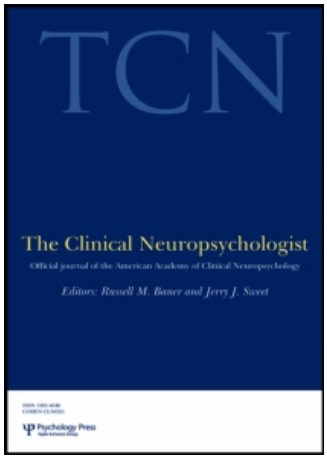

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THE INFLUENCE OF NEUROPATHOLOGY ON THE fMRI SIGNAL: A MEASUREMENT OF BRAIN OR VEIN?

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There is a rapidly growing literature using fMRI technology to investigate the various forms of behavioral impairment associated with brain injury and disease. Given this, surprisingly little work has been conducted to examine the influence of neuropathophysiological processes on the fMRI signal. This paper reviews the literature examining baseline alteration in cerebrovascular parameters associated with normal aging, brain injury, and brain disease. In addition, findings from three cases of individuals with severe brain trauma will be presented to show the influence of brain trauma on baseline cerebrovascular parameters measured by fMRI. The methods used here can be implemented by other investigators to accurately isolate specific hemodynamic changes that can influence the BOLD fMRI signal.

Keywords: Blood flow; CBF; fMRI; Functional imaging; Lesions; TBI

INTRODUCTION

Advances in MRI technology have permitted the measurement of local hemodynamics through quantification of cerebral blood volume (Mandeville et al., 1998; Zaharchuk, Mandeville, Bogdanov, Weissleder, Rosen, & Marota, 1999), cerebral blood flow (Barbier, Lamalle, & Decorps, 2001; Kastrup, Li, Takahashi, Glover, & Moseley, 1998), and tissue oxygenation (Kastrup, Li, Glover, & Moseley, 1999; Turner, Le Bihan, Moonen, Despres, & Frank, 1991). Functional magnetic resonance imaging (fMRI) has been used extensively to characterize sensory, motor, and cognitive functioning in healthy adults and, more recently, in individuals with neurological impairment. There is enormous potential for the use of fMRI to better understand the influence of neurologic insult on a variety of human behaviors. It is anticipated that over the next decade, fMRI will receive wider application both in research and in the assessment and evaluation of clinical syndromes.

Proliferation of fMRI work, thus far, has been attributed to the accessibility of MRI technology, its non-invasiveness, and its low cost relative to other imaging

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methods (Desmond & Annabel Chen, 2002; Hennig, Speck, Koch, & Weiller, 2003; Ricker, Hillary, & DeLuca, 2001). Even during this period of expanded application, examiners have cautioned that appropriate use of fMRI in special samples will require further investigation of the influence of cerebrovascular changes on the fMRI signal (D'Esposito, Deouell, & Gazzaley, 2003; Desmond & Annabel Chen, 2002). To date, there has been virtually no direct examination of the influence of brain pathology on the fMRI signal. If the potential for applying fMRI technology to examine neuropathology is to be realized, it will be important to develop methods that guarantee reliable and valid application of fMRI in clinical samples.

The current paper briefly reviews several pathophysiological mechanisms responsible for altered cerebrovascular functioning, outlines the cerebrovascular basis of the fMRI signal, and provides case examples of individuals with severe brain trauma illustrating the influence of brain pathology on cerebrovascular factors relevant for fMRI work. The ultimate purpose of this paper is to outline an important practical consideration when using fMRI technology in clinical samples.

fMRI AND CLINICAL SAMPLES

There is a rapidly growing literature using fMRI technology to investigate the various forms of behavioral impairment associated with brain injury and disease. For example, fMRI has been used to investigate cognitive deficits in individuals with traumatic brain injury (TBI) (Chen, Johnston, Frey, Petrides, Worsley, & Ptito, 2004; Christodoulou et al., 2001; McAllister et al., 1999; McAllister, Sparling, Flashman, Guerin, Mamourian, & Saykin, 2001; Perlstein et al., 2004; Prigatano, Johnson, & Gale, 2004), multiple sclerosis (Au Duong et al., 2005; Audoin et al., 2003, 2005; Hillary et al., 2003; Mainero et al., 2004; Staffen et al., 2002; Wishart et al., 2004), cortical and subcortical dementias (Grossman et al., 2003a; Grossman et al., 2003b; Mandzia, Black, Grady, McAndrews, & Graham, 2002), schizophrenia (Manoach et al., 2000; Perlstein, Carter, Noll, & Cohen, 2001; Perlstein, Dixit, Carter, Noll, & Cohen, 2003), and HIV (Chang, Ernst, Leonido-Yee, & Speck, 2000; Chang et al., 2001; Ernst, Chang, & Arnold, 2003; Ernst, Chang, Jovicich, Ames, & Arnold, 2002). Clinical researchers have emphasized that advanced neuroimaging techniques, such as fMRI, may provide important opportunities for assessing outcomes and the success of novel rehabilitation treatments and interventions (Levin, 1995; Ricker et al., 2001). Ultimately, fMRI technology provides clinical researchers with advanced methods and unique dependent variables to examine the influences of brain injury and disease on human behavior.

As noted, however, very little work has been conducted to examine the influence of neuropathological processes on the fMRI signal. This remains an outstanding gap in the literature given the established relationship between alterations in cerebrovascular functioning and across a variety of brain pathologies (see below). Without considering the influence of cerebrovascular changes on the BOLD signal, examinations designed to examine brain recovery through the use of fMRI may be confounded with chronic, but as yet undocumented, alterations in cerebrovascular physiology over the recovery period. That is, activation changes secondary to *vascular* changes could be incorrectly interpreted as activation change secondary to *neuronal* changes reflecting, for example, neural compensation mechanisms.

In order to guarantee accurate and consistent interpretation of fMRI data in individuals with neurologic compromise, baseline cerebrovascular parameters like cerebral blood flow (CBF), timing of blood flow (or transit time), and oxygen extraction fraction (OEF) should be quantified. This paper reviews the literature examining baseline alteration in cerebrovascular parameters associated with normal aging, brain injury, and brain disease. In addition, findings from three cases of individuals with severe brain trauma will be presented to show the influence of brain trauma on baseline cerebrovascular parameters measured by fMRI. The methods used here can be implemented by other investigators to accurately isolate specific hemodynamic changes that can influence the BOLD fMRI signal.

