Elevated Cerebral Energy Use Without Vascular Response

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INTRODUCTION: Brain activation is accompanied by a series of physiological alterations, including focal changes in CBF, CBV and blood oxygenation. Fundamental to the understanding of such phenomena is the relationship between neuronal activity and blood flow, i.e. how does the increase in neuronal activity elicit an increase in local CBF. To date, the precise mechanism of this neurovascular coupling is still not clear. However, it is widely accepted that vasodilatation is a consequence of increased energy consumption, mediated through metabolites such as H+ and CO2, often referred to as flow-metabolism coupling. Recently, the classical interpretation of a CBF response due to energy needs has been challenged by the notion that the brain has excess glucose and oxygen delivery compared to demand (1, 2). In addition, there is evidence indicating that the production of metabolites is not sufficient to account for the CBF increase during activation (3). Furthermore, it was suggested that the hemodynamic response may be coupled to neurotransmitter signaling rather than energy demand (4). Here we use multi-modality (BOLD, ASL and VASO (5)) fMRI to provide experimental evidence of the absence of a causal correlation between transient increases in energy demand and CBF.

METHODS Experiment: Studies were performed on a 1.5T MR scanner (Philips Medical Systems) using body coil transmission and head coil reception. FMRI used visual stimulation (n=8, with written consent, checkerboard, visual angle=25º, frequency=8Hz, 30s ON, 50s OFF, 3 repetitions, ~5min/exp) with the following parameters: single slice (5mm), TR=2000ms, Flip angle=90º, matrix=64x64, FOV=240mm. FMRI were performed using BOLD, ASL (CBF-based) and VASO (CBV-based), respectively. For ASL, TI=1200ms, labeling slab thickness=10cm using TILT (6). For VASO, TI=665ms. Data processing using MATLAB: spatial filtering with 5mm FWHM, baseline correction. Activation detection: cross-correlation, |cc|>0.18, cluster size 3, minimal SNR=10, p<0.005. Hemodynamic time-course of each fMRI modality was calculated. The CBV percentage changes were calculated from the VASO signal by assuming a resting state blood volume fraction of 4.7%. The CBF percentage changes were assumed to be the same as the ASL signal percentage changes**. Quantification of Oxygen extraction fraction (OEF) and Cerebral Metabolic Rate of O2 (CMRO2):** Briefly, venous oxygenation (Yv) can be calculated using CBV and BOLD signals considering both intravascular and extravascular contributions. OEF can be calculated from Yv using $(1-Y_v) = 1 - Y_a + OEF \cdot Y_a$. And CMRO2 changes can then be obtained from $\left(1+\frac{\Delta OEF}{OEF}\right)\cdot\left(1+\frac{\Delta CBF}{CBF}\right)=\left(1+\frac{\Delta CMRO_2}{CMRO_2}\right)$.

RESULTS and DISCUSSION: Fig. 1 shows the time-courses of the hemodynamic responses for these physiological parameters using a temporal resolution of 2s. When selecting all activated voxels for each of the different fMRI approaches (Fig. 1a), the hemodynamic responses for oxygenation and flow return to baseline within approximately 8-10s after stimulus cessation, while the return of the blood volume response takes 5-10 seconds longer. The positive BOLD response is followed by a post-stimulus undershoot that has been the topic of much debate (7, 8). This oxygenation undershoot and the delayed CBV return have also been observed in rat studies, leading to the proposal that delayed venous/venular compliance may explain this phenomenon (7, 8). However, it can be seen that the BOLD undershoot lasts much longer than the prolonged blood volume increase, as long as 30s after the stimulation is stopped, and thus cannot be explained solely by such a delayed CBV return (7). This discrepancy becomes even more pronounced when focusing attention on the subset of voxels that show activation in all of the three methods (Fig. 1b), which should mainly contain microvascular areas. This prolonged post-stimulus BOLD undershoot when CBF and CBV had already returned to baseline levels indicates that it can only be interpreted as a continued post-stimulus elevation in CMRO2. Interestingly, the time scale of the prolonged elevation in CMRO2 matches well with previous observations in cultured neuronal tissues that a period of 30-40s is needed for restoration of ionic gradients after neuronal activity is stopped (9), suggesting that the reversal of ions across the membrane is the major component of brain energy use (10) and the cause of the post-stimulus BOLD signal undershoot.

When calculating OEF and the relative changes in CMRO2 with respect to baseline, the results (Fig. 2) show that CMRO2 is still elevated by more than 10% at a time when CBF and CBV have settled, and returns to normal levels over a period of about 30s. Based on the prolonged and complete dissociation of vascular response and neuronal energy metabolism after activation, we conclude that it is unlikely that the flow response at the onset of activation is directly coupled to energy demands.

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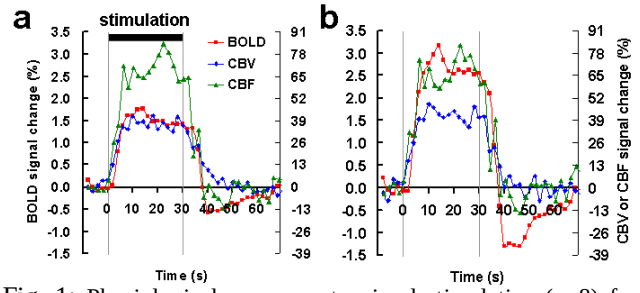

Fig. 1: Physiological responses to visual stimulation (n=8) for (a) all activated voxels in each fMRI modality and (b) voxels that showed activation in all of the 3 methods, i.e. overlapped voxels.

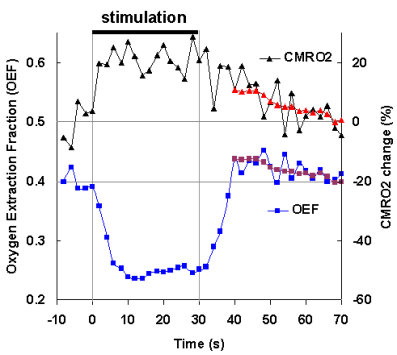

Fig. 2: Stimulation response curves for OEF and CMRO2. The brown and red curves were obtained using only the BOLD response, at the time when no CBV and CBF changes were detectable. This removes the effect of noise from the CBV and CBF curves on these calculated parameters.