Mapping the Distinct Single-Vessel Vascular Contribution to BOLD and CBV fMRI

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Target Audience Scientists studying neurovascular coupling and the mechanisms of functional MRI will be interested in this work.

Purpose The functional MRI (fMRI) signal is indirectly coupled to neural activity by hemodynamic responses, such as increased blood flow, blood volume, and blood oxygenation level in the vasculature of the activated brain area [1]. This exquisite neurovascular coupling has ensured the success of mapping large-scale brain function and connectivity. However, due to the limited spatiotemporal resolution, the detailed neurovascular response at the single-vessel level has not been characterized by fMRI. Optical microscopy can image the neurovascular response within the superficial layers of the cortex with sufficient spatial and temporal resolution [2], but cannot decipher the vascular signal from deeper cortical layers noninvasively without resorting to invasive procedures. Previously, we have mapped the BOLD-fMRI signal from individual penetrating venules in cortical layers 4/5 [3]. That work demonstrated that the BOLD signal is dominated by penetrating venules as early as 1s after the stimulus onset. In contrast, the BOLD signal within 1s following stimulus onset comes from the microvasculature [3]. In the present work, we compared CBV and BOLD fMRI signals from layers 4/5 in rat somatosensory cortex to better characterize neurovascular changes in deep cortex,. Penetrating venules and arterioles in deep cortex were separated and visualized based on inflow effects of penetrating vessels and susceptibility differences of the vessels. CBV and BOLD signals were mapped with 100ms temporal solution from deep cortex with high in-plane resolution (150x150 μm). Distinctly different voxels were activated in BOLD vs CBV fMRI. While voxels of BOLD activation were primarily assigned to penetrating venules, CBV activation was dominated by penetrating arterioles.

Methods Detailed experimental procedures have been described previously [3]. Briefly, all images were acquired with an 11.7T/31cm horizontal bore magnet (Magnex, UK) interfaced to an AVANCE III console (Bruker) and equipped with a 12 cm gradient set (Resonance Res. MA). A custom-built 9 cm inner diameter transmitter coil was used for transmit and a custom-built surface coil was used for receive. To detect individual arterioles and venules, a 2D-MGE (multi-gradient echo) sequence was used with the following parameters: TR, 30ms; TE, 1.8, 4.3, 6.8, 9.3ms; flip angle, 50°, matrix: 160x256, in-plane resolution: 75x75μm; slice thickness, 500μm). BOLD/CBV-fMRI was performed in α-chloralose anesthetized rats. CBV-fMRI was performed directly following BOLD fMRI. CBV-weighted signals were obtained after intravenous administration of 15 mg Fe/kg dextran coated iron oxide (Biopal, MA). A FLASH sequence was adjusted to acquire each k space line per image during an fMRI block design paradigm and repeated for the number of phase-encoding steps required to make an image [4, 5]. The FLASH-fMRI sequence used the following parameters: TE 4ms (CBV)/16ms (BOLD), TR 100ms; matrix 80x32, BW ~20kHz, flip angle 22°. In both sequences, electrodes were placed on the forepaw to deliver a 2.5mA pulse sequence (300μs duration repeated at 3Hz). The coronal 2D slice (in-plane resolution 150x150μm, 500μm thickness) covered the forepaw S1 areas based on the Paxinos atlas. The horizontal slice angle was set at 15° and the center of the slice was positioned 0.75mm from the cortical surface to cover layers 4/5. Block design was 1s on/16s off (repeated 3 times) for FLASH-fMRI.

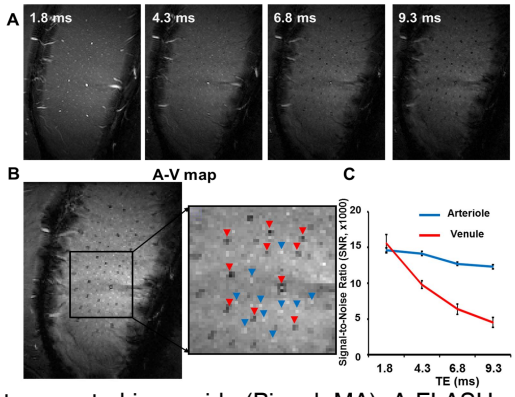

Fig 1. A. MRI images at different TE. **B.** Arteriole and venule map (A-V map). The arterioles are detected as the bright spots (blue arrowhead) due to inflow effects. The venules are detected as the dark spots (red arrowhead). **C.** The signal intensity of arteriole and venule voxels at a function of TE (n=10 voxels).

Results Fig 1 shows the arteriole and venule map (A-V map) acquired by 2D-MGE sequence. Due to inflow effects, vessel voxels (including both arterioles and venules) appear as bright spots in the short TE images. In contrast, in long TE images, venular voxels appear as dark spots due to the faster T2* decay of deoxygenated blood. Thus, by averaging the MGE images acquired at different TEs, we can separate the arterioles and venules penetrating the deep cortex. Fig 2 shows that the peak BOLD signal primarily overlapped with the venule voxels (black arrowhead). In contrast, the peak CBV signal overlapped with the arteriole voxels. Based on the A-V map, the fMRI response from three ROIs (arteriole, venule, and tissue voxels) of the activated cortex were analzyed to show that the BOLD signal from arterioles and tissue voxels precedes the venule voxels, as previously reported [3]. The CBV signal is primarily dominated by arteriolar voxels, but the CBV response also includes the tissue and venules voxels. The stronger arteriole signal started before the weaker venule signal. The CBV and BOLD signal changes will be further analzyed for individual vessel voxels to better understand the the neurovascular coupling at the level of single-vessels.

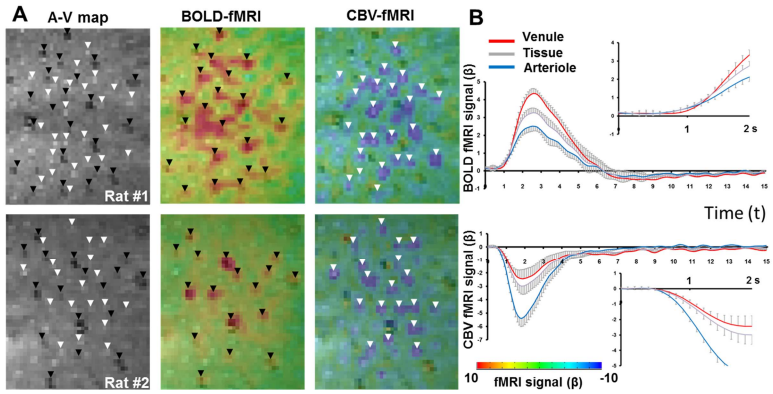

Fig 2. A. Left panel is the A-V map of two rats (arterioles in white and venules in black arrowhead). Middle panel is the BOLD signal overlapped on the A-V map. Right panel is the CBV signal overlapped on the A-V map. **B**. BOLD and CBV-weighted time courses of Venule, Arteriole, and Tissue ROIs (n=3).

Reference 1.Ugurbil et al. TN 26, 108-114 (2003) 2. Hutchinson et al. NI, 32:520-30, (2006). 3. Yu et al. NI, 59:1451-60, (2012). 4. Yu et al. ISMRM, 4370, (2012), 5. Silva & Koretsky, PNAS, 99:15182-7, (2002)