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● *Original Contribution*

THE LAG OF CEREBRAL HEMODYNAMICS WITH RAPIDLY ALTERNATING PERIODIC STIMULATION: MODELING FOR FUNCTIONAL MRI

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A mathematical model that characterizes the response of venous oxygenation to changes in cerebral blood flow (rCBF) and oxygen consumption has been previously presented. We use this model to examine the dampening phenomenon in functional MRI (fMRI) signals with rapidly alternating periodic stimulation bursts. Using a mass balance approach, the equations for an input-output model are derived and solved using Matlab (the Math Works Inc.). Changes in venous oxygenation are related to the results of fMRI experiments using progressively shorter periods of stimulation. An impulse-response function for the model is derived in an attempt to explore the source of the lag in cerebral hemodynamics. Increasing the frequency of stimulation bursts eventually produces a dampening in the fMRI signal. The dampening phenomenon in fMRI signals occurs with stimulation of high frequency on-off alternation. The dynamics of signal dampening, as well as the impulse-response function of a blood oxygen level-dependent model, lend strong indirect support to the hypothesis that blood oxygen level-dependent contrast at the level of the venous blood pool, rather than R1 inflow effects or changes in oxygenation at the level of the capillary bed, underlies the observed signal changes in fMRI. © 1998 Elsevier Science Inc.

Keywords: **MR activation; Functional MRI; Cerebral blood flow; Blood oxygenation; Cerebral hemodynamics; Impulse–Response.**

INTRODUCTION

With the maturation of functional MRI (fMRI) as a field of active investigation, various groups are now beginning to use fMRI to examine the physiology of cerebral activation.[1–8]

Central to extracting information regarding cerebral hemodynamics with activation, however, is an understanding of the contrast mechanisms in fMRI. Only when we better understand what the fMRI signals represent can we begin to extract information about cerebral physiology from the dynamics of such signals.

Thus far, most investigators have utilized conventional gradient-echo or T_2*-weighted echo planar magnetic resonance (MR) to display signal increases in appropriate anatomical locations with motor and sensory stimulation.[1–14] The generally proposed mechanism for the observed signal enhancement has been termed blood oxygen level-dependent (BOLD), and involves local increases in the venous oxyhemoglobin/deoxyhemoglobin ratio thought to accompany neuronal activation.[1–3,9,12] The signal increases accompanying functional stimulation have been widely considered to represent an initial uncoupling of cerebral blood flow and oxidative metabolism following a neuronal activation burst, leading to an excess of flow over metabolism.[15–18] More recently, mathematical modeling suggests that the excess of flow over metabolism represents instead a tight coupling of flow and oxidative metabolism in the setting of a relative limitation in O_2 availability.[19] With increases in arterial well-oxygenated blood flow in excess of local O_2 con-

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sumption,[16,18] the venous blood pool will show a significant decrease in deoxyhemoglobin concentration. This decrease in paramagnetic deoxyhemoglobin will in turn lead to less intravoxel dephasing, and result in signal increases with T_2*- (or T_2)-weighted sequences.[1–3,9,12]

There is some evidence that the postulated decreases in deoxyhemoglobin with functional stimulation have been demonstrated with near-infrared spectroscopy.[20,21] Further evidence in support of the BOLD mechanism has been in the form of several studies directly demonstrating the effect of altering cerebral oxygenation on MRI signal.[22–24]

More recently, however, some investigators have called into question the basic validity of the notion of BOLD contrast as the predominant mechanism underlying contrast in fMRI.[8]

It has been variously postulated that inflow R1 effects may contribute significantly to the observed fMRI signal,[25] and that the observed signal may in large part be due to changes in CSF oxygenation and CSF flow and to stimulus correlated motion effects.[8]

Mathematical modeling of cerebral venous oxygenation may aid in understanding the basic mechanisms underlying fMRI signal, and may shed light on the cerebral hemodynamics that accompany functional activation.[26,27]

Specifically, this paper seeks to examine the fMRI signal response to rapidly alternating periodic stimulation, using both a mathematical model of cerebral venous oxygenation and actual subject data of motor stimulation with progressively shorter bursts of "on-off" stimulation. The hypothesis presented is that the changes in cerebral hemodynamics that accompany cerebral activation occur in finite time, on the order of a few seconds;[10,28] hence, as the frequency of periodic stimulation bursts increases, changes in cerebral venous oxygenation begin to lag behind the alternation frequency of the on-off bursts, with a dampening in the peaks and troughs of the fMRI signal. This dampening phenomenon is, on the surface, nonspecific. It may result predominantly from a lag in the rCBF response to cortical activation, a lag in the change of cerebral venous oxygenation in response to increases in cerebral blood flow (CBF), or a mixture of both.

The model presented accounts explicitly for both sources of lag and demonstrates that the dampening phenomenon is well-modeled, vis-a-vis previously presented empiric data, with an assumption that CBF adjusts fairly rapidly to cortical activation, and with a natural ensuing lag as the new end-capillary blood washes into the venous pool. This tentative conclusion is further tested by comparing mammalian and human flowmetry data in the setting of cortical activation to the time course of fMRI signals, and by examining the impulse response function of our proposed model.

The observed dampening of fMRI signals with rapidly alternating periodic stimulation in fact closely resembles a convolution of a stimulus pattern with an impulse response function which accounts for the time lags discussed above. Previous investigators have also presented impulse–response function analyses of the fMRI response, using a linear time-invariant model.[29]

To further test the above model, it was used to examine a recently described phenomenon of non-linearity in some fMRI experiments.[29,30] This topic will be treated more fully in a forthcoming manuscript, but an initial exposition helps to validate our present model.

