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Vascular dynamics and BOLD fMRI: CBF level effects and analysis considerations

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Changes in the cerebral blood flow (CBF) baseline produce significant changes to the hemodynamic response. This work shows that increases in the baseline blood flow level produce blood oxygenation-level dependent (BOLD) and blood flow responses that are slower and lower in amplitude, while decreases in the baseline blood flow level produce faster and higher amplitude hemodynamic responses. This effect was characterized using a vascular model of the hemodynamic response that separated arterial blood flow response from the venous blood volume response and linked the input stimulus to the vascular response. The model predicted the baseline blood flow level effects to be dominated by changes in the arterial vasculature. Specifically, it predicted changes in the arterial blood flow time constant and venous blood volume time constant parameters of +294% and −24%, respectively, for a 27% increase in the baseline blood flow. The vascular model performance was compared to an empirical model of the hemodynamic response. The vascular and empirical hemodynamic models captured most of the baseline blood flow level effects observed and can be used to correct for these effects in fMRI data. While the empirical hemodynamic model is easy to implement, it did not incorporate any explicit physiological information.

Keywords: BOLD, CBF; fMRI; Linear Analysis; Hypercapnia; Hypocapnia; Vascular Reactivity; CBV

Introduction

Vasculature dynamics play a very important role in hemodynamics, especially in the generation of the blood oxygenation-level dependent (BOLD) response observed during brain activation using functional magnetic resonance imaging (fMRI) (Ogawa et al., 1990; Kwong et al., 1992). The vascular response is believed to arise in response to the metabolic needs of the working brain, in particular, the supply and delivery of oxygen and glucose (Fox et al., 1988; Magistretti et al., 1999). Temporally, the vascular response is slower compared to the changes in neuronal activity, questioning the degree to which the vasculature may be under direct neuronal control. This is not necessarily detrimental to studies that make inferences on working brain patterns from information encoded in the hemodynamic response since vascular responses have been measured to stimuli tens of milliseconds in duration (Savoy et al., 1995; Menon et al., 1998; Lewis and Miall, 2003). However, the close temporal correlation between the vascular and BOLD responses to brain stimulation is affected by properties of the vascular response that are not dependent on the neuronal activity. For example, the vascular response has been shown to vary as a function of the blood flow level (Bandettini and Wong, 1997; Cohen et al., 2002; Riecker et al., 2003; Kannurpatti et al., 2003).

A hypercapnia challenge is known to increase cerebral blood flow (CBF) globally in the brain. Hypercapnia manipulations have been shown to also increase the BOLD baseline (Davis et al., 1998; Cohen et al., 2002) with regional variations that may be related to differences in baseline cerebral blood flow and/or volume (Kastrup et al., 1999). Moreover, visual stimulation under normocapnia and hypercapnia conditions produces different BOLD fMRI responses although these manipulations do not produce known changes in oxygen metabolism (Cohen, 2002). Cohen et al. (2002), reported slower BOLD responses with increases in the baseline blood flow and faster BOLD responses with decreases in the baseline blood flow level. This is not the only known non-linear behavior of the BOLD response; other non-linear properties have been reported, such as non-linearities in the hemodynamic response with respect to stimulus duration (Vazquez and Noll, 1998; Miller et al., 2001).

The objective of this manuscript is to characterize the effect of the cerebral blood flow baseline on the hemodynamic response using a vascular hemodynamic model. The vascular hemodynamic

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model implemented provided a separate characterization of arterial and venous properties of the vascular response given blood flow and BOLD fMRI responses. Additionally, the model linked the vascular response to the stimulus via an assumed neuronal tissue response. The vascular model was compared to an empirical model of the hemodynamic response that also captured the baseline blood flow level effects on the hemodynamic response. Both vascular and empirical hemodynamic models provide guidance on how to account and correct for these effects in fMRI data analysis.

Materials and methods

Two experiments were performed to investigate the impact of the vascular dynamics on the hemodynamic response. One experiment measured evoked BOLD responses under increases and decreases in the blood flow baseline, while the other experiment measured blood flow and BOLD evoked responses under increases in the blood flow baseline. The data from these experiments were used to estimate the parameters of the vascular hemodynamic model.

Experiment 1: Visual BOLD fMRI data at 7 T

The first experiment consisted of two sessions for which subjects were recruited and scanned. In the first session, visual stimuli were presented to the subjects during normocapnia and hypercapnia conditions (Cohen et al., 2002). The visual stimulus consisted of a full-field black and white checkerboard alternating at a frequency of 4.5 Hz for 4 s followed by 41 s of rest (uniform grey screen). The first stimulus in each scan was presented after 30 s of rest and the stimulus and rest periods were repeated 9 times. Hypercapnia was induced at the onset of the third stimulus in the scan and maintained for 3 min via the administration of a 5% carbon dioxide enriched air mixture where nitrogen gas was displaced to maintain a constant oxygen concentration. In a separate session, visual stimuli were presented under normocapnia and hypocapnia conditions in similar fashion to the previous session. Hypocapnia was induced by rehearsed hyperventilation. The scans in each session were repeated 3 to 6 times.