CAUSES FOR ALTERED CEREBROVASCULAR ACTIVITY

While there have been occasional findings to the contrary, (see Meltzer et al., 2000), it is now generally accepted that normal aging results in diminished CBF and OEF values throughout the brain (D'Esposito, Zarahn, Aguirre, & Rypma, 1999; Kamper, Spilt, de Craen, van Buchem, Westendorp, & Blauw, 2004). In fact, when comparing younger and older adults, D'Esposito and colleagues (1999) noted that the reduced baseline CBF values observed in older adults resulted in decreased signal to noise ratio in BOLD datasets. Because of the changes in cerebrovascular parameters during normal aging, these same examiners have cautioned against simple interpretation of fMRI findings comparing young and old adults (D'Esposito et al., 2003). These findings have extended what had been observed over two decades ago; CBF values may be highest early in life and decrease consistently over the life course (Swank, Roth, & Woody, 1983). Considering these findings, it is important that investigators account for altered baseline cerebrovascular parameters when using fMRI technology to examine sensory, motor, and cognitive functioning in healthy older adults.

When considering disease processes that influence the human nervous system, examiners have noted alterations in baseline CBF both locally (at or near the lesion site) and globally. For example, in multiple sclerosis (MS), mean CBF values have been shown to be reduced not only in lesioned areas, but also in areas of normal-appearing white matter (NAWM) (Law et al., 2004). In fact, early work in MS revealed an important link between diminished CBF and disease progression (Swank et al., 1983). While using Xenon tomographic methods to examine the influence of HIV on cerebrovascular activity, other examiners have also noted diminished CBF and OEF in both symptomatic and asymptomatic participants (Tran Dinh, Mamo, Cervoni, Caulin, & Saimot, 1990). Other HIV investigators have noted widespread derangements in CBF values even in cases where CT and MRI findings were negative (Maini et al., 1990). Taken together these findings indicate that CBF alterations may occur as the result of disease processes both locally due to apparent lesions as well as in cases where focal lesions are not detectable with traditional structural imaging.

In cases of non-traumatic brain injury such as cerebrovascular accident (CVA) or aneurysm, there are often changes in baseline CBF secondary to normal aging and concomitant disruption of blood flow due to embolic, thrombotic, or hemorrhagic processes. By definition, CVA results in the disruption in local blood flow, which

has important implications for the fMRI signal (Kim et al., 2005). Moreover, investigators have shown that even chronic hypertension, without evidence of overt ischemia, may result in diminished CBF (Sierra, de la Sierra, Chamorro, Larrousse, Domenech, & Coca, 2004). Unfortunately, few studies examining motor and language recovery following stroke use methods that allow for quantification of the influence of CBF disruption on the fMRI signal. Certainly alterations in baseline cerebrovascular activity will be critical to consider for investigators using fMRI to examine recovery of function following cerebrovascular accident.

There have been repeated observations in both animal and human models of TBI that brain trauma significantly alters baseline CBF (Bouma, Muizelaar, Choi, Newlon, & Young, 1991; Golding, 2002; Kochanek, Hendrich, Dixon, Schiding, Williams, & Ho, 2002; Schroder, Muizelaar, Kuta, & Choi, 1996) and rate of cerebral metabolism of oxygen (Forbes et al., 1997; Martin et al., 1997). In fact, investigators have shown a relationship between acute elevation in CBF following TBI and recovery following TBI, and the degree of decline in baseline CBF has been correlated with the severity of injury in experimental models of TBI (Kochanek et al., 2002). Using cortical impact models that result in focal brain lesions, examiners have consistently observed reduced CBF at or near the lesion site (Biagas, Grundl, Kochanek, Schiding, & Nemoto, 1996; Kochanek et al., 1995; Sutton, Hovda, Adelson, Benzel, & Becker, 1994) and, in at least one study, diminished cerebral blood flow remained at 1 year post injury (Kochanek et al., 2002). In humans, PET imaging has revealed reductions in CBF and blood volume in perilesional areas following TBI (Hattori et al., 2003, 2004). This work in both animals and humans has important implications for the potential long-term effects of TBI on cerebral blood flow and provides important considerations for employing techniques such as fMRI to examine behavior in brain-injured individuals.

Taken together, investigations of brain injury, brain disease, and even normal aging reveal altered baseline cerebrovascular functioning. Because baseline cerebrovascular parameters are influenced by a variety of normal/subtle (e.g., aging, hypertension) and pathological (e.g., brain injury, brain disease) mechanisms, these changes are important to consider when using fMRI in special populations. The following provides a basic overview of the neural and vascular components that comprise the fMRI signal and provides case examples quantifying the baseline differences in cerebrovascular functioning between healthy adults and individuals with TBI.

BIOPHYSICAL CHARACTERIZATION OF THE fMRI RESPONSE

Neural activity results in vasodilation, with concomitant increases in blood flow, and measurable differences between oxyhemoglobin and deoxyhemoglobin which are observed as BOLD fMRI. As noted, blood flow and tissue oxygenation are important cerebrovascular characteristics that influence MRI signal intensity. Because of this, when using fMRI to examine brain and behavior relationships, changes in MRI signal intensity may be most accurately conceptualized as an increase in neural activity convolved with an *individualized hemodynamic response function*, or iHRF. The paradigm for almost all fMRI experiments consists of measuring the task-induced signal changes in response to a specific time-varying stimulus

condition. Let f(t) represent the time course of the stimulus condition, and y(t) represent the measured fMRI signal response for a particular voxel. The typical fMRI experiment can be represented as:

$$f(t) \rightarrow \underbrace{\text{Neuronal} \otimes \text{Hemodynamic}}_{\text{Physiologic Response}} \rightarrow y(t).$$