Boynton et al., in their seminal recent work, have modeled the fMRI response as a linear time-invariant system fully characterizing the spatial and temporal averaging of neural activity.[29] Among the experiments performed in that work was an attempt to reconstruct an fMRI signal of a longer pulse duration from time-shifted summed copies of the fMRI signals to pulses of shorter duration. For example, according to their presented linear system, the response to a stimulus pulse of 12-s duration should be predictable by summing four shifted copies of the fMRI response to a stimulus pulse of 3-s duration. The results of Boynton et al. revealed that although fMRI signals are in general consistent with a linear transform model, there was a subtle yet systematic failure of the predictions: the responses to the shorter (3 s) pulse tend to overestimate the responses to longer pulses. The reason for this discrepancy was unclear, but was attributed to possible neural adaptation with the longer pulses.[29]

If, as our model suggests, the main source of lag is in the adjustment of cerebral venous oxygenation in response to flow, then the impulse response function of our model should be able to, at least partially, explain the observed deviations from linearity, and to accurately model the results obtained by Boynton et al.

MATERIALS AND METHODS

Mathematical Model

In prior work, we have developed a model to estimate changes in venous oxyhemoglobin concentrations ($[O_2]_v$) based upon changes in regional cerebral blood flow (F), cerebral blood volume (V) and regional O_2 consumption (C′) and correlated it with existing fMRI data.[26] A simplified derivation is presented here, for the purposes of examining the form of the impulse response function. A mass-balance approach is used to calculate end-capillary O_2 concentrations with activation, and associated changes in blood flow and O_2 consumption. This is termed $[O_2]'_v(t)$, denoting the O_2 concentration from the local capillary bed being emptied into the venous pool.

At baseline, by Fick's law, regional O_2 consumption can be written as the product of cerebral blood flow (F) and the difference between arterial O_2 concentration ($[O_2]_a$) and end-capillary O_2 concentration ($[O_2]'_v$):

$$C'[O_2] = F * \{[O_2]a - [O_2]'v\} \quad (1)$$

Rewriting this equation as a time variable equation in terms of an O_2 extraction function E(t), we get:

$$C'(t)[O_2] = F(t) * [O_2]a * E(t) \quad (2)$$

where if consumption remains constant, then E(t)F(t) remains constant, and where end-capillary O_2 concentration is a time variable described by:

$$[O_2]'v(t) = [O_2]a * \{1 - E(t)\} \quad (3)$$

To yield a true venous oxyhemoglobin level at time t, $[O_2]_v(t)$, the incremental $[O_2]'_v(t)$ is assumed to be flowing into, and instantaneously mixing with, the venous pool, where the existing venous O_2 concentration is $[O_2]_v(t)$. If the venous blood volume is considered a constant V, then a mass-balance equation for venous O_2 concentration can be written:

$$F(t) * [O2]'v(t) - F(t) * [O2]v(t) = \frac{d}{dt}([O2]_v(t) * V) \quad (4)$$

where the right hand side of the equation represents the time derivative of total venous O_2 content, and the left-hand side represents the difference between inflowing and outflowing O_2 flux. The solution of a more general form of this equation, where cerebral blood volume is considered a time variable, and where an exponential form of E(t) is assumed, has been presented elsewhere.[26]

Equation (4) describes the dynamic change of $[O_2]_v(t)$ to a new equilibrium value after a change in CBF, and hence models the lag inherent in the response of cerebral venous oxygenation to changes in CBF. This equation can now be used to derive an impulse response function for this system. For ease of readability, the variables can be relabeled as follows:

$y(t) = [O_2]_v(t)$
$a(t) = F(t)/V$
$x(t) = [F(t)/V] * [O_2]'_v(t)$

The system can now be rewritten as

$$dy/dt + a(t)y(t) = x(t) \quad (5)$$

This can be multiplied by an integrating factor of the form

$e^{\int_0^t a(\sigma)d\sigma}$, and rewritten such that we have

$$\frac{d}{dt}[e^{\int_0^t a(\sigma)d\sigma} y(y)] = e^{\int_0^t a(\sigma)d\sigma} x(t) \quad (6)$$

This can be solved directly as follos:[31]

$$e^{\int_0^t a(\sigma)d\sigma}\, y(t) = \int_0^\tau e^{\int_0^\tau a(\sigma)d\sigma} x(\tau)d\tau \quad (7)$$

Equation (7) can be re-expressed in terms of y(t) as follows:[31]

$$y(t) = \int_0^t (e^{\int_0^\tau a(\sigma)d\sigma} e^{-\int_o^t a(\sigma)d\sigma}) x(\tau)d\tau \quad (8)$$

Equation (8) can be further simplified into the following form:[31]

$$y(t) = \int_0^\tau e^{\int_t^\tau a(\sigma)d\sigma} x(\tau)d\tau \quad (9)$$

Assuming that the system stays at baseline prior to t = 0, and introducing a unit step function, Eq. (9) can once more be rewritten to directly yield the impulse-response function of this system:[31]

$$y(t) = \int_{-\infty}^{\infty} e^{\int_t^\tau a(\sigma)d\sigma} U(t-\tau) x(\tau)d\tau \quad (10)$$

In this form, the impulse-response function is readily apparent as

$$h(t, \tau) = e^{\int_t^\tau a(\sigma)d\sigma} U(t-\tau) \quad (11)$$

Now substituting back for the function a(t), the impulse-response function can be written explicitly in terms of flow F(t) as:

$$h(t, \tau) = e^{\int_t^\tau (F(\sigma)/V)d\sigma} U(t-\tau) \quad (12)$$

and the explicit solution to the entire system can be written from Eq. (9) as:

$$[O2v](t) = \int_0^t e^{\int_t^\tau (F(\sigma)/V)d\sigma} \{(F(\tau)/V)[O2]a(1-E(\tau)\}d\tau \quad (13)$$

