reduction in oxidative metabolism (see studies by Yamauchi et al[13] and Ito et al[14] but also see study by Baron et al[21]) should increase the concentration of HHb per unit volume of tissue, which theoretically could decrease the baseline BOLD signal without affecting the capacity of the brain to increase blood flow (but not oxidative metabolism) in response to neuronal demand. This mechanism could theoretically enhance BOLD responses. However, regionally decreased CBV in areas of diaschisis[13, 14] could decrease the concentration of HHb per unit volume of tissue and exert the opposite effect. The inverse relation between rCBF and CBV and their influence on the BOLD signal are described in detail in Yablonskiy and Haacke[22] and may, in part, account for the reason why fMRI responses are minimally, if at all, affected by diaschisis.

In summary, although demonstrated in a limited data set, our results indicate that BOLD responses are essentially normal in areas of chronic diaschisis. Therefore, the present findings suggest that chronic diaschisis presents no interpretive difficulties for using fMRI to study brain recovery following stroke. As mentioned above, the results in the manuscript would benefit from a follow-up replication study with a larger number of subjects and tasks. Future work would also benefit from other independent measures of neuronal function to see if, beyond BOLD, the level of transient activation in humans for these measures is also unaffected by diaschisis.

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Figure 1. Quantitative and Qualitative Observations of Homologous Regional Time Series

Note: A, Quantitative measures of the blood oxygen level dependent (BOLD) response obtained using Fourier analysis of the regional time series. The 4 quantitative measures included (1) slow modulation, (2) fast modulation, (3) fundamental amplitude, and (4) fundamental phase. See Figure 2 for results. B, Homologous pairs of regions that were significantly activated were identified using functional magnetic resonance imaging. Depicted are the BOLD time courses of 3 homologous pairs with 1 region of each pair located in an area of diaschisis. A qualitative comparison of the time series showed a similar BOLD response between all homologous pairs.

Figure 2. Functional Magnetic Resonance Imaging Response Asymmetry Assessed with 4 Quantitative Measures of Blood Oxygen Level Dependent (BOLD) Modulation

Note: Top row: BOLD response AI versus regional cerebral blood flow AI (formula given in the text). No systematic relation between BOLD response asymmetry and severity of diaschisis. Bottom row: regression analysis (left hemisphere on right hemisphere) of the 4 BOLD response measures. Patients and control subjects are represented as red and blue symbols. Note: for both patients and controls, generally consistent proportionality of responses in the 2 hemispheres. Analysis of covariance demonstrated no significant patient:control differences for 3 of the 4 response measures.

Table 1rCBF in Affected Homologue Regions Versus Nonaffected Homologue Regions for Each Patient^{*}

	Affected – Nonaffected Regions (in PET Counts)	<i>t</i> -Test <i>P</i> Value	SD	df
Patient 1	–250.28	<.0001	133.76	14
Patient 2	–163.24	.0002	194.57	21
Patient 3	–243.63	—	—	—
Total PET	–199.71	<.0001	174.49	37
Mean MR units	35.68	.481	119.41	37

Abbreviations: rCBF, regional cerebral blood flow; PET, positron emission tomography; SD, standard deviation; df, degrees of freedom; MR, magnetic resonance.

^{*} Values are obtained from homologous region pairs (see Methods section). Only 1 homologous pair was obtain from patient 3.