Manipulation of BOLD Resting-State Functional Connectivity and Task Related BOLD fMRI Signal by Different Anesthetic Dosages

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Introduction: Blood Oxygen Level Dependent (BOLD) resting-state physiological fluctuations have been shown to be diminished (1) or enhanced (2) by anesthesia. Data is presented in support of the hypothesis that this phenomