Direct Imaging of Microvascular and Macrovasular contributions by Time Resolved BOLD fMRI Allows Better Separation of Whisker Rows in the Rodent Barrel Cortex

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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]. Our previous study showed that BOLD response can be detected as early as 0.6-0.8s after stimulus onset [2]. High spatial resolution allowed separation of the active voxels into those containing large intracortical vessels (macrovasculature) and those enriched with capillary and venules (microvasculature) in a preliminary study [3]. In this case the early BOLD response observed at 0.8s encompassed mainly the voxels containing the microvasculature. Approximately 1.2s following stimulus onset, the BOLD signal propagated to the voxels containing cortical veins. These results suggest the earliest hemodynamic changes to increased neural activity occur in the microvasculature and spread towards the macrovasculature. In the present study, the time-dependent spatial patterns of BOLD response were analyzed in the whisker row-specific functional maps. It clearly showed more confined active areas for the two whisker rows at 0.8s, which became overlapped on large penetrating vessels in the late phase. Thus, the spatial specificity of fMRI can be significantly improved by analyzing data obtained within the first second following stimulus onset.

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 [4]. 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 surface coil was used for receive employing a transmit/receive decoupling device. Using the single surface coil, a single shot sequence with a 64 x 64 matrix was run with the following parameters: effective TE 18ms, TR 800ms, bandwidth 138kHz, flip angle 45°, FOV 0.96 x 0.96 cm. The slice thickness is 500μm. According to the rat brain atlas by Paxinos, the coronal 2D slice was positioned to bregma -2.0 to -2.5mm to cover the barrel S1 area of the animals. The angle of the horizontal slice was set at 50° to the horizontal line and the slice center was set at 0.95mm cortical depth to cover the IV-V layer of the barrel cortex. To stimulate different rows of the whisker pad, a two-pin electrode pad was designed with 3 mm distance between two pins. Given the current spread of the 5-pin electrode, to match a similar electrical current level, the electrical pulse was set at 0.75mA (300μs duration repeated at 3Hz) when delivered by the two-pin electrode to specific rows of the whisker. 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 0.8 sec) gave the IRF (impulse response function).

Results The somatotopic representation of whisker row B and D has been specified at the caudal barrel area for row B and the rostral barrel area for row D (Fig1.inset)[5]. Fig 1B showed functional beta maps of row B and D derived from a linear regression fit to the entire 16s hemodynamic response. The two functional maps overlapped on a large vessel between the two representational areas (Fig 1B red arrow). Fig 1C showed the time-dependent beta maps from 0 to 3.2s after stimulus onset. At 0.8s, the two beta maps were clearly separated and overlapped on the large vessel after 1.6s. Time-course analysis showed a lower mean beta value on the vessel ROI than the tissue ROIs located in row B or row D (Fig 2). This result provides evidence that the macrovascular contribution to BOLD-fMRI can be excluded by mapping the early onset BOLD response. Thus, the spatial pattern of the early onset BOLD response has better spatial specificity and provides more localized functional maps.

Ref [1]Ugurbil et al. Trends Neurosci 26, 108-114 (2003) [2] Afonso & Koretsky, PNAS, 99:15182-7. [3]Yu et al., ISMRM, 5144 (2010) [4] Yu X. et al., NI, 49 :1667-76 (2010).[5]. Chapin & Lin *J Comp Neurol* 229:199-213 (1984)

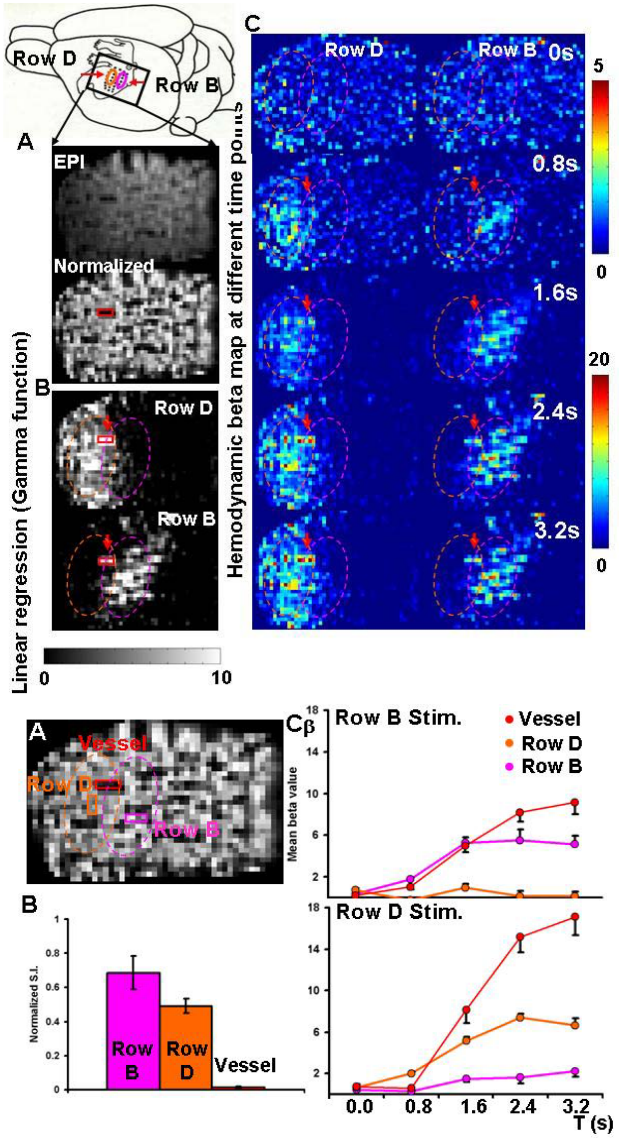

Fig 1. The representative barrel areas for whisker row B (purple circle) and D (orange circle) was shown in the figure inset. The averaged EPI image and the uniformity corrected images were shown in figure A. Figure B is the beta map derived from linear regression of the whole time course. The large vessel was highlighted in red rectangular square (red arrow). Figure C demonstrated the color-coded beta maps from 0 to 3.2s after stimulus onset.
Fig 2. ROIs on the large vessel (red), and tissue voxels in the row B (purple) and row D (orange) barrel area were highlighted in figure A. The mean signal intensity (SI) of each ROI on the uniformity normalized EPI images were shown in figure B. Figure C demonstrated the BOLD signal changes of the three ROIs by either stimulating row B (upper panel) or row D (lower panel).