Physiologic Response

The function above indicates that the important components comprising the observed BOLD fMRI signal are both neural and vascular. Because examiners of cognition are typically interested in isolating the *neural* mechanisms and not the *vascular* response associated with specific tasks, between-group differences in brain "activation" are interpreted as differences in the neural network associated with carrying out the task. One important assumption associated with this interpretation is that the vascular contribution to the BOLD signal is constant across subjects. However, fMRI signal intensity at the individual level is largely determined by baseline CBF parameters that vary on a subject-to-subject basis. Moreover, voxelwise analyses have revealed small differences in baseline cerebrovascular parameters between brain regions *within the same individual* (Biswal, Pathak, Ulmer, & Hudetz, 2003; Kannurpatti, Biswal, & Hudetz, 2003). While, in many instances, these within- and between-subject differences in cerebrovascular physiology have been deemed negligible (or at least acceptable) in healthy adults, this is a tenuous assumption in clinical samples. To better characterize the neural response to cognitive, motor, and sensory stimuli, the vascular and the neural contributions to the fMRI signal should be separated and quantified.

To date, alterations in baseline cerebrovascular parameters secondary to brain injury and disease have been examined using methods other than fMRI (e.g., PET, doppler imaging). Because of this, the direct influence of neuropathology on the fMRI signal remains unclear. Three important quantifiable components comprising the BOLD fMRI signal are: (1) regional cerebral blood flow (CBF), (2) time to peak, or transit time, of blood flow (t_0), and (3) oxygen extraction fraction (OEF). These factors can be examined on a voxelwise basis using MR-based methods in order to better characterize the potential differences in the cerebrovascular physiology between individuals with brain dysfunction and healthy adults. If the cerebrovascular factors contributing to the fMRI signal can be quantified and isolated, investigators can more reliably estimate the true neural response within the observed brain "activation" evoked by the experimental stimulus. Pilot data are presented here that employ MRI technology to examine the influence of severe brain trauma on the fMRI signal and its constituents.

METHOD

Participants

The pilot data presented here are part of a larger study examining cerebrovascular reactivity in individuals sustaining severe brain trauma. Participants were three

individuals diagnosed with severe TBI and five healthy adults. All study participants were between the ages of 18 and 55. This restricted age range was chosen in order to minimize the influences of neurodevelopment in children and young adults, and cerebrovascular physiology in older adults, on CBF and OEF. Participants with TBI had a definitive diagnosis based on the TBI Model Systems National Database definition adapted from the CDC: ''damage to brain tissue caused by an external mechanical force, as evidenced by loss of consciousness due to brain trauma, post-traumatic amnesia, skull fracture, or objective neurological findings that can be reasonably attributed to TBI on physical examination or mental status examination'' (Harrison-Felix et al., 1996).

TBI severity was determined by monitoring Glasgow Coma Scale (GCS) scores over the first 24 hours in order to eliminate confounding factors such as psychoactive substance use at the time of injury (Segatore & Way, 1992). Moderate TBI included GCS scores of 9–12 and severe TBI included GCS scores of 3–8, and all three participants with TBI showed evidence of brain lesion on CT/MRI. Mild TBI was not examined due to the significant difficulty in accurately diagnosing and categorizing cases of mild TBI (for review see Rosenthal & Ricker, 2000) and the already established relationship between blood flow changes in more moderate and severe injuries (Kochanek et al., 2002; Yamaki et al., 1996a, 1996b).

Healthy adults were solicited from within the local community through newspaper advertisement and by public postings of flyers (e.g., in local supermarkets, hospitals etc.). Individuals with substance dependence and people prone to having altered cerebrovascular physiology (e.g., deep sea divers, mountaineers, etc.) were excluded. People undergoing hormone replacement therapies were excluded from this pilot study as a number of studies have shown that estrogen does influence cerebral blood flow.

Procedure for Lesion Identification and Analysis

An important goal was to determine the influence of brain pathology on the fMRI signal. To do so, three sets of ''masks'' were made in order to isolate cerebrovascular effects in the subjects with TBI: (1) mask of lesion; (2) masks of perilesional area; (3) mask of contralateral homologue to serve as a control region. A semi-automated procedure was used to determine the size and extent of lesion masks and control region masks. The brain regions determined to be considered ''lesions'' were manually traced by a clinical neuropsychologist with 10 years of experience in TBI research and a radiologic physicist with over 12 years of MRI experience. In creating masks for region of interest analyses, both investigators were required to agree on the distribution of the lesioned area as well as the peri-lesional and control regions. All areas considered brain lesions were reconciled with medical records and initial CT or MRI findings at the time of injury. Perilesional masks were created and enclosed a 4 mm wide area around the perimeter of lesions (see Figure 1).

AFNI software was used for identifying brain regions to be analyzed and for processing and viewing functional imaging data (http://afni.nimh.nih.gov/afni/). Peri-lesional areas were determined through an automated procedure that allowed for subtraction of the lesion mask from the lesioned and peri-lesioned area (see Figure 1). The tracing was performed manually in order to distinguish between

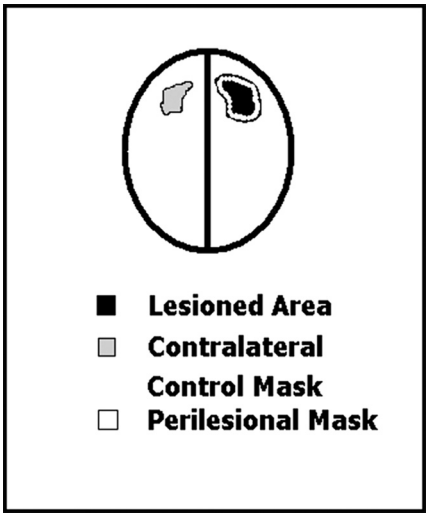

Figure 1 A schematic representing the procedure for comparing areas adjacent to large brain lesions (white area) with a contralateral "control" region (gray area).

a number of regions including lesion and peri-lesional areas and control regions (a contralateral mirror image of the lesion). Through the use of these masks, within-subject comparisons, between areas adjacent to brain lesions and a contralateral homologue were possible. In order to make comparisons with healthy adult control subjects, masks were made of the primary motor cortices. For each of the five healthy adults, the right and left motor cortex were compared in order to determine the natural variation in differences between hemispheres for CBF, OEF, and t_0. Figure 1 provides a model of the Breath Hold paradigm and a schematic representation of the between-hemisphere comparisons for all subjects.