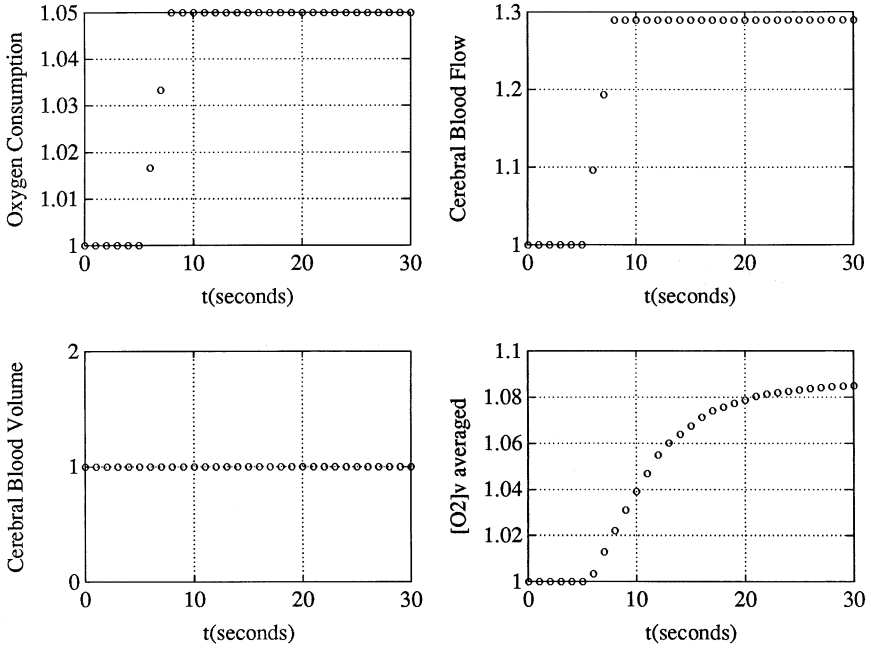

Fig. 1. Model simulation of human visual activation using actual physiologic data. Visual stimulation is assumed to commence at 5 s. In response, CBF increases by 29% over 3 s, while O_2 consumption increases by only 5%, demonstrating the known uncoupling of flow and oxidative metabolism at the initiation of a neuronal activation burst. As a result of these hemodynamic changes, venous oxygenation is calculated to increase by 8.1%, while the O_2 extraction fraction is calculated to decrease by 19% (see Discussion).

Simulations

Simulations are performed to estimate the changes in cerebral venous oxygenation with changes in flow. The following assumptions are made: with functional stimulation, CBF is assumed to increase by 30%, drawing upon the positron emission tomography (PET) results of Fox et al.[16] Also, CBF is assumed to increase and decrease linearly over a time course of 3 s at the beginning and end of a functional stimulation "on" period.[28] Simulations are performed for on-off periods of progressively shorter duration: 20, 12, 6, 3, and 1 s.

Then, the effect of changes in the rate of adjustment of CBF with functional stimulation are simulated for varying time courses of flow adjustment, as well for different levels of peak flow. To test the linearity of the system, the predicted venous oxygenation in response to a 12-s pulse is compared to a linear summation of the time-shifted response to a 3-s pulse.

MRI Imaging

Single-shot 64 × 64 resolution echo planar imaging on a standard clinical 1.5 Tesla GE Signa scanner with an inserted three-axis balanced torque head gradient coil designed for rapid gradient switching was performed. A shielded quadrature elliptical endcapped transmit/receive birdcage radiofrequency (RF) coil, inserted inside the gradient coil, is used to obtain high-quality images through the entire brain volume. Images were obtained on five subjects, with TR 1000, TE 40 ms, and field of view 24 cm with slice thickness 10 mm. Subjects were cued to tap, bilaterally, their fingers to thumb in a self-paced consistent pattern. On-off cycles ranged from 0.02 Hz (25 s on and 25 s off) to 0.5 Hz (1 s on, 1 s off). A region of interest in the left motor cortex, of approximately 30 voxels, was used to generate a time-course of average fMRI signal.

RESULTS

The General Workings of the Mathematical Model

The general workings of the mathematical model are displayed in Fig. 1. A simulation is performed using data generated by Fox et al. in their landmark PET study of cortical activation in response to somatosensory stimulation.[16] In that study, blood flow increased by 29%, whereas O_2 consumption increased by only 5%. In response to those prescribed parameters, our model shows an asymptotic increase in venous oxyhemoglobin by 8.6%, with 75% of peak change attained by approximately 8 s post stimulation.

Modeling the Dampening Phenomenon

Figure 2 (A-E) displays the simulation results of changes in venous oxygenation with progressively

