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Investigation of the neurovascular coupling in positive and negative BOLD responses in human brain at 7 T

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ABSTRACT

Decreases in stimulus-dependent blood oxygenation level dependent (BOLD) signal and their underlying neurovascular origins have recently gained considerable interest. In this study a multi-echo, BOLD-corrected vascular space occupancy (VASO) functional magnetic resonance imaging (fMRI) technique was used to investigate neurovascular responses during stimuli that elicit positive and negative BOLD responses in human brain at 7 T. Stimulus-induced BOLD, cerebral blood volume (CBV), and cerebral blood flow (CBF) changes were measured and analyzed in 'arterial' and 'venous' blood compartments in macro- and microvasculature. We found that the overall interplay of mean CBV, CBF and BOLD responses is similar for tasks inducing positive and negative BOLD responses. Some aspects of the neurovascular coupling however, such as the temporal response, cortical depth dependence, and the weighting between 'arterial' and 'venous' contributions, are significantly different for the different task conditions. Namely, while for excitatory tasks the BOLD response peaks at the cortical surface, and the CBV change is similar in cortex and pial vasculature, inhibitory tasks are associated with a maximum negative BOLD response in deeper layers, with CBV showing strong constriction of surface arteries and a faster return to baseline. The different interplays of CBV, CBF and BOLD during excitatory and inhibitory responses suggests different underlying hemodynamic mechanisms.

Introduction

Negative blood oxygenation level dependent (BOLD) responses (NBR) have been observed both in animals and humans. NBR can be caused by several independent mechanisms (Kim and Ogawa, 2012) including inhibitory neurogenically driven decreases in cerebral blood flow (CBF) (Shmuel et al., 2002), vasoconstriction in the absence of decreases in neural activity (Shih et al., 2009), or increases in the cerebral metabolic rate of oxygen ($CMRO_2$) with no or insufficient CBF increases (Schridde et al., 2008; Zappe et al., 2008). Under which circumstances the NBR has a vascular or metabolic origin has remained controversial. For this reason, and due to the potential of the negative signal to shed further light on neurovascular coupling, NBR is in the focus of current research (Hutchison et al., 2013; Mullinger et al., 2014; Schäfer et al., 2012; Smith et al., 2004; Tajima et al., 2010; Vafaee and Gjedde, 2004). Early work suggested that the NBR was a result of non-neurally driven hemodynamic mechanisms, such as vascular steal (Harel et al., 2002; Woolsey et al., 1996). However, recent work obtaining electrophysiological recordings simultaneously with BOLD-based functional magnetic resonance imaging (fMRI), in anesthetized macaque monkeys, suggests that decreases in the CMRO2 and neural activity are the major contributors (>60%) to NBR (Shmuel et al., 2006). Further studies (Kennerley et al., 2012b; Pasley et al., 2007) leave no room for non-neurally driven CBF contributions to NBR, and suggest that neurovascular coupling is conserved for both the positive and negative BOLD responses. There is now a general consensus that the NBR is accompanied by decreases in CBF and $CMRO_2$, as shown with fMRI in human visual and motor cortex (Pasley et al., 2007; Shmuel et al., 2002; Stefanovic et al., 2004), with fMRI in monkey visual cortex (Shmuel et al., 2006), and

Abbreviations: BOLD, blood oxygenation level dependent; CBF, cerebral blood flow; CBV, cerebral blood volume; CBV_a, 'arterial' CBV; CBV_{tot}, total CBV; CBV_v, 'venous' CBV; $CMRO_2$, cerebral metabolic rate of O_2; CNR, contrast to noise ratio; CSF, cerebrospinal fluid; ΔCBV, change in CBV; EPI, echo planar imaging; fMRI, functional magnetic resonance imaging; GE, gradient echo; GM, gray matter; MION, monocrystalline iron oxide nanocolloid; NBR, negative BOLD response; OIS, optical imaging spectroscopy; PBR, positive BOLD response; ROI, region of interest; SAR, specific absorption rate; SNR, signal to noise ratio; SS-SI-VASO, slice selective slab inversion VASO; TE, echo time; TI, inversion time; TR, repetition time; VASO, vascular space occupancy; WM, white matter.

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with fMRI and optical imaging spectroscopy (OIS) in rat somatosensory cortex (Boorman et al., 2010; Kennerley et al., 2012b).

More refined layer-dependent studies of NBR in sensory motor cortex of rats and visual cortex of monkeys suggest that the NBR peaks in deeper cortical layers, while the positive gradient echo (GE) BOLD response (PBR) peaks at the cortical surface (Boorman et al., 2010; Goense et al., 2012). The role of cerebral blood volume (CBV) in NBR has remained elusive. Measurements with OIS and monocrystalline iron oxide nanoparticles (MION) reveal vasoconstriction in regions of NBR in rat somatosensory cortex (Boorman et al., 2010; Kennerley et al., 2012b) and cat extrastriate cortex (Harel et al., 2002). Goense et al. (2012), on the other hand, investigated CBV changes in regions of NBR with vascular space occupancy (VASO) (Lu et al., 2003; Yang et al., 2004) and MION in visual cortex of monkeys. They reported a significant and surprising increase of CBV in deeper layers of the cortex during inhibitory tasks (Smirnakis et al., 2007). Follow-up studies suggest that this increase of CBV in regions of interest (ROIs) showing NBR is specific to stimulus and area (Bohraus et al., 2013). These and earlier studies (Smirnakis et al., 2007) suggest that BOLD and CBV do not necessarily represent equivalent fMRI processes and mechanisms.

In contrast to animal research, the role of CBV with regard to PBR and NBR has not yet been investigated in the human brain. In this study, a recently developed multi-echo CBV-sensitive Slice-Saturation Slab-Inversion Vascular Space Occupancy (SS-SI-VASO) variant with BOLD correction (Huber et al., 2013b) was used to investigate the spatiotemporal characteristics of the hemodynamic response during stimuli that elicit positive and negative BOLD signal changes in human brain at 7 T. The goal of this study is to understand the underlying hemodynamic mechanisms of both PBR and NBR. This is achieved by breaking down the vascular response from BOLD signal changes, distinguishing larger pial (macro) vessels from microvasculature, and by separately investigating CBV components with arterial and venous-like oxygenation levels.

Materials and methods

Theory of BOLD-dependent T_2^* in SS-SI-VASO

The signal intensity, S, of a parenchyma voxel acquired with blood nulling (bn) and in a control condition without blood nulling (ctr) can be considered as a sum of magnetizations from gray matter (GM) tissue and arterially oxygenated (a) and venously oxygenated (v) blood:

$$S_{bn}/_{ctr} \sim \sum_{i\in\{GM,a,v\}} V_i\,\rho_i\,M_i\left(TI_{bn}/_{ctr}\right)e^{-\frac{TE}{T_{2,i}^*}}, \tag{2.1}$$

where V_i, ρ_i, and M_i denote the volume, relative proton density, and the z-magnetization of GM and blood within a voxel respectively. TI is the inversion time and TE is the echo time. In SS-SI-VASO, BOLD-contaminated VASO images with blood nulling are acquired interleaved with purely BOLD-weighted control images without blood nulling.

Extravascular BOLD contaminations are assessed and eliminated by dynamic division of images obtained with and without blood nulling. By means of the division, the transverse relaxation term cancels out, and the resulting signal is dependent on M_z only (Huber et al., 2013b).

$$S' \approx \frac{M_{GM}\,e^{-\frac{TE}{T_{2,GM}^*}}}{M_{GM}\,e^{-\frac{TE}{T_{2,GM}^*}} + M_a\,e^{-\frac{TE}{T_{2,a}^*}} + M_v\,e^{-\frac{TE}{T_{2,GM}^*}}} \approx \frac{M_{GM}\,e^{-\frac{TE}{T_{2,GM}^*}}}{\underbrace{\left(M_{par}\right)}_{const.}\,e^{-\frac{TE}{T_{2,par}^*}}}. \tag{2.2}$$

However, this formulation does not consider the fact that there are different blood compartments with different baseline T_2^* values. Thus, we need to extend the model to distinguish blood components with long and short T_2^* values.