The scans in this experiment were performed using a 7 T MRI scanner (Magnex Scientific, Abington, UK) controlled with a Varian Unity console (Varian, Palo Alto, CA, USA) at the University of Minnesota. For further details please refer to Cohen, 2002.

Experiment 2: Motor FAIR and BOLD fMRI data at 3 T

In the second experiment the subjects were instructed to perform a visually cued motor task (finger opposition) while being scanned. The subjects performed the motor task under hyperoxia and hyperoxic–hypercapnia conditions. Hypercapnia and hyperoxia were induced in this experiment using a 5% carbon dioxide, 95% oxygen gas mixture (i.e., carbogen) and 100% oxygen gas, respectively. The duration of the motor task varied over the scan session with durations of 12 and 6 s and resting periods of 38 and 34 s, respectively. Each stimulation and rest condition was repeated 20 times in each experiment. Hyperoxia was induced prior to the beginning of each scan and hypercapnia was induced at the onset of the 10th stimulus and lasted for the following 10 stimuli and rest conditions. One additional experiment was performed under hyperoxia conditions where the stimulus and rest periods lasted 60 s each, repeated 10 times.

The imaging in this experiment was performed using a standard quadrature birdcage head coil and a 3 T MRI scanner (GE Medical Systems, Milwaukee, WI USA) at the University of Michigan. Blood flow and BOLD measurements were performed in this experiment using a flow-sensitive alternating inversion recovery (FAIR), gradient-echo acquisition (Kim, 1995). A single axial slice (7 mm thick) over the motor cortex of the subjects, localized from a whole-brain block design BOLD acquisition, was scanned using a dual-echo, gradient-echo FAIR acquisition with spiral readouts. The imaging parameters were: 20×20 cm^2 FOV, 64×64 matrix, $2.0\times$ inversion slab width, 8 ms TE (echo 1), 28 ms TE (echo 2), 1900 ms TI, 2000 ms TR and 90° flip angle. The data from the first echo was used to determine the CBF changes while the data from the second echo was used to determine the BOLD signal changes. The images from the selective and non-selective inversion conditions of the FAIR acquisition were linearly interpolated to every TR in order to obtain CBF and BOLD images at every TR. Informed consent was obtained from all subjects in this experiment ($n = 8$) in accordance with the University of Michigan Institutional Review Board. All subjects were screened to be in good health.

Vascular hemodynamic model

A vascular model of the hemodynamic response was used to characterize the vascular effects present in the data by describing the arterial vascular response to neuronal stimulation and the eventual generation of the BOLD effect in the venous side. This model is referred to in this manuscript as the vascular hemodynamic model or the vascular model (Fig. 1, top).

The vascular hemodynamic model consisted of a pre-vascular portion that linked the stimulus (of duration w) to the vascular response via the neuronal tissue response. A summary of the parameters of the vascular hemodynamic model is provided in Table 1. The neuronal response (f_{neu}) was assumed to resemble neuronal adaptation effects observed with cortical local field potential (LFP) measurements as well as the possibility of a sustained neuronal response following evoked stimulation (Logothetis et al., 2001; Muller et al., 1999). The sustained neuronal response was modeled as a prolonged neuronal response period of additional duration (w_{ex}) while the neuronal adaptation effect was represented by the product of the stimulus with a time-locked exponential function of amplitude N and time constant k_{lpf} (Eq. (1)). The time constant for the neuronal adaptation effect was fixed to 1/1.5 s^{-1} (Logothetis et al., 2001). These sharp changes in the neuronal response were smoothed prior to producing the vascular response using a first-order linear model, analogous to a passive intermediary process (U in Eq. (2)). The time constant of this intermediary process (τ_{n}) was fixed to 2 s and can be related to the diffusion of small vasoactive chemicals across a distance of about 100 μm.

$$f_{\text{neu}} = S(w + w_{\text{ex}}, t - t_0)(1 + N\exp(-k_{\text{lfp}}(t - t_0)) \quad (1)$$

$$\frac{dU}{dt} = \frac{1}{\tau_{\text{n}}}(f_{\text{neu}}(S) - U(t)) \quad (2)$$

The changes in arterial blood flow (F_{in}) were then produced considering the intermediary and neuronal responses assuming a