Mapping the early spatiotemporal BOLD fMRI response in the barrel cortex of rats

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Introduction There continues to be much interest in the determination of spatial specificity of BOLD fMRI signals with respect to neuronal activity [1]. It is clear that large venous vessels lead to mislocalization of fMRI signals. Two major strategies have been used to eliminate the contribution of large venous vessels. One strategy relies on the MRI sequence to minimize vessel effects such as using spin echos vs gradient echos. Another strategy relies on the spatial and temporal response of large vessels. For example, cortical surface voxels are sometimes eliminated from analysis to avoid draining veins [2]. It has been shown that BOLD fMRI responses in the rat somatosensory cortex (S1) begin at least as early as 600 msec after stimulation [3]. Interestingly this is sooner than the transit time for blood to move from arterioles to venules in the rat cortex [4]. To determine the spatial changes of BOLD signals from tissue to large venules in the rodent brain, gradient echo (GE) BOLD fMRI was obtained at a resolution of 150μmx150μmx500μm. At this spatial resolution, the penetrating venules can be identified in the rat S1 cortex. The spatial pattern of the BOLD response was measured at a temporal resolution of 0.2s. Significant BOLD signal changes were first observed in the cortical areas between MRI detectable vessels at 0.8s. BOLD signal changes shifted to the adjacent voxels covering the penetrating vessels by 1-1.2s, and later propagated to the superficial draining veins. The propagation of the appearance of active voxels from inter-vessel area to the adjacent vessels and surface veins was consistent with transit times measured using two-photon microscopy [4]. The signals from the penetrating vessels begin to dominate the spatial distribution by 1s after stimulation starts. This indicates that it may be possible to avoid the contribution of draining venules in the cortex to BOLD fMRI maps by using data obtained within 0.8-1s after stimulation.

Methods BOLD-fMRI was performed in 4 rats anesthetized with α-chloralose. Detailed procedures of the imaging and animal preparation for fMRI were similar to those previously described [3]. Briefly, all images were acquired with an 11.7T/31cm horizontal bore magnet (Magnex, Abingdon, UK), interfaced to an AVANCE III console (Bruker, Billerica, MA) and equipped with a 12 cm gradient set. A custom-built 9 cm diameter transmitter coil was used for transmit and a custom-built 4-array surface coil was used for receive employing a transmit/receive decoupling device. A 2D gradient-echo, EPI sequence was used for the fMRI studies. MRI was run with the following parameters: effective echo time (TE) 18ms, repetition time (TR) 200ms, bandwidth 300 kHz, flip angle 20°. This sequence gave in-plane resolution of 150 microns with a 128 x 64 matrix and 500 micron thickness. A sub-skin electrical stimulation with 2.5 mA, 300μs pulses repeated at 3Hz was delivered to the whisker pads to stimulate the barrel cortex. A block design paradigm was applied for fMRI studies with 8 epochs of 4s on and 16s off for whisker pad stimulation. AFNI software was used for image analysis. For deconvolution analysis, a series of basic tent functions was fit to the hemodynamic response via linear regression. The estimated coefficient for each tent function at different time points (0-16 sec, every 0.2 sec) gave the IRF (impulse response function).

Results Fig1 shows the t-statistic maps superimposed on the 2D GE EPI images of the barrel cortex from two rats as a function of time after stimulation. Using deconvolution analysis, the activity pattern at different time points after stimulation onset can be estimated. In addition, we highlighted the most significant voxels at different time points in a manner to better visualize the spatial relationships of the active voxels and the underlying penetrating vessels. These were directly visualized by the T2* weighted EPI sequence (purple mask in Fig 2). As can be seen in Fig2, there was a clear displacement of active voxels from inter-vessel areas to the adjacent vessels after 0.8s. After 1.2 seconds, the most active voxels were mainly located on the underlying vessels (Fig 1). In Fig 3, by drawing ROIs from three different places (inter-vessel areas, penetrating vessels and surface vein) for each rat, the normalized time course confirmed the order of the activity-induced BOLD response from the area between vessels to penetrating vessel, and to the surface vein (Fig3).

Fig. 1

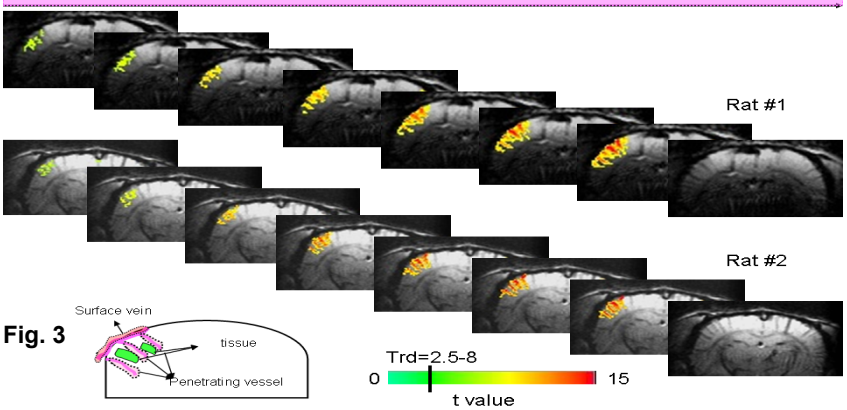


Fig. 2

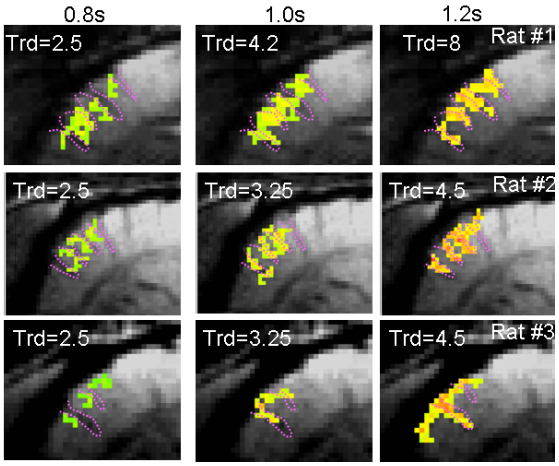
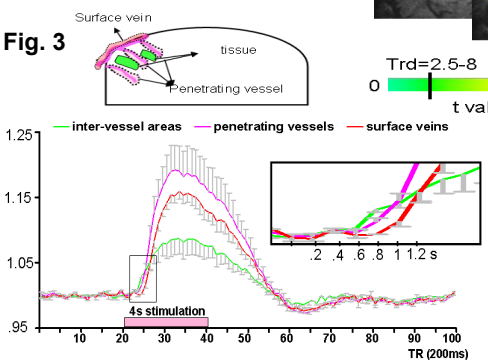


Fig. 3



Conclusion This work demonstrates the spatial evolution of the BOLD responses as a function of time in GE fMRI from inter-vessel areas to draining vessels can be detected and occur with a time delay in agreement with the transmit time detected by two-photon fluorescent imaging on rats [4]. Better localization of neuronal activity may be achievable with fMRI maps made within 1 sec after stimulation onset in the rat although at significantly reduced sensitivity (~35% of peak BOLD response).

Ref: [1] Ugurbil et al. Trends Neurosci 26, 108-114 (2003) [2] Yu X. et al., Neuroimage (2009) in press. [3].Silva et al., PNAS, 99, 15182-7 (2002) [4] Hutchinson et al., Neuroimage, 32: 520-530 (2006).