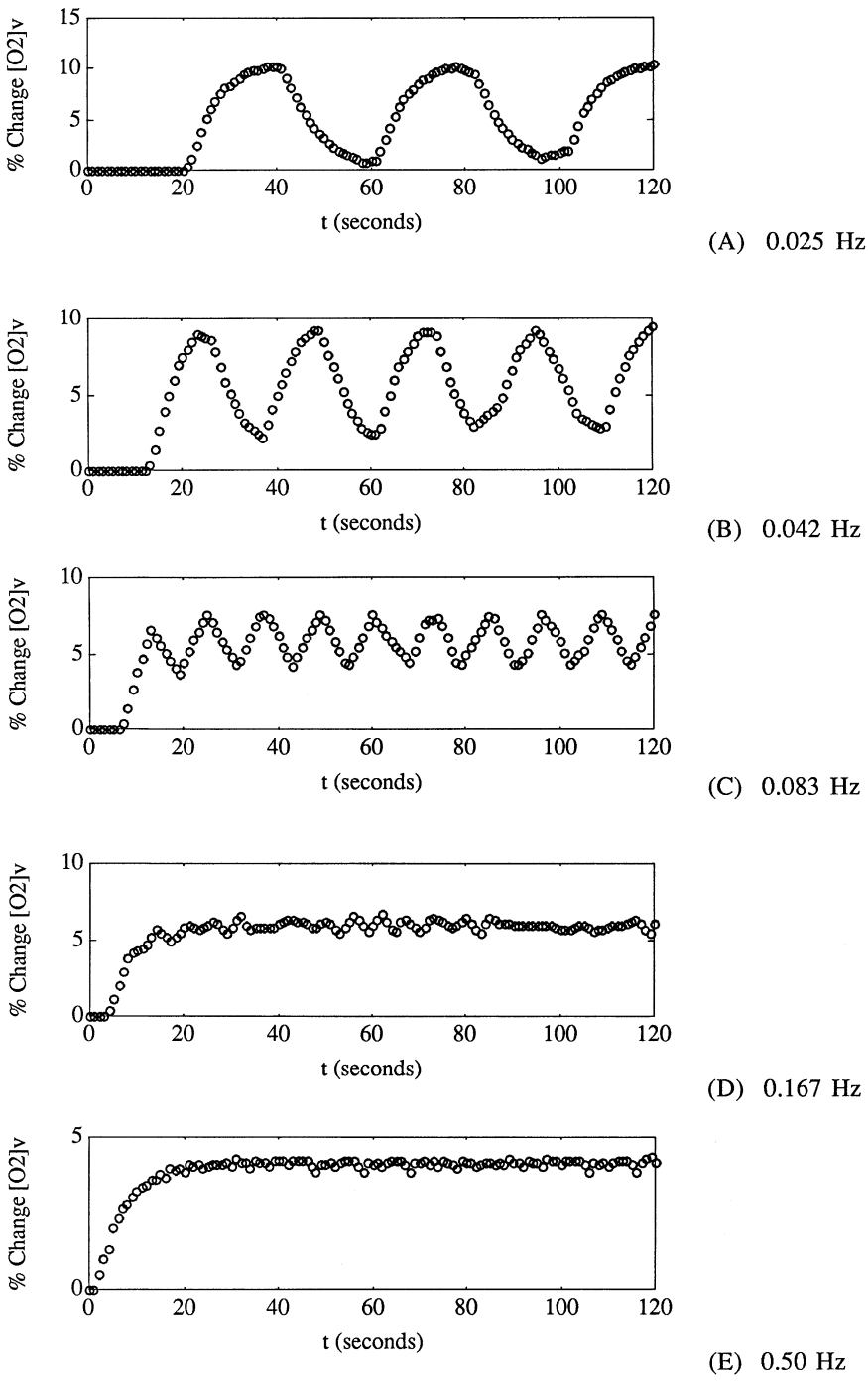

Fig. 2. Model simulation results of percentage change in cerebral venous oxygenation for progressively shorter on-off stimulation periods, ranging from 20 s "on": 20 s "off" (0.025 Hz), to 1 s "on": 1 s "off" (0.5 Hz). Hysteresis is clearly evident at a frequency of 0.167 Hz.

shorter periods of on-off stimulation. It is noted that at periods of 20 and 12 s, there are well-defined peaks and troughs of venous oxygenation corresponding to the on and off periods of stimulation respectively. At 20 s (Fig. 2A), there is 12% increase in venous oxyhemoglobin between the on and off periods, presumably leading to the strongly observed peaks in fMRI signal. At a switching frequency of 0.042 Hz (12 s on, 12 s off) there are

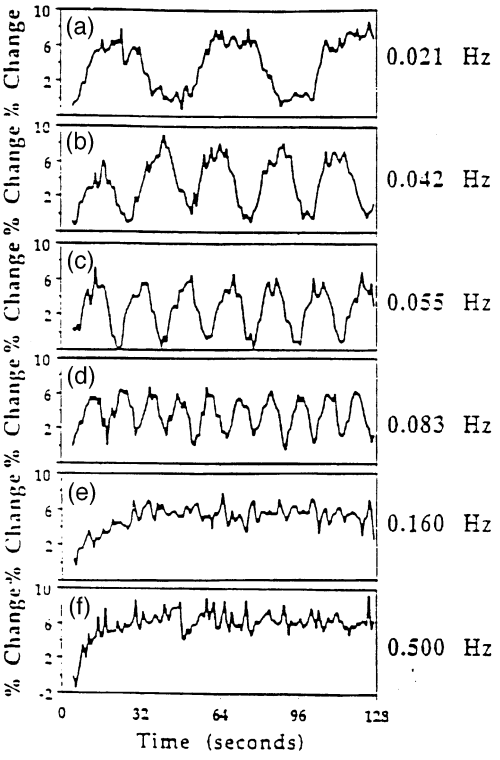

Fig. 3. Measured fMRI percent signal change in motor cortex with progressively shorter on-off stimulation periods.

still well-defined peaks and troughs of venous oxygenation (Fig. 2B). The on-off phase oxygenation differences are mildly blunted, decreasing to approximately 8%. This would be reflected in a mild decrease in relative fMRI signal strength. At a shorter on-off period of 6 s (0.083 Hz), there is significant blunting of on-off phase differences. Although peaks and troughs are still quite discernible, the calculated differences in venous oxygenation are now between 3 and 4% (Fig. 2C). This would be expected to correlate to a significantly diminished signal in fMRI experiments. Shortening the on-off period further to 3 s (0.167 Hz), fMRI signal dampening becomes clearly evident, with venous oxygenation rising with initial onset of stimulation, and then undulating around a new equilibrium value, without well-defined peaks or troughs. The differences in venous oxygenation are now less than 1% (Fig. 2D). At a frequency of 0.5 Hz, there is no discernible phase difference at all (Fig. 2E).

