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Coupling of cerebral blood flow and oxygen metabolism is conserved for chromatic and luminance stimuli in human visual cortex

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ABSTRACT

The ratio of the changes in cerebral blood flow (CBF) and cerebral metabolic rate of oxygen ($CMRO_2$) during brain activation is a critical determinant of the magnitude of the blood oxygenation level dependent (BOLD) response measured with functional magnetic resonance imaging (fMRI). Cytochrome oxidase (CO), a key component of oxidative metabolism in the mitochondria, is non-uniformly distributed in visual area V1 in distinct blob and interblob regions, suggesting significant spatial variation in the capacity for oxygen metabolism. The goal of this study was to test whether CBF/$CMRO_2$ coupling differed when these subpopulations of neurons were preferentially stimulated, using chromatic and luminance stimuli to preferentially stimulate either the blob or interblob regions. A dual-echo spiral arterial spin labeling (ASL) technique was used to measure CBF and BOLD responses simultaneously in 7 healthy human subjects. When the stimulus contrast levels were adjusted to evoke similar CBF responses (mean 65.4% ± 19.0% and 64.6% ± 19.9%, respectively for chromatic and luminance contrast), the BOLD responses were remarkably similar (1.57% ± 0.39% and 1.59% ± 0.35%) for both types of stimuli. We conclude that CBF–$CMRO_2$ coupling is conserved for the chromatic and luminance stimuli used, suggesting a consistent coupling for blob and inter-blob neuronal populations despite the difference in CO concentration.

Introduction

The physiological connections between neural activity, cerebral blood flow and energy metabolism are fundamental for understanding and interpreting current functional brain imaging studies. Functional magnetic resonance imaging (fMRI) exploits the sensitivity of the local MR signal to shifts in deoxyhemoglobin content associated with altered brain activity. The central phenomenon behind blood oxygenation level dependent (BOLD) imaging is that cerebral blood flow (CBF) increases much more than cerebral metabolic rate of oxygen ($CMRO_2$) with brain activation such that blood oxygenation increases with brain activity (Fox and Raichle, 1986). The physiological function of this mismatch is still poorly understood (Buxton, 2010), but it nevertheless provides a detectable signal for mapping patterns of brain activity. However, the magnitude of the BOLD response depends strongly on the exact degree of mismatch between the CBF and $CMRO_2$ responses to a stimulus (Ances et al., 2008). The coupling of CBF and $CMRO_2$ can be described empirically by an index n, the ratio of the fractional change in CBF to the fractional change in $CMRO_2$ for a particular experiment. A number of studies in human subjects with positron emission tomography (PET) and calibrated-BOLD fMRI methods have found a wide range of coupling ratios, although most fall in the approximate range of $n \sim 1.6–4$ (Ances et al., 2008, 2009; Chiarelli et al., 2007a, 2007b; Davis et al., 1998; Hoge et al., 1999b; Kastrup et al., 2002; Kim et al., 1999; Leontiev and Buxton, 2007; Leontiev et al., 2007; Perthen et al., 2008; Pike, 2012; Stefanovic et al., 2004, 2005).

The sources of the variability of CBF/$CMRO_2$ coupling are still unclear. A number of studies suggest that a simple feedback mechanism in which neural activity drives energy metabolism changes, and these in turn drive blood flow changes, is likely to be incomplete (Attwell and Iadecola, 2002). Instead, a number of mechanisms have been identified in which aspects of neural signaling itself drive CBF changes, either through direct signaling effects or through activation of astrocytes (Hamel, 2006; Iadecola and Nedergaard, 2007; Koehler et al., 2009). While feedback mechanisms from energy metabolism to CBF exist (e.g., vascular reactivity to pH changes that result from accumulation of carbon dioxide or lactate), current evidence suggests that the acute CBF response to a stimulus is driven by aspects of neural signaling, so that effectively CBF and $CMRO_2$ are driven in parallel by neural activation (Attwell and Iadecola, 2002; Bonvento et al.,

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2002; Buxton et al., 2004; Raichle and Mintun, 2006; Uludag et al., 2004). Variability of the CBF/$CMRO_2$ coupling ratio could then result if particular aspects of the stimulus-evoked neural activity drive CBF and $CMRO_2$ to different degrees.

Human primary visual cortex (area V1) is potentially an important test-bed for probing the connections between neural activity, CBF and $CMRO_2$ because of the nonuniform distribution of cytochrome oxidase (CO) (Wong-Riley, 1989). In addition to variations across cortical layers, tangential sections of supragranular cortical layers show a pattern of cytochrome oxidase (CO)-rich blobs (also called "puffs" or "patches") roughly 200 μm across surrounded by interblob regions with lower CO concentration (Horton, 1984; Horton and Hubel, 1981; Wong-Riley, 1979). In the mitochondria, CO is the last enzyme of oxidative metabolism, catalyzing electron transfer to oxygen, and so the CO concentration reflects the local capacity for oxygen metabolism. Importantly, though, the CO concentration is dynamically controlled, changing over weeks in response to shifts in neural activity, such as suppressing input from one eye (Wong-Riley, 1989). In addition, a recent study demonstrated that the nuclear transcription factor that regulates CO concentration also is involved in regulation of a subunit of the NMDA receptor (Dhar and Wong-Riley, 2009), suggesting a close link between CO concentration and average level of excitatory neural activity.