MR Imaging Parameters

Data were obtained using a 3.0 T research Siemens Allegra scanner. Images were acquired using a custom-built three-axis balanced-torque head gradient coil with end-capped birdcage RF coils. Localizer images were obtained in the axial and sagittal planes using a spin-echo T2 pulse sequence followed by the acquisition of axial whole brain axial T1-weighted conventional spin-echo images for anatomic overlays (TR = 450, TE = 14, contiguous 5 mm, 256×256 matrix, FOV = 24, NEX = 1), yielding an in-plane resolution of 0.94 mm^2. Sequential time-series of 180 echo-planar images (360 seconds) was obtained using a gradient echo EPI sequence. Images were acquired with matrix size 64×64, FOV = 22 cm and slice thickness = 5 mm resulting in a spatial resolution of $3.75 \times 3.75 \times 5\,mm^3$. For examination of CBF, a pulsed arterial spin labeling technique that uses endogenous water as a tracer by alternating between slice selective and non-slice selective inversion, was also used. For each volunteer, resting state as well as task-activation time courses of 240 ASL images were acquired using a TR = 2500 ms, TE = 40 ms, and

slice-selective inversion width = 14 mm. Additional imaging parameters included: FOV = 22 cm, matrix size 64×64, and slice thickness = 7 mm. The TI value was 1400 ms, which suppresses signal at 3 T from CSF and blood. For ASL imaging, six axial slices covering the lesioned areas were acquired.

At the time of imaging, subjects were positioned supine on the gantry of the scanner with the head in a midline location in the coil. All subjects were instructed to limit head motion. To minimize fMRI signal changes due to motion artifact, foam padding was routinely used. In addition, a contour-based cross-correlation algorithm developed for detecting the presence of head motion was employed (Biswal & Hyde, 1997). Data sets that exhibit head motion by more than 2 voxels were discarded. For review of this motion correction methodology see Biswal and Hyde (1997).

Functional Imaging Task

Breath hold task. Subjects were instructed to perform expirational breath hold in response to a cue. The duration of each breath hold stimulus was 20 seconds and carried out in three epochs interspaced with 80-second resting periods with normal respiration. In order to quantify CBF values, arterial spin labeling methods were used in conjunction with the Breath Hold (BH) task (see MRI scanning parameters). BH tasks used with arterial spin labeling methods have been shown to be a viable method for examining CBF (Kastrup, Kruger, Neumann-Haefelin, & Moseley, 2001; Kastrup et al., 1999; Kastrup et al., 1998; Li, Kastrup, Takahashi, & Moseley, 1999). The BH task used in the current proposal is completely noninvasive, requires about 5 minutes to conduct, does not require additional MR-compatible equipment, and provides the opportunity for region of interest and whole brain measurements of CBF, OEF, and t_0.

Isolating Three Cerebrovascular Parameters

Baseline blood flow and O_2 metabolism characterization. As noted, baseline CBF values are highly susceptible to disruption and contribute significantly to the fMRI signal. Due to its non-invasiveness and high temporal and spatial resolution, MRI is ideal for the examination of alterations in CBF and OEF secondary to pathophysiology. Arterial spin labeling (ASL) labels moving spins in flowing blood through the use of a radiofrequency (RF) pulse, thus providing a quantitative measure of cerebral perfusion and oxygen metabolism. When ASL is used in conjunction with a simple perturbation such as the Breath Hold task described above, reliable indices of cerebrovascular functioning can be quantified.

Transit delay. At the outset of neuronal firing, it is not only the amount of blood flow but also the timing of blood flow that contributes to the fMRI signal. The differences in total transit delay between voxels can be decomposed into *neural* (due to differences in the neural contribution), *vasomotor* (due to flow changes during activation), and *transit delay* (due to differences in the blood arrival time) (Biswal et al., 2003). The Breath Hold task was used here to decouple the inter-voxel task-induced delay from the inter-voxel intrinsic delay. Briefly, this method entails

subtraction of transit delay from the corresponding total delay for each voxel yielding the delay attributable to factors other than the intrinsic delay, i.e., the *task-induced* delay (for review of this method see Biswal et al., 2003).

Cross-Correlation Analysis

Task-induced signal changes during the BH task from normal subjects were analyzed by cross-correlation, which assumes that neural activity and fMRI task-induced signals change proportionally with the stimulus paradigm. In this method, the number of activated voxels is calculated for each activation correlation coefficient (ACC) threshold. A synthesized box-car waveform corresponding to the stimulus presentation is cross-correlated with all voxel time courses on a voxel-by-voxel basis to identify stimulus-locked response. The statistical significance p is calculated using a semi-empirical method that was described in an earlier paper (Biswal, DeYoe, & Hyde, 1996). Essentially, the ideal reference waveform used for cross-correlation fMRI analysis of filtered task-activation voxel time courses is applied to all filtered voxel time courses in the resting-state data set. All voxels that pass the ACC threshold in the task-activated datasets are considered activated and their locations noted.

RESULTS

Blood flow data from the three individuals with TBI reveal a pattern of baseline alterations in the three cerebrovascular parameters measured. Each of the individuals with TBI exhibited diminished CBF values, reduced transit times, and an increased OEF in peri-lesional areas. Figure 2 provides images and cerebrovascular measurements for an acute and a chronic case of severe brain trauma.