Figure 3 (A–F) displays actual functional MRI data previously obtained by Bandettini et al. using a motor stimulation paradigm with progressively shorter periods in a single subject.[32] Well-defined fMRI signal peaks are evident at the longer periods. However, there is a definite decline in fMRI signal strength at an on-off frequency of 0.083 Hz (6 s on, 6 s off) At an on-off stimulation frequency of 0.16 Hz (corresponding to on-off periods of 3 s), the phenomenon of dampening is evident. An initial rise to peak is observed, with signal undulating around the new equilibrium level, with peaks and troughs no longer distinguishable from background noise.

The Impact of CBF Peak and Rate of Change on Dampening

Another useful aspect of modeling is that it allows us to investigate the impact of changes in the flow rate, or the level of peak flow, on venous oxygenation, and on the phenomenon of dampening. Figure 4A displays a simulation wherein peak flow is allowed to increase by 70% over 3 seconds, with on-off periods of 6 s. Comparison with Fig. 2C (period: 6 s; flow increases by 30% over 3 s) reveals that at the higher flow rate, the peaks and troughs are now better defined, with peak-trough differences in venous oxygenation on the order of 5.5 to 6%. Figure 4B reveals the effect of lengthening the flow response time to 6 s to peak flow, with other parameters identical to Fig. 2C. Now, the peaks and troughs are slightly more blunted, with peak-trough differences on the order of 1.5 to 2%. Figure 4C reveals the impact of shortening the flow response time to 1 second, with other

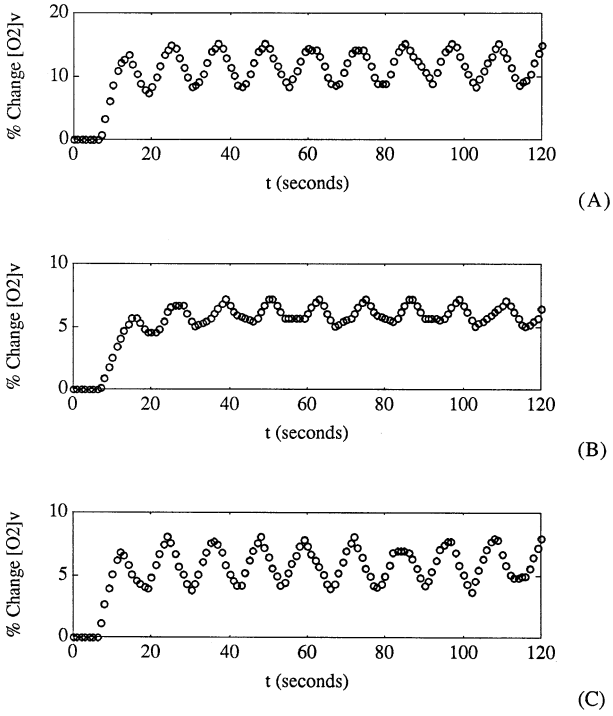

Fig. 4. Model simulation results of cerebral venous oxygenation for varying levels of peak CBF increase with activation, as well as different rates of rise to peak CBF. The on-off frequency is maintained at 0.083 Hz (compare with Fig. 2c). A: CBF increases by 70% over 3 s. B: CBF increases by 30% over 6 s. C: CBF increases by 30% over 1 s.

parameters identical to Fig. 2C. In this case, the peaks and troughs are slightly more pronounced than in Fig. 4B (flow increases over 6 s), but not significantly different from Fig. 2C (flow increases over 3 s).

The Impulse Response Function and Prediction of Non-linearities

To further test the above model, it was used to examine a recently described phenomenon of non-linearity in some fMRI experiments.[29,30] Figure 5A (○) shows the venous oxygenation response to a stimulation pulse of 12-s duration, assuming linear 2 s rises and falls in flow, giving a trapezoidal shape to the flow envelope.[33] The venous oxygenation response is then predicted as the time-shifted sum of the response to a 3-s stimulation pulse [Fig. 5A (*)]. It is noted that when 3-s pulse responses are used to reconstruct a 12-s pulse response, there is an overestimate, or "non-linearity" of the type observed by Boynton et al.[29]

For comparison, Fig. 5B is adapted from the work of Boynton et al., with the thin curve revealing the time-shifted sum of four 3-s pulse responses, and the bold curve representing the fMRI signal response to a 12-s stimulation pulse. The reconstruction of the 12-s pulse response from the 3-s pulse responses produces an overestimate.

DISCUSSION

This paper presents a model of cerebral venous oxygenation as a function of cerebral blood flow, and applies this model to predict that at high frequencies of on-off stimulation, a phenomenon of dampening in the response of cerebral venous oxygenation, and hence fMRI signal, would be observed (Fig. 2). Experimental data also reveals the presence of a well-defined dampening phenomenon, with matching dynamics to those established by modeling (Fig. 3).

The presence of this phenomenon is important in several respects. On a practical level, it reveals certain limitations that should be observed in the design of fMRI experiments—namely, that the frequency of the on-off periods should not exceed a certain level, probably in the vicinity of 0.167 Hz, otherwise fMRI subtraction images would be of little yield, as there would be little difference between on and off phase images. This consideration, however, is of minor importance, because in practical experimental design, such on-off periodicities would probably not be attained.

More importantly, the presence and characteristics of the dampening phenomenon sheds light on important aspects of cerebral hemodynamics, as well as on the possible origin of the fMRI signal itself. At present, there continues to be debate on two central issues: first, whether oxygenation or CBF changes are primarily responsible for the observed fMRI signal, and second, if oxygenation is primarily responsible, whether the main contribution occurs at the level of the capillary bed or the larger draining veins.[3]

With any of these mechanisms, a dampening phenomenon would be expected once the on-off flow rate exceeded the brain's hemodynamic capacity; for example, a dampening of the fMRI signal would be observed from a lag between changes in venous oxygenation and the changes in flow that accompany neural activation, or may be due to a lag in the flow response itself after the onset of stimulation.

