MICRO- AND MACROVASCULAR CONTRIBUTIONS TO LAYER-DEPENDENT BLOOD VOLUME FMRI: A MULTI-MODAL, MULTI-SPECIES COMPARISON

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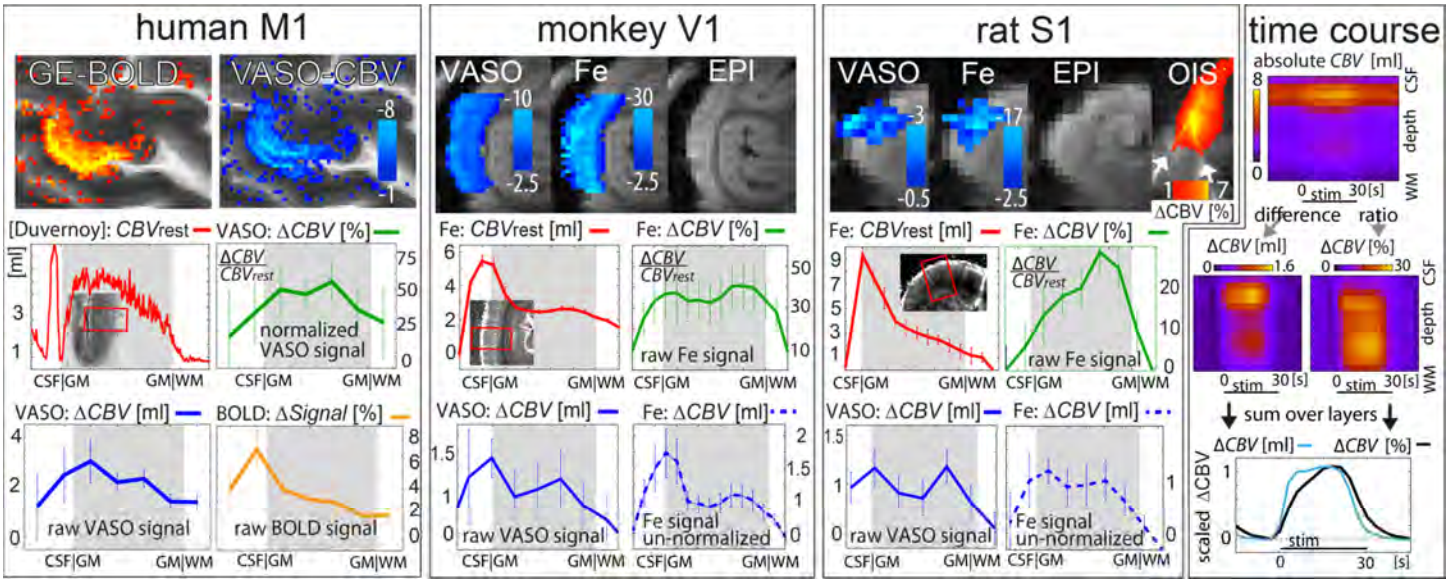
Target audience: Researchers interested in layer-dependent fMRI or neuro-vascular coupling.

Purpose: Layer-dependent fMRI has the potential to address questions of the feedforward and feedback connectivity of different brain regions. However, the relative sensitivity of fMRI contrasts to layer-unspecific macrovascular responses in addition to layer-specific microvascular responses can make it difficult to disentangle the activity of specific layers. It has been suggested that blood-volume-sensitive iron-oxide fMRI has a more specific cortical layer dependence and reduced contribution from large pial vessels [1, 2]. Optical imaging results, on the other hand, show a clear signature of pial macrovascular contributions to changes in cerebral blood volume (*CBV*) [1]. The purpose of this study is to investigate the layer-dependence of *CBV* responses in humans, monkeys and rats with multiple modalities sensitive *to CBV* changes. By this means, we seek to analyze the sensitivity of layer-specific microvascular and layer-unspecific macrovascular contributions in *CBV*-based fMRI.

Methods: Vascular space occupancy (VASO) is a non-invasive *CBV*-sensitive method that be applied across species. Layer-dependent CBV results were acquired with SS-SI VASO in humans (0.8×0.8×1.8 mm^3) [3], in monkeys (0.6×0.7×3 mm^3) [4] and rats (0.5×0.5×3 mm^3) [1]. To obtain sufficient SNR for layer-dependent VASO in humans, a set of advanced signal acquisition strategies was applied [5]. Signal from only a limited number of coil elements was obtained, enabling the use of a small field of view (5 cm) and subject-specific aligned imaging slices perpendicular to the cortex at 7 T [5]. For comparison with the VASO results, iron-oxide fMRI was performed in monkeys and rats. Optical imaging spectroscopy (OIS) results were acquired concomitant with MRI in rats [1].

VASO signal is proportional to $\Delta S/S\text{rest} \sim 1 - \Delta CBV$ and provides a quantitative measure of ΔCBV in units of ml/100ml. The raw iron-oxide signal is proportional to $\Delta S/S\text{rest} \sim \Delta CBV/CBV\text{rest}$ and provides a normalized measure of *CBV* in units of %. To compare the two modalities, *CBV*rest must be known. Here, *CBV*rest is estimated from iron-oxide data (animals) and the literature (humans) [6], respectively.

Results: Relative ΔCBV (in %) peaks in deeper cortical layers in each species studied (green profiles). Since *CBV*rest is highest at the cortical surface (red profiles), the relatively small relative *CBV* change (in %) at the cortical surface (green profiles) corresponds to a large absolute *CBV* change in units of ml (blue profiles). When compared in the same physical units of ml, ΔCBV profiles are the same for VASO and iron-oxide fMRI within error (compare solid and dotted blue profiles). Due to the different temporal responses in upper- and deeper layers (right panel), the *CBV* time courses also differ when they are analyzed in absolute units of ml, or in relative units in % (bottom right), which has implications, for instance, in the interpretation of the BOLD post-stimulus undershoot.



Discussion: SS-SI-VASO provides sufficient SNR to map cortical layer-dependent activity across species (upper row). The iron-oxide signal profiles are highest in deeper layers consistent with the literature [1, 2, 4]. The fact that absolute *CBV* profiles (blue profiles in ml) have a considerable contribution from the cortical surface is consistent with results obtained by optical imaging, which show that surface arteries dilate during activity (white arrows). The allegedly high spatial specificity of iron-oxide fMRI to deeper cortical layers might actually be a result of inverse macrovascular contamination and a large denominator in the equation ΔCBV [%] = (ΔCBV [ml])/(*CBV*rest [ml]). Note that these specificity discussions are independent of the brain areas and species, despite variations of the underlying microvascular morphology and cortical input-characteristics.

Conclusion: *CBV*-based fMRI is more layer-specific than GE-BOLD signal (left panel). However, we show here that *CBV*-based fMRI is not sensitive solely to layer-specific microvasculature response. Depending on the units in which the evaluation is performed (quantitative in ml or semi-quantitative in %), *CBV* fMRI can have amplifying (ml) or attenuating (%) macrovascular signal contaminations: A) *CBV* fMRI in quantitative units of ml is undesirably sensitive to large pial arteries. B) CBV fMRI in semi-quantitative units of % is inversely sensitive to macrovasculature, which might lead to undesirably reduced sensitivity of microvascular responses in upper cortical layers.

References: [1] Kennerley et al., MRM, 2005; **[2]** Kim et al., NMR Biomed, 2013; **[3]** Huber et al., MRM, 2014; **[4]** Goense et al., MRI, 2010; **[5]** Huber et al., ISMRM Brain function workshop, Charleston, 2014; **[6]** Duvernoy et al., Brain Reseach, 1981. Funded by EU through Marie Curie HiMR ITN (PITN-GA-2012-316716).