Table 1 provides the baseline CBF, OEF, and t_0 information for the five HCs. The between-hemisphere comparisons for the five healthy adults revealed very small mean differences in baseline CBF, OEF, and t_0. These small mean differences were dissimilar to findings observed in all three cases of TBI. These data indicate that

Table 1 Cerebrovascular data comparing the right and left primary motor areas in five healthy adults

	CBF			OEF			t_0		
Subject	Left	Right	Absolute difference	Left	Right	Absolute difference	Left	Right	Absolute difference
1	15.8	15.3	0.5	23.9	23.4	0.5	7.9	8.1	0.2
2	13.7	12.9	0.8	25.8	25.5	0.3	12.7	13.2	0.5
3	9.6	9.3	0.3	19.9	19.7	0.2	9.6	8.9	0.7
4	11.4	11.6	0.2	22.7	21.9	0.8	11.3	11.2	0.1
5	13.2	13.2	0	24.3	23.8	0.5	7.4	7.3	0.1
Avg. Diff			0.36			0.46			0.32

The unit of measurement for t_0 is seconds, CBF is ml/sec, and OEF is percent change from baseline. Note the relatively small within-subject differences in t_0, CBF, and OEF in these healthy adults compared to the two TBI cases shown in Figure 2.

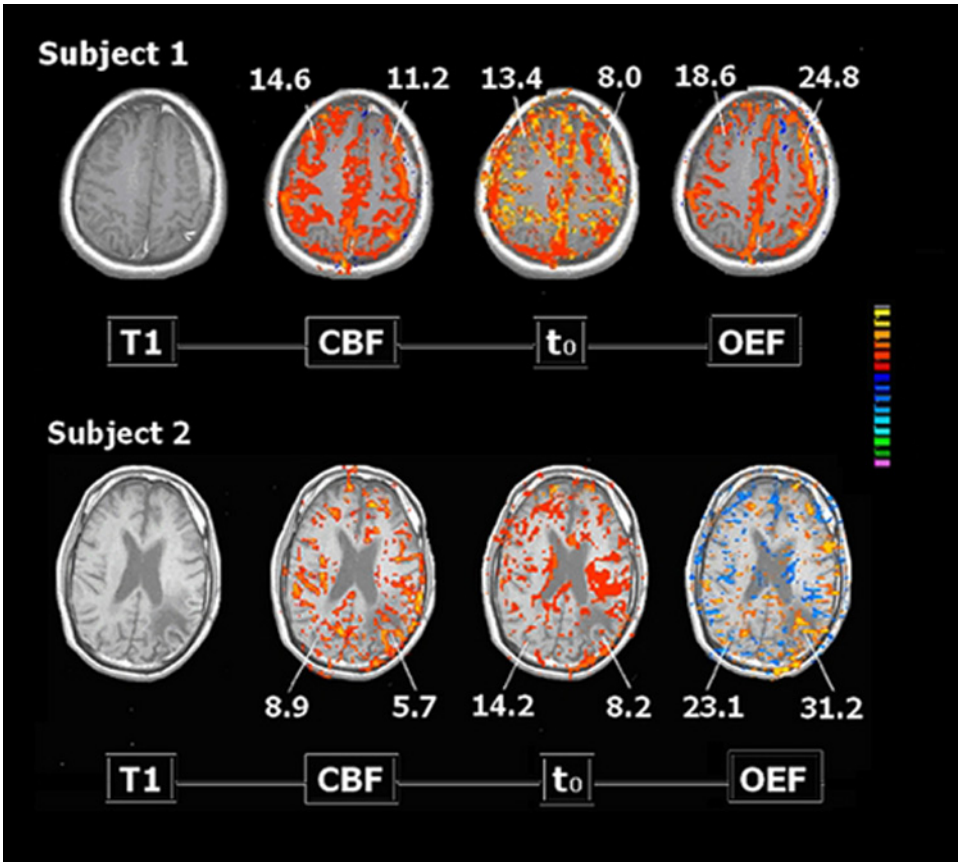

Figure 2 Data presented from two individuals with severe TBI. CBF is measured in ml/100 gm/min, OEF measured in percent change from baseline, and t_0 measured in seconds. For both subjects, the first image is a T1 weighted image revealing significant pathology (e.g., fronto-parietal hyperintensities in Subject 1 and significant tissue loss secondary to massive subdural hematoma and underlying contusion in sensory-motor areas of Subject 2). Images labeled CBF, t_0, and OEF were obtained using ASL (QUIPPS) and a BH task (see method for details; consistent with An, Lin, Celik, & Lee, 2001). In both subjects, brain regions adjacent to lesion sites reveal diminished CBF, shorter transit times, and greater OEF when compared to homologous contralateral brain regions. (Image printed with permission by the author.) *Subject 1*: Images obtained from a 20-year-old male 27 days status post motor vehicle accident in which he sustained severe head trauma. His initial GCS score was 7 and his duration of loss of consciousness was roughly 5 days. *Subject 2*: Images obtained from a 42-year-old male 4 years status post work-related landscaping accident where a branch from a tree struck the left posterior portion of his skull. His initial GCS was 3 and his duration of loss of consciousness was greater than 2 weeks.

within-subject comparisons in healthy adults reveal comparable inter-hemispheric baseline cerebrovascular physiology.

These results also provide evidence that severe brain trauma may influence baseline cerebrovascular parameters that contribute to the fMRI signal. In addition, consistent with work in animals, the case examples in this study reveal that peri-lesional areas show the greatest alterations in baseline cerebrovascular functioning.

Finally, these data indicate that fMRI-based methods are sensitive in detecting trauma-induced baseline alterations in cerebrovascular activity.

DISCUSSION

It has been the purpose of this paper to examine the use of fMRI in clinical samples and to document potential influences of brain trauma on the primary vascular factors contributing to the fMRI signal. Past work investigating brain injury, brain disease, and even normal aging reveals fundamental alterations in baseline cerebrovascular parameters. Using MRI-based methods, the pilot data here point to important differences in cerebrovascular physiology in individuals with severe brain trauma (both acute and chronic). Specifically, in individuals with TBI, perilesional areas were more likely to exhibit diminished CBF and t_0 and elevated OEF compared to a contralateral homologous region. Compared to individuals with TBI, healthy adults showed much less between-hemisphere variability in CBF, OEF, and t_0 values. These findings begin to corroborate with fMRI what has been previously established using other imaging methods in both animals and humans. The fact that alterations in CBF, OEF, and t_0 were observed here using MRI-based methods is important, as it allows for detection and control of these factors without the use of additional, and potentially invasive, methods.