However, a close examination of the dynamics of the dampening phenomenon as predicted in this model and as empirically demonstrated by subject data, in conjunction with human and mammalian flowmetry data, lends strong indirect evidence that the predominant contributor to fMRI signal change with stimulation is an increase in the venous oxyhemoglobin to deoxyhemoglobin ratio, i.e., the BOLD mechanism.

The above model accounts for both the flow response time, as well as the lag between changes in CBF and the resultant changes in venous oxygenation as more highly oxygenated blood washes into the venous blood pool. Using a trapezoidal flow function,[33] and assuming that there is a 3-s CBF rise time, there is good agreement between the predicted and observed dynamics of the dampening phenomenon. At low switching frequencies, there is no significant changes in on-off phase venous oxygenation nor in fMRI signal (Figs. 2 and 3). However, at a frequency of 0.083 Hz, there is significant blunting of both venous oxygenation differences as per the model, and observed fMRI signal strength as per the experimental data, and at a frequency of 0.167 Hz, complete dampening of the fMRI signal occurs.

The excellent agreement between the calculated changes in venous oxyhemoglobin/deoxyhemoglobin and the observed fMRI signal in and of itself suggests that venous oxygenation is the central determinant of the fMRI signal, and that the dampening phenomenon is predominantly a result of the lag between changes in CBF and the resultant changes in venous oxygenation.

However, a more detailed analysis is still required in order to validate this conclusion in the face of the other possible competing mechanisms: that the fMRI signal is based on R1 inflow effects, or based on changes in oxygenation at the level of the capillary bed.

The issue of fMRI signal dependence on R1 inflow effects versus the BOLD mechanism has been extensively studied outside the scope of this model and the issue of signal dampening. Some investigators have suggested that R1 inflow effects are predominant, because saturation of tissue outside of the slice of interest sup-

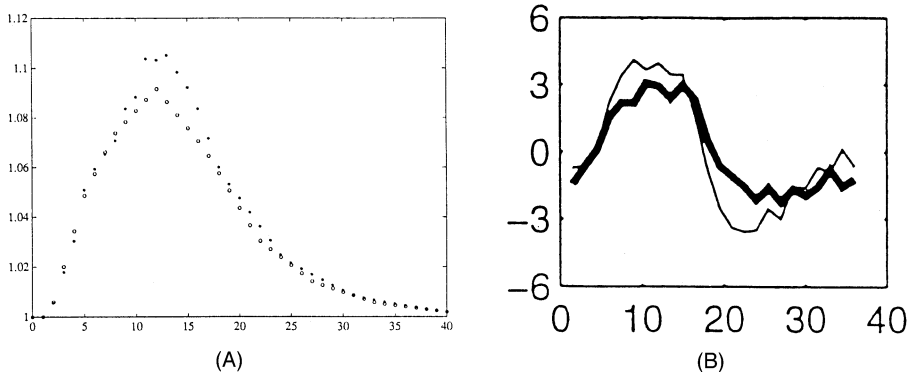

Fig. 5. (A) shows the calculated venous oxygenation response to a stimulation pulse of 12-s duration (○). The venous oxygenation response is then predicted as the time-shifted sum of the response to four 3-s pulses (*). It is noted that when 3-s pulse responses are used to reconstruct a 12-s pulse response, there is an overestimate, or "non-linearity." (B) is adapted from the work of Boynton et al. (see text), with the thin curve revealing the time-shifted sum of four 3-s pulse responses, and the bold curve representing the fMRI signal response to a 12-s stimulation pulse. The reconstruction of the 12-s pulse response from the 3-s pulse responses also produces an overestimate.

presses fMRI signal at 1.5 Tesla.[25] However, it has been demonstrated that at low flip angles and long TR, $\Delta R2^*$ is independent of TE, consistent with a BOLD-based MRI signal.[34,35]

There is also strong direct evidence in support of the BOLD mechanism: that increases in venous oxygenation, and corresponding decreases in venous deoxyhemoglobin, cause increases in MR signal with susceptibility-sensitive sequences. Original work by Ogawa et al. demonstrated oxygenation-sensitive contrast in rodent cerebral vessels using gradient-echo imaging at 7 T.[36] Likewise, Turner et al. observed oxygenation-dependent signal changes in cat brain at 2 T, attributed to increases in the concentration of deoxyhemoglobin in veins and capillaries.[37] More recently, it has been demonstrated that inhaled O_2 causes global signal increases in human brain, presumably secondary to a net conversion of venous deoxyhemoglobin to oxyhemoglobin.[22,23] Rostrup et al. directly investigated the signal changes in human brain with hypo- and hyperoxia using gradient echo imaging, and correlated these changes with observed changes in blood flow using a phase mapping technique.[24] They concluded that in their experiment, fMRI signal changes are predominantly due to the BOLD mechanism, with flow signal being only a minor contributor. CBF was observed to decrease with hyperoxia, and to increase with hypoxia, but such changes did not abolish the fMRI changes expected according to a BOLD contrast mechanism.[24]

In the context of this model, and the phenomenon of dampening, there are expected differences between an fMRI signal based on BOLD contrast in the venous blood pool, and an fMRI signal based on R1 inflow effects or changes in oxygenation at the level of the capillary bed. In the latter two scenarios, the fMRI signal profile in this model would change as flow changes, rising and falling over 2 to 3 s. No dampening would develop, and there would be signal blunting only at the ultra-high frequency range of 0.5 Hz. Observed fMRI signal, however, follows the dynamics of venous oxygenation, rather than rCBF.

