"Functional Unit" of BOLD and CBV fMRI in Rat Whisker Barrel Cortex at 3T

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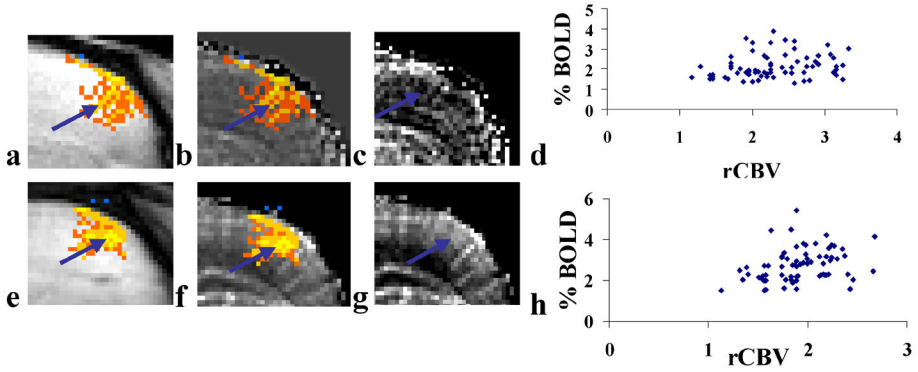
INTRODUCTION The spatial precision of fMRI methods are fundamentally limited by the anatomy of the microcirculation and the dynamics of the hemodynamic response. Changes in blood oxygenation begin at the site of oxygen utilization and persist down the intracortical penetrating veins to the pial veins. Duvernoy *et al*. (1) referred to the structure of single penetrating veins surrounded by arterial rings as the "venous unit". It is hypothesized that these venous units impose the up limit of spatial precision in T_2*-weighted BOLD fMRI at 3T. Microscopic studies of vessel changes in response to hypercapnia challenge demonstrated disproportional increases in microvessel diameters, with the smallest vessels (10 – 20 μm) showing the greatest increases (2,3). Assuming that the hemodynamic change induced by hypercapnia is a good model for changes induced by neuronal activity, we hypothesize that fMRI based on CBV contrast can be localized to small vessels with minimal extension to intracortical penetrating veins, breaking the resolution barrier imposed by venous unit. In the present study, we explore the spatial precision of fMRI using BOLD and CBV contrast in rat whisker barrel cortex at *laminar* spatial resolution. Results support the hypotheses that the venous unit limits the spatial precision in T_2*-weighted BOLD fMRI while CBV fMRI is sensitive to microvasculature instead of the venous unit.

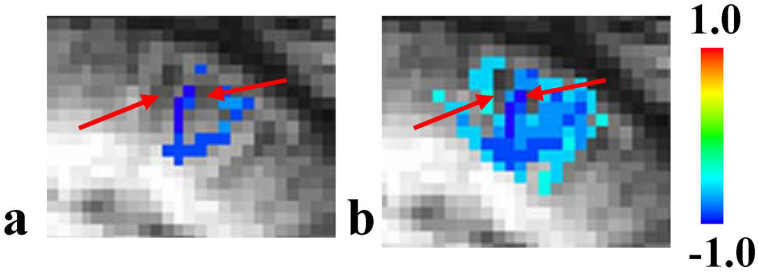
METHODS Fourteen α-chloralose anesthetized rats were artificially ventilated and scanned at a 3T scanner equipped with a high efficiency local gradient coil and RF coils (4); A homemade computer-controlled whisker stimulator was used to deliver stimulus to a comb that was used to move long whiskers (no facial hairs). Scan sequence was interleaved partial/full k-space EPI employing phase-encoded reference scans (5). Scan parameters: FOV = 2.0 cm, matrix = 128 × 128 (BOLD) or 96 × 96 (CBV), effective TR = 4s, TE = 20 ms, slice thickness = 2 mm. MION was injected at 12 mg/kg. **Data Analysis**: cross-correlation method was used to generate activation maps in AFNI (6,7). CBV time courses were fit with a Gama variant function (*F* statistics typically < 10^{-8} in the barrel cortex). Cross-correlation (C.C.) maps, peak percent signal change and mean percent signal change maps were generated.

RESULTS Figures 1a and b are the same activation map superimposed on pre- and post-MION EPI anatomical images respectively, while Fig. 1c is the baseline rCBV map. Arrows indicate pixels with high BOLD response. Fig. 1d shows % BOLD signal changes vs. rCBV values. Those pixels have high rCBV vcalues as shown in Fig. 1c. Similar phenomena can be seen in Fig. 1e-h. (rat #2).



Right: FIG. 1. Data from two rats. a (e) and b (f): activation maps on pre-, post-MION EPI anatomical images. c (g): rCBV map. d (h): % BOLD vs. rCBV.

Figures 2a and 2b are CBV cross correlation maps on MION-enhanced anatomical image (rat #3). These maps were generated from the same data with different thresholds. Figure 2a has $p<9.5\times10^{-8}$, while Fig. 2b has $p<0.005$. Arrows indicate "black holes" after MION injection. *These black holes have high blood volume weightings, but have no or low CBV response.*



Right: FIG. 2. CBV fMRI maps with different thresholds (a: $p<9.5\times10^{-8}$, b $p<0.005$).

Figures 3a-c show cross-correlation, peak percent CBV response and mean CBV response from the same data (rat #4). Pixels with high CBV response were located in deep cortical layers (layers IV-V) with some yellow pixels in layer I-III and VI. Peak percent CBV response from cortical layer I-III, IV-V and VI were calculated (n=5) and is shown in Fig. 3d. Significant difference exist in peak percent response between layer IV-V and I-III, VI ($p<0.05$), no significant difference between I-III and VI.

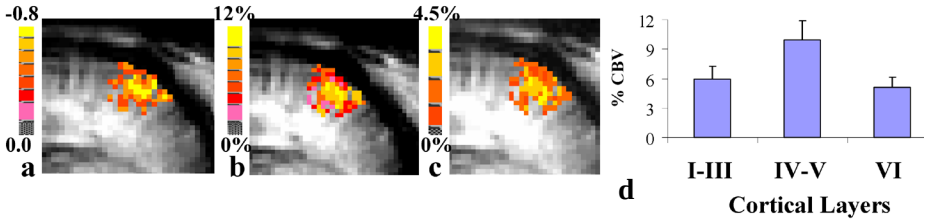


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FIG 3. Laminar specific CBV response. a: C.C.map. b and c: peak and mean CBV response, respectively. d: averaged peak CBV response across cortical layer I-III, IV-V and VI. Significant difference exist in peak percent response between layer IV-V and I-III, VI (n=5, p<0.05)

DISCUSSION BOLD response and CBV response are sensitive to hemodynamic responses from different vessel sizes. The data support the hypothesis that venous unit limits spatial precision in BOLD fMRI while the spatial precision of CBV fMRI is limited by microvessel densities, breaking venous unit limitations.