A consideration for the current findings is the severity of brain injury in the case examples; these data reflect the cerebrovascular alterations associated with severe TBI (and in one case very severe TBI). It will be important to determine if similar changes in baseline alterations in blood flow are evident following milder forms of brain injury and if those differences are large enough to influence the fMRI signal.

In summary, the current data indicate that brain trauma influences the basic components contributing to the fMRI signal. The observed changes in CBF, OEF, and t_0 were particularly evident in perilesional areas. These data indicate that, in clinical studies, failure to account for cerebrovascular changes may result in between-group differences in brain ''activation'' that primarily reflect vascular, as opposed to neural, alterations. Given the apparent ubiquity of cerebrovascular alterations in special samples, any injury or disease process significant enough to influence behavior may also influence baseline cerebrovascular physiology. Because of this, the specific vascular characteristics that influence the fMRI signal and methods that correct for these vascular changes demand systematic examination. An important future step will be to standardize MRI-based manipulations (like those used here) that isolate and quantify the cerebrovascular factors influencing the fMRI signal. Such standardization will permit greater accuracy in interpreting fMRI data sets in special samples.

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REFERENCES

An, H., Lin, W., Celik, A., & Lee, Y. Z. (2001). Quantitative measurements of cerebral metabolic rate of oxygen utilization using MRI: A volunteer study. *NMR in Biomedicine*, *14*(7–8), 441–447.

Au Duong, M. V., Boulanouar, K., Audoin, B., Treseras, S., Ibarrola, D., Malikova, I. et al. (2005). Modulation of effective connectivity inside the working memory network in patients at the earliest stage of multiple sclerosis. *Neuroimage*, *24*(2), 533–538.

Audoin, B., Ibarrola, D., Ranjeva, J. P., Confort-Gouny, S., Malikova, I., Ali-Cherif, A. et al. (2003). Compensatory cortical activation observed by fMRI during a cognitive task at the earliest stage of ms. *Human Brain Mapping*, *20*(2), 51–58.

Audoin, B., Van Au Duong, M., Ranjeva, J. P., Ibarrola, D., Malikova, I., Confort-Gouny, S. et al. (2005). Magnetic resonance study of the influence of tissue damage and cortical reorganization on PASAT performance at the earliest stage of multiple sclerosis. *Human Brain Mapping*, *24*(3), 216–228.

Barbier, E. L., Lamalle, L., & Decorps, M. (2001). Methodology of brain perfusion imaging. *Journal of Magnetic Resonance Imaging*, *13*(4), 496–520.

Biagas, K. V., Grundl, P. D., Kochanek, P. M., Schiding, J. K., & Nemoto, E. M. (1996). Posttraumatic hyperemia in immature, mature, and aged rats: Autoradiographic determination of cerebral blood flow. *Journal of Neurotrauma*, *13*(4), 189–200.

Biswal, B., DeYoe, A. E., & Hyde, J. S. (1996). Reduction of physiological fluctuations in fMRI using digital filters. *Magnetic Resonance in Medicine*, *35*(1), 107–113.

Biswal, B. B. & Hyde, J. S. (1997). Contour-based registration technique to differentiate between task-activated and head motion-induced signal variations in fMRI. *Magnetic Resonance in Medicine*, *38*(3), 470–476.

Biswal, B. B., Pathak, A. P., Ulmer, J. L., & Hudetz, A. G. (2003). Decoupling of the hemodynamic and activation-induced delays in functional magnetic resonance imaging. *Journal of Computer Assisted Tomography*, *27*(2), 219–225.

Bouma, G. J., Muizelaar, J. P., Choi, S. C., Newlon, P. G., & Young, H. F. (1991). Cerebral circulation and metabolism after severe traumatic brain injury: The elusive role of ischemia. *Journal of Neurosurgery*, *75*(5), 685–693.

Chang, L., Ernst, T., Leonido-Yee, M., & Speck, O. (2000). Perfusion mri detects rCBF abnormalities in early stages of HIV-cognitive motor complex. *Neurology*, *54*(2), 389–396.

Chang, L., Speck, O., Miller, E. N., Braun, J., Jovicich, J., Koch, C. et al. (2001). Neural correlates of attention and working memory deficits in HIV patients. *Neurology*, *57*(6), 1001–1007.

Chen, J. K., Johnston, K. M., Frey, S., Petrides, M., Worsley, K., & Ptito, A. (2004). Functional abnormalities in symptomatic concussed athletes: An fMRI study. *Neuroimage*, *22*(1), 68–82.

Christodoulou, C., DeLuca, J., Ricker, J. H., Madigan, N. K., Bly, B. M., Lange, G. et al. (2001). Functional magnetic resonance imaging of working memory impairment after traumatic brain injury. *Journal of Neurology, Neurosurgery and Psychiatry*, *71*(2), 161–168.

D'Esposito, M., Deouell, L. Y., & Gazzaley, A. (2003). Alterations in the bold fMRI signal with ageing and disease: A challenge for neuroimaging. *Nature Reviews Neuroscience*, *4*(11), 863–872.

D'Esposito, M., Zarahn, E., Aguirre, G. K., & Rypma, B. (1999). The effect of normal aging on the coupling of neural activity to the bold hemodynamic response. *Neuroimage*, *10*(1), 6–14.

Desmond, J. E. & Annabel Chen, S. H. (2002). Ethical issues in the clinical application of fMRI: Factors affecting the validity and interpretation of activations. *Brain and Cognition*, *50*(3), 482–497.

Ernst, T., Chang, L., & Arnold, S. (2003). Increased glial metabolites predict increased working memory network activation in HIV brain injury. *Neuroimage*, *19*(4), 1686–1693.

Ernst, T., Chang, L., Jovicich, J., Ames, N., & Arnold, S. (2002). Abnormal brain activation on functional MRI in cognitively asymptomatic HIV patients. *Neurology*, *59*(9), 1343–1349.

Forbes, M. L., Hendrich, K. S., Kochanek, P. M., Williams, D. S., Schiding, J. K., Wisniewski, S. R. et al. (1997). Assessment of cerebral blood flow and Co_2 reactivity after controlled cortical impact by perfusion magnetic resonance imaging using arterial spin-labeling in rats. *Journal of Cerebral Blood Flow and Metabolism*, *17*(8), 865–874.