Since the discovery of the blob structure in V1 there have been numerous studies investigating the functional significance of these regions in terms of neural processing (Horton, 1984; Horton and Hubel, 1981; Tootell et al., 1988a, 1988b; Wong-Riley, 1979). Although electrophysiology studies of the responses of neurons in the blob and interblob regions to different types of visual stimulus have produced mixed results (see Horton and Adams, 2005 for a review), there is substantial evidence for a preferential response of blob neurons to color stimuli. Using optical imaging techniques sensitive to reflectance changes related to oxy- and deoxy-hemoglobin, Lu and Roe (2008) compared responses in macaque V1 to gratings alternating color (red/green) and luminance (black/white). Subtracting maps of these two responses showed "blob-like" patterns of color response that were strongly associated with CO blobs in stained tissue.

Other studies have investigated capillary density differences between blob and interblob regions as an indirect test of whether CBF was matched to the capacity for $CMRO_2$ as reflected in CO concentration. In an early study in the squirrel monkey, Zheng et al. (1991) found a 42% higher capillary density in the blob regions compared with the interblob regions. In a more recent study in macaque visual cortex, Weber and colleagues found a good correlation between laminar differences in CO concentration and capillary density (Weber et al., 2008) but a much weaker (although statistically significant) difference in capillary density of only about 4% between blob and interblob regions (Keller et al., 2011). Both capillary density and CO concentration, however, likely reflect the capacity for CBF and $CMRO_2$ in a region, as modified by the average level of neural activity, and it is still an open question whether such anatomical differences translate into a different coupling of CBF and $CMRO_2$ responses to acute changes in neural activity.

In human fMRI experiments a typical imaging voxel in area V1 contains both blob and interblob regions. The ability to alter the balance of activation between blob and interblob neurons with color or luminance stimuli provides an opportunity to test whether the specific subpopulations of stimulated neurons alters the macroscopic coupling of CBF and $CMRO_2$ responses. In a pioneering study, Hoge et al. (1999b) used a calibrated BOLD methodology to test for differences in the coupling ratio n for different visual stimuli. The calibrated BOLD approach, introduced by Davis and co-workers, involves measuring the CBF response with an arterial spin labeling (ASL) technique in addition to the BOLD changes accompanying separate periods of brain activation and mild hypercapnia (Davis et al., 1998). Assuming that mild hypercapnia increases CBF while producing a negligible change in $CMRO_2$ (Jones et al., 2005; Sicard and Duong, 2005), this allows determination of a BOLD scaling factor M, which reflects the maximum BOLD signal change upon washout of all deoxyhemoglobin. By analyzing the data in the context of a biophysical model for the BOLD signal, activation-induced $CMRO_2$ changes, and thus n, can be calculated. Hoge et al. (1999b) used a FAIR acquisition for CBF measurement, and a retinotopically determined V1 for region of interest (ROI) selection, and found that a wide range of graded visual stimuli were consistent with constant $n \sim 2$. However, FAIR is a qualitative measure of CBF (Buxton et al., 1998) that might underestimate the global CBF change with hypercapnia and thus overestimate M. In addition, we recently found that the use of a V1 localizer also systematically overestimates M compared with a CBF localizer (Leontiev et al., 2007), and Chiarelli et al. (2007b) have shown that an overestimate of M tends to drive all calculations from activation data to a similar low value of n. Finally, other recent studies have challenged the assumption that $CMRO_2$ is not altered by the levels of CO_2 administered for the calculation of M (Zappe et al., 2008), and if $CMRO_2$ decreases with hypercapnia M will be overestimated. A recent study comparing hypercapnia calibration with an alternative hyperoxia calibration method found somewhat higher values for M with the hypercapnia method (Mark et al., 2011).

Therefore, in light of these recent findings, we revisited these experiments with a different experimental design that exploits the sensitivity of the BOLD response to the exact ratio of the CBF and $CMRO_2$ changes. To remove the dependence on the estimation of M, we adjusted the chromatic and luminance stimuli to yield the same CBF responses in human subjects, and then compared the BOLD responses in the same region of interest for the two stimuli to test for a difference that would indicate a difference in the $CMRO_2$ response. Our primary finding was that the BOLD and CBF responses for the two stimuli were virtually identical.

Methods

Subjects

Seven healthy subjects (4 males, 3 females, ages 22–42) were recruited and scanned in a 3 T MR imaging system after obtaining informed consent according to the guidelines set by the University of California San Diego (UCSD) Institutional Review Board (IRB). All subjects underwent a preliminary scan session on a different day in which retinotopic mapping was performed. A pilot study on four additional subjects was performed beforehand in order to determine the necessary contrast level of the luminance stimulus to approximately match the CBF change elicited by the chromatic stimulus.

Retinotopic mapping

In a preliminary scan session on a different day, subjects were presented with standard visual stimuli for retinotopic mapping (Engel et al., 1997; Press et al., 2001). During presentation of visual stimuli, images were acquired with an EPI sequence with the following parameters: TR = 2 s, TE = 30 ms, flip angle 90°, FOV 19 cm, matrix 64 × 64, 3-mm isotropic resolution, 20 interleaved slices. The entire set of stimuli (meridian, ring and wedge) yielded a single representation of V1. A high-resolution whole brain structural scan (3D FSPGR with 1-mm isotropic resolution) was acquired for each subject. The segmented cortical gray matter of occipital cortices was flattened using surface rendering methods described in (Wandell et al., 2000). Linear trends were removed from the datasets. Activation was assessed by correlating detrended data with the first harmonic of the stimulus variation frequency (Press et al., 2001). Representations of the primary visual area V1 of each subject were delineated on the computationally flattened visual cortex to define the retinotopic ROI for each subject. A combination of in-house Matlab (www.mathworks.com) code and the *mrLoadRet-1.0*