T_2^* model to estimate 'arterial' and 'venous' CBV

It is well known that there is a direct correlation between intravascular blood T_2^* and oxygenation level (Ivanov et al., 2013). In the present study, the multi-echo VASO sequence enabled comparisons between the T_2^* of parenchyma (tissue and vessels) and GM (tissue without vessels), which were used to estimate the T_2^* of the blood component showing the majority of the blood volume changes. This was further evaluated to estimate whether blood volume changes occur in the portion of blood volume with longer baseline T_2^*, which we denote by 'arterial' oxygenation values, or in the portion blood volume with shorter T_2^*, which we denote as 'venous' oxygenation. Since 'arterial' and 'venous' blood portions are here considered based on their oxygenation level and not on anatomical structure, the terms 'arterial' and 'venous' are denoted in quotes. The separate consideration of 'arterial' and 'venous' CBV change based on their T_2^* can be regarded as distinguishing between BOLD-specific and BOLD-nonspecific CBV changes (Chen and Pike, 2010).

A comprehensive quantitative model of the algorithm to separate the 'arterial' and 'venous' compartment of blood volume change is provided in Appendix A. Estimation of venously oxygenated CBV change can be intuitively understood as follows; with the procedure of dynamic division, SS-SI-VASO is sensitive to volume changes of the blood component that is nulled in one condition (bn) and not nulled in the other condition (ctr). Hence, for very short TE, both 'arterial' and 'venous' blood compartments are nulled for the bn condition, but in the control condition they both contribute to the signal. Using a longer TE (e.g. $TE > 30$ ms), there is a difference in signal arising from 'arterial' and 'venous' blood. For long TEs, 'arterial' blood will be nulled for the bn condition, but not for the control condition—while 'venous' blood will be nulled in both conditions. In the blood nulled condition, 'venous' CBV is nulled due to T_1 selective nulling of the VASO contrast. In the control condition 'venous' blood contributions will be highly suppressed due to fast T_2^* relaxation and dephasing of signal from deoxygenated blood ('venous' $T_2^* \approx 12$ ms (Ivanov et al., 2013)). When the signal intensities of these two images are divided, 'venous' CBV change does not result in functional VASO signal change. 'Arterial' blood volume change, on the other hand, which is suppressed in the bn condition only, can contribute to the functional contrast.

Hence, SS-SI-VASO reflects the total CBV change at short TE and arterial-weighted CBV changes at longer TE. A comparison of these, almost simultaneously acquired contrasts can be used to estimate 'venous' CBV change.

For quantitative estimates of 'arterial' and 'venous' CBV changes, literature values of 'arterial' and 'venous' T_2^* were used (Appendix A). In this study, 'arterial' and 'venous' CBV were defined by their T_2^* values and oxygenation characteristics, and not by an anatomical vessel classification. Hence, we have assumed that changes in 'venous' CBV take place in microvasculature already containing a significant concentration of deoxyhemoglobin.

Image acquisition

SS-SI-VASO was implemented on a Siemens MAGNETOM 7 T scanner (Siemens Healthcare, Erlangen, Germany). For radiofrequency (RF) transmission and reception, a 24-channel receive and circularly polarized single-channel transmit head coil (Nova Medical, Wilmington MA, USA) was used. To circumvent the effects of inflow of fresh (non-inverted) blood magnetization into the microvasculature of the imaging slice, which can be problematic in VASO at 7 T (Hua et al., 2013), the inversion efficiency of the inversion pulse was reduced, so that the blood nulling time of the VASO sequence was shorter than the arterial arrival time. In order to achieve proper inversion despite inhomogeneity of the RF field B_1 and limitations imposed by the specific absorption rate (SAR), a TR-FOCI adiabatic inversion pulse (Hurley et al., 2010) was implemented and redesigned to achieve partial inversion in a B_1-independent manner (Huber et al., 2013b). Data were acquired in five axial slices aligned along the calcarine sulcus with a two-

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