This conclusion is not significantly impacted by the choice of a flow function in which CBF changes over 3 s. Such a choice avoids the inherent difficulty in trying to predict the flow response with periodic stimulation when the switching frequency is less than the CBF rise time, and is consistent with existing flowmetry data. While Kwong et al., using IR flow-sensitive spin labeling techniques found that fMRI signal peaks at 8.9 ± 2.8 s,[4] it is possible that this data reflects a mixture of flow and oxygenation lags. Direct measurements of the CBF response in rats in response to sensory stimulation show a rapid CBF response, peaking at 2 to 3 s.[28] In humans, Conrad and Klingelhofer have demonstrated that with a 10 Hz-dynamic checkerboard stimulus, CBF reached 50% of maximum velocity in 2.0 ± 0.8 s, and 90% of maximum at 4.2 ± 1.7 s.[38] However, in fMRI experiments with visual stimulation, it has been observed that mean signal rise times range from 6 to 9 s.[10] This discrepancy, however, is well explained by the above model. Figure 1 reveals that when flow changes over 3 s, it takes approximately 7.5 s to attain 75% of peak changes in venous oxygenation.[26] Therefore, an assumed CBF rise time of 3.0 s is compatible with these empiric results

Moreover, this model allows a direct assessment of the impact of the CBF rise time, and the CBF peak value vis-a-vis the inherent lag required for the new capillary

oxygenation to "percolate" through the venous pool, as separate variables in producing the dampening phenomenon. However, as there is yet no well-defined quantitative link between changes in venous oxygenation and observed fMRI signal, the quantitative effects on venous oxygenation must be translated into qualitative effects on fMRI signal.

Correlation with actual data suggests that significant signal blunting in our subjects occurs at an on-off frequency of 0.083 Hz (Fig. 3D). According to our model, assuming a 30% increase in CBF over 3 s, this corresponds to a peak-trough oxygenation difference of approximately 3.5 to 4%. With increases in the rate of change of CBF, such as assuming that peak changes in flow are reached over 1 s, and using an on-off frequency of 0.083 Hz, this model predicts only a slight increase in on-off phase differences in venous oxygenation, with the average difference now being approximately 4% (Fig. 4C). Conversely, if there is a decrease in the rate of change of CBF to 6 s, the on-off differences become slightly more blunted, with the difference in venous oxygenation decreasing to approximately 1.5 to 2% (Fig. 4B).

Changes in peak CBF also impact the peak-trough differences in venous oxygenation, and appear to have a more profound effect than changes in the rate of increase of CBF. Figure 4A demonstrates that for an on-off frequency of 0.083 Hz, flow going to peak over 3 s, and a peak flow increase of 70%, there is a definite increase in on-off phase differences in venous oxygenation, which are now calculated to be 5.5 to 6%.

However, the most significant variable in the development of dampening is the on-off frequency itself. This is due to the lag in changes in venous oxygenation with changes in cerebral blood flow, as displayed in Fig. 1, and as modeled by Eq. (4). This lag is physiologically reasonable, as changes in CBF would be paralleled by changes in capillary oxygenation; however, it would take some finite time for the new level of capillary oxygenation to "percolate" through the venous blood pool, and shift venous oxygenation to a new equilibrium. If periodic stimulation is occurring with a time scale less than that required for the establishment of this new venous oxygenation equilibrium, the phenomenon of dampening would become manifest. Hence, even if flow is assumed to increase by 70%, and to attain this peak in only 1 s, if the on-off frequency is 0.167 Hz, on-off oxygenation differences are only 2.5 to 3%.

It is once again stressed that such conclusions, while drawn from a quantitative model, are only qualitative in nature. This is due in part to the absence of a definite quantitative link between changes in venous oxygenation and cortical MRI signal. They do demonstrate, however, that the rise time of CBF, within physiologically reasonable limits, is not a significant factor in the dynamics of the dampening phenomenon. It is less important than the actual flow peak attained, and by far the most important factor is the inherent lag between the changes in CBF and the change in venous oxygenation.

As stated above, a capillary-bed contribution to fMRI signal would be expected to have a time dynamic similar to inflow R1 effects, and different from BOLD effects in the venous blood pool. Our data and model support that in the setting of periodic stimuli with increasing on-off alternation frequencies, the dynamics of the dampening phenomenon point strongly to a signal based upon BOLD effects in the venous pool. This conclusion is supported by work of Menon et al. on the assessment of capillary bed contributions at 4 T.[3] It has been suggested that while a capillary bed contribution is detectable, and may be spatially more accurate to the cortical ribbon, and provide an explanation of the undershoot phenomenon, it contributes significantly less to the fMRI signal rise than the venous blood pool, even at 4 T.[3] At 1.5 T, the capillary bed contribution is expected to be quite small, and possibly negligible.[3] Similar results were observed by Buxton et al., who demonstrated that areas of large perfusion change in fMRI are associated with only moderate BOLD signal changes, and a post-stimulus undershoot, presumably corresponding to the capillary bed, while the largest BOLD signal changes are not closely linked to perfusion, and are likely due to large draining veins.[39]

It has been noted above that the development of the dampening phenomenon can be viewed in the context of a linear systems approach, as a convolution of a periodic stimulus with a response function. Hence, an entirely different approach to the validation of the above model, basing fMRI signal changes on the changes in venous oxygenation as expressed in equation 4, is through an examination of the impulse response function of this model. Specifically, the impulse response function of this BOLD model should be able to explain certain "nonlinearities" in the fMRI signal, which would not be present if the signal were based on flow effects, whether R1 inflow phenomenon, or changes in the capillary bed oxygenation, which occur essentially simultaneously with changes in CBF.