Golding, E. M. (2002). Sequelae following traumatic brain injury. The cerebrovascular perspective. *Brain Research and Brain Research Review*, *38*(3), 377–388.

Grossman, M., Koenig, P., DeVita, C., Glosser, G., Moore, P., Gee, J. et al. (2003a). Neural basis for verb processing in Alzheimer's disease: An fMRI study. *Neuropsychology*, *17*(4), 658–674.

Grossman, M., Koenig, P., Glosser, G., DeVita, C., Moore, P., Rhee, J. et al. (2003b). Neural basis for semantic memory difficulty in Alzheimer's disease: An fMRI study. *Brain*, *126*(Pt 2), 292–311.

Harrison-Felix, C., Newton, N., Hall, K. M., & Kreutzer, J. S. (1996). Descriptive findings from the traumatic brain injury model systems national database. *Journal of Head Trauma Rehabilitation, 11*(5), 1–14.

Hattori, N., Huang, S. C., Wu, H. M., Liao, W., Glenn, T. C., Vespa, P. M. et al. (2003). Pet investigation of post-traumatic cerebral blood volume and blood flow. *Acta Neurochirurgica Supplement*, *86*, 49–52.

Hattori, N., Huang, S. C., Wu, H. M., Liao, W., Glenn, T. C., Vespa, P. M. et al. (2004). Acute changes in regional cerebral (18)f-FDG kinetics in patients with traumatic brain injury. *Journal of Nuclear Medicine*, *45*(5), 775–783.

Hennig, J., Speck, O., Koch, M. A., & Weiller, C. (2003). Functional magnetic resonance imaging: A review of methodological aspects and clinical applications. *Journal of Magnetic Resonance Imaging*, *18*(1), 1–15.

Hillary, F. G., Chiaravalloti, N. D., Ricker, J. H., Steffener, J., Bly, B. M., Lange, G. et al. (2003). An investigation of working memory rehearsal in multiple sclerosis using fMRI. *Journal of Clinical and Experimental Neuropsychology*, *25*(7), 965–978.

Kamper, A. M., Spilt, A., de Craen, A. J., van Buchem, M. A., Westendorp, R. G., & Blauw, G. J. (2004). Basal cerebral blood flow is dependent on the nitric oxide pathway in elderly but not in young healthy men. *Experimental Gerontology*, *39*(8), 1245–1248.

Kannurpatti, S. S., Biswal, B. B., & Hudetz, A. G., (2003). Regional dynamics of the fMRI-BOLD signal response to hypoxia-hypercapnia in the rat brain. *Journal of Magnetic Resonance Imaging*, *17*(6), 641–647.

Kastrup, A., Kruger, G., Neumann-Haefelin, T., & Moseley, M. E. (2001). Assessment of cerebrovascular reactivity with functional magnetic resonance imaging: Comparison of co(2) and breath holding. *Magnetic Resonance Imaging*, *19*(1), 13–20.

Kastrup, A., Li, T. Q., Glover, G. H., & Moseley, M. E. (1999). Cerebral blood flow-related signal changes during breath-holding. *AJNR American Journal of Neuroradiology*, *20*(7), 1233–1238.

Kastrup, A., Li, T. Q., Takahashi, A., Glover, G. H., & Moseley, M. E. (1998). Functional magnetic resonance imaging of regional cerebral blood oxygenation changes during breath holding. *Stroke*, *29*(12), 2641–2645.

Kochanek, P. M., Hendrich, K. S., Dixon, C. E., Schiding, J. K., Williams, D. S., & Ho, C. (2002). Cerebral blood flow at one year after controlled cortical impact in rats: Assessment by magnetic resonance imaging. *Journal of Neurotrauma*, *19*(9), 1029–1037.

Kochanek, P. M., Marion, D. W., Zhang, W., Schiding, J. K., White, M., Palmer, A. M. et al. (1995). Severe controlled cortical impact in rats: Assessment of cerebral edema, blood flow, and contusion volume. *Journal of Neurotrauma*, *12*(6), 1015–1025.

Law, M., Saindane, A. M., Ge, Y., Babb, J. S., Johnson, G., Mannon, L. J. et al. (2004). Microvascular abnormality in relapsing-remitting multiple sclerosis: Perfusion MR imaging findings in normal-appearing white matter. *Radiology*, *231*(3), 645–652.

Levin, H. S. (1995). Prediction of recovery from traumatic brain injury. *Journal of Neurotrauma*, *12*(5), 913–922.

Li, T. Q., Kastrup, A., Takahashi, A. M., & Moseley, M. E. (1999). Functional MRI of human brain during breath holding by BOLD and FAIR techniques. *Neuroimage*, *9*(2), 243–249.

Mainero, C., Caramia, F., Pozzilli, C., Pisani, A., Pestalozza, I., Borriello, G. et al. (2004). fMRI evidence of brain reorganization during attention and memory tasks in multiple sclerosis. *Neuroimage*, *21*(3), 858–867.

Maini, C. L., Pigorini, F., Pau, F. M., Volpini, V., Galgani, S., Rosci, M. A. et al. (1990). Cortical cerebral blood flow in HIV-1-related dementia complex. *Nuclear Medicine Communications*, *11*(9), 639–648.

Mandeville, J. B., Marota, J. J., Kosofsky, B. E., Keltner, J. R., Weissleder, R., Rosen, B. R. et al. (1998). Dynamic functional imaging of relative cerebral blood volume during rat forepaw stimulation. *Magnetic Resonance in Medicine*, *39*(4), 615–624.

Mandzia, J., Black, S., Grady, C., McAndrews, M. P., & Graham, S. (2002). Encoding and retrieval in aging and memory loss, a fMRI study. *Brain and Cognition*, *49*(2), 225–228.

Manoach, D. S., Gollub, R. L., Benson, E. S., Searl, M. M., Goff, D. C., Halpern, E. et al. (2000). Schizophrenic subjects show aberrant fMRI activation of dorsolateral prefrontal cortex and basal ganglia during working memory performance. *Biological Psychiatry*, *48*(2), 99–109.

Martin, N. A., Patwardhan, R. V., Alexander, M. J., Africk, C. Z., Lee, J. H., Shalmon, E. et al. (1997). Characterization of cerebral hemodynamic phases following severe head trauma: Hypoperfusion, hyperemia, and vasospasm. *Journal of Neurosurgery*, *87*(1), 9–19.

McAllister, T. W., Saykin, A. J., Flashman, L. A., Sparling, M. B., Johnson, S. C., Guerin, S. J. et al. (1999). Brain activation during working memory 1 month after mild traumatic brain injury: A functional MRI study. *Neurology*, *53*(6), 1300–1308.

McAllister, T. W., Sparling, M. B., Flashman, L. A., Guerin, S. J., Mamourian, A. C., & Saykin, A. J. (2001). Differential working memory load effects after mild traumatic brain injury. *Neuroimage*, *14*(5), 1004–1012.

Meltzer, C. C., Cantwell, M. N., Greer, P. J., Ben-Eliezer, D., Smith, G., Frank, G. et al. (2000). Does cerebral blood flow decline in healthy aging? A pet study with partial-volume correction. *Journal of Nuclear Medicine*, *41*(11), 1842–1848.

Perlstein, W. M., Carter, C. S., Noll, D. C., & Cohen, J. D. (2001). Relation of prefrontal cortex dysfunction to working memory and symptoms in schizophrenia. *American Journal of Psychiatry*, *158*(7), 1105–1113.

Perlstein, W. M., Cole, M. A., Demery, J. A., Seignourel, P. J., Dixit, N. K., Larson, M. J. et al. (2004). Parametric manipulation of working memory load in traumatic brain injury: Behavioral and neural correlates. *Journal of the International Neuropsychological Society*, *10*(5), 724–741.

Perlstein, W. M., Dixit, N. K., Carter, C. S., Noll, D. C., & Cohen, J. D. (2003). Prefrontal cortex dysfunction mediates deficits in working memory and prepotent responding in schizophrenia. *Biological Psychiatry*, *53*(1), 25–38.

Prigatano, G. P., Johnson, S. C., & Gale, S. D. (2004). Neuroimaging correlates of the Halstead finger tapping test several years post-traumatic brain injury. *Brain Injury*, *18*(7), 661–669.

Ricker, J. H., Hillary, F. G., & DeLuca, J. (2001). Functionally activated brain imaging (o-15 PET and fMRI) in the study of learning and memory after traumatic brain injury. *Journal of Head Trauma Rehabilitation*, *16*(2), 191–205.

Rosenthal, M., & Ricker, J. H. (2000). Traumatic brain injury. In R. G. Frank & T. R. Elliot (Eds.), *Handbook of rehabilitation psychology* (pp. 56–57). Washington DC: American Psychological Association.

Schroder, M. L., Muizelaar, J. P., Kuta, A. J., & Choi, S. C. (1996). Thresholds for cerebral ischemia after severe head injury: Relationship with late CT findings and outcome. *Journal of Neurotrauma*, *13*(1), 17–23.

Segatore, M., & Way, C. (1992). The Glasgow Coma Scale: Time for a change. *Heart & Lung, 21*, 548–557.

Sierra, C., de la Sierra, A., Chamorro, A., Larrousse, M., Domenech, M., & Coca, A. (2004). Cerebral hemodynamics and silent cerebral white matter lesions in middle-aged essential hypertensive patients. *Blood Pressure*, *13*(5), 304–309.

Staffen, W., Mair, A., Zauner, H., Unterrainer, J., Niederhofer, H., Kutzelnigg, A. et al. (2002). Cognitive function and fMRI in patients with multiple sclerosis: Evidence for compensatory cortical activation during an attention task. *Brain*, *125*(Pt 6), 1275–1282.

Sutton, R. L., Hovda, D. A., Adelson, P. D., Benzel, E. C., & Becker, D. P. (1994). Metabolic changes following cortical contusion: Relationships to edema and morphological changes. *Acta Neurochirurgica Supplement (Wien)*, *60*, 446–448.

Swank, R. L., Roth, J. G., & Woody, D. C. Jr. (1983). Cerebral blood flow and red cell delivery in normal subjects and in multiple sclerosis. *Neurological Research*, *5*(1), 37–59.

Tran Dinh, Y. R., Mamo, H., Cervoni, J., Caulin, C., & Saimot, A. C. (1990). Disturbances in the cerebral perfusion of human immune deficiency virus-1 seropositive asymptomatic subjects: A quantitative tomography study of 18 cases. *Journal of Nuclear Medicine*, *31*(10), 1601–1607.

Turner, R., Le Bihan, D., Moonen, C. T., Despres, D., & Frank, J. (1991). Echo-planar time course MRI of cat brain oxygenation changes. *Magnetic Resonance in Medicine*, *22*(1), 159–166.

Wishart, H. A., Saykin, A. J., McDonald, B. C., Mamourian, A. C., Flashman, L. A., Schuschu, K. R. et al. (2004). Brain activation patterns associated with working memory in relapsing-remitting MS. *Neurology*, *62*(2), 234–238.

Yamaki, T., Imahori, Y., Ohmori, Y., Yoshino, E., Hohri, T., Ebisu, T. et al. (1996a). Cerebral hemodynamics and metabolism of severe diffuse brain injury measured by pet. *Journal of Nuclear Medicine*, *37*(7), 1166–1170.

Yamaki, T., Yoshino, E., Fujimoto, M., Ohmori, Y., Imahori, Y., & Ueda, S. (1996b). Chronological positron emission tomographic study of severe diffuse brain injury in the chronic stage. *Journal of Trauma*, *40*(1), 50–56.

Zaharchuk, G., Mandeville, J. B., Bogdanov, A. A. Jr., Weissleder, R., Rosen, B. R., & Marota, J. J. (1999). Cerebrovascular dynamics of autoregulation and hypoperfusion. An MRI study of CBF and changes in total and microvascular cerebral blood volume during hemorrhagic hypotension. *Stroke*, *30*(10), 2197–2204; discussion, 2204–2195.