In the Model section, the impulse response function for this model is derived [Eq. (11–12)]. A close examination of the form of the impulse response function reveals that it is time invariant only when $a(\sigma)$ is a constant function. It is only under this circumstance that $h(t,\tau)$ as expressed in equations 11 and 12, would have the form of $h(t-\tau)$, i.e., a time-invariant impulse response function. However, $a(\sigma)$ is not a constant function, since it reflects the time variance of CBF (function F(t) above). Therefore, while the model is linear, it is not time-

invariant. Hence, the assumption used by Boynton et al., that a 12-s pulse response could be reconstructed by the linear summation of time-shifted 3-s pulse responses, becomes invalid, as it would require a linear, time-invariant system.[29] As shown in Fig. 5, when this reconstruction is attempted, the reconstructed signal overshoots the original signal by a small amount, as observed by Boynton et al., and as predicted by our model. Thus, the ability of this model to explain the observed nonlinearities in fMRI signal provides perhaps the strongest support of the conclusion that the BOLD response in the venous blood pool is the central determinant of fMRI signal, and the primary etiology of the dampening phenomenon.

Finally, it is noted that for this initial investigation, the role of possible changes in cerebral O_2 consumption and changes in CBV were not addressed explicitly, and they are assumed to be constant.

Ignoring possible changes in cerebral O_2 consumption may be justified secondary to the generally expected small magnitude of such changes at the onset of stimulation, and the generally accepted BOLD assumption of an initial uncoupling of flow and metabolism.[12,16–18] More recent work, however, suggests that these assumptions may not be entirely valid. Hyder et al. have demonstrated that in the setting of functional stimulation, oxidative glycolysis is the main source of energy for increased brain activity.[6] Davis et al. have provided evidence of modulation in the BOLD signal secondary to changes in oxidative metabolism, possibly by up to 30%, using a mathematical model linking CBF, oxidative metabolism and BOLD signal changes, as well as pulse sequences designed to simultaneously estimate BOLD and flow changes.[40] Also, Buxton et al. have introduced a model of O_2 delivery to the brain which suggests that there is a tight coupling of flow to oxidative metabolism with cerebral activation, and that relatively large changes in flow are required to support relatively small changes in oxidative metabolism due to the absence of capillary recruitment in the brain and a unidirectional O_2 extraction fraction.[19] This would be consistent with the results of Hyder et al. regarding a more prominent role for oxidative metabolism in the setting of brain activation than initially assumed.[6]

There are some differences in the expected fMRI signal between the model of Buxton et al. and a model such as ours, which assumes an uncoupling of flow from metabolism, but these are dependent on the resting O_2 extraction fraction (E). At a flow increase of 30%, these differences are negligible for values of E less than 20%, and show a slight divergence at an E of 30%, but become significantly different at an E of 50%.[19] In prior work, our estimated cerebral O_2 extraction fraction equivalent to the function E(t) above was approximately 31%.[26] Hence, the expected divergence is not large, but further work is needed on the full implications of the model of Buxton et al. on the results presented here. Overall, however, the impact of ignoring changes in O_2 consumption is not expected to have a qualitative difference on the results presented, as changes in O_2 consumption, as measured by both PET and MRI techniques, are significantly less than corresponding changes in flow.[16,41]

The question of CBV is more complex. In a fuller treatment of this model, it has been shown that the significant variable for the dynamics of signal change is not CBF alone, but the CBF/CBV ratio.[26] It is noted that blood volume plays no role in determining the eventual level of venous oxygenation with changes in flow and consumption [Eq. (1–3)]. However, blood volume acts in determining the total amount of deoxyhemoglobin per voxel. Although increases in CBF decrease deoxyhemoglobin levels, increases in blood volume lead to greater total deoxyhemoglobin content for any given deoxyhemoglobin level. Thus, the net impact of simultaneous changes in flow and volume will depend on the ratio of changes in flow to changes in volume.[4,26,27,42] Recently, Buxton et al. have also demonstrated, using a theoretical biomechanical model of CBF and CBV, that CBV changes are capable of affecting the shape of the fMRI signal curve, producing such phenomenon as the initial undershoot, based on the relative time course of flow and volume changes.[33]

When the overall effect on total deoxyhemoglobin, and fMRI signal change is modeled, it is found that changes in CBF must definitely exceed changes in CBV to produce discernible decreases in total deoxyhemoglobin with functional stimulation.[26] A study in rhesus monkeys supports this notion, indicating that changes in CBV are indeed of a significantly lesser magnitude than changes in CBF, with CBV varying approximately as the cube root of CBF.[43] Also, in a hypoxia-hyperoxia model, it has been demonstrated that MRI signal changes are dominated by changes in magnetic susceptibility from blood oxygenation, rather than from blood volume changes.[5] Thus, it may be justified to assume CBV as constant for the purposes of this initial investigation, as increases in CBV do not affect the qualitative conclusions established. However, with more in-depth investigations to establish the quantitative link between fMRI signal and venous oxygenation, both deoxyhemoglobin levels and total deoxyhemoglobin content will become important variables, and the role of CBV will need to be considered explicitly.

CONCLUSIONS

Mathematical modeling of cerebral venous oxygenation in response to functional activation may aid in

understanding the basic mechanisms underlying fMRI signal, and may shed light on the cerebral hemodynamics that accompany functional activation. This paper examined the phenomenon of high-frequency periodic stimulation, using both a mathematical model of cerebral venous oxygenation, and actual subject data of motor stimulation with progressively shorter bursts of "on-off" stimulation. The phenomenon of signal dampening was predicted and observed, serving as strong indirect evidence that fMRI signal is indeed mostly dependent upon changes in venous deoxyhemoglobin, rather than either R1 inflow effects or changes in oxygenation at the level of the capillary bed. The dampening effect was also presented in light of an impulse-response function, and it was demonstrated that the impulse response function of our model is compatible with previously observed results regarding the "non-linearity" of fMRI signals. The agreement between the predicted and observed dynamics of signal dampening, as well as the ability of the impulse-response function of a venous pool BOLD model to account for non-linearities in fMRI signal response, is supportive evidence that this and similar efforts at modeling venous oxygenation may enhance our understanding of cerebral hemodynamics in the setting of functional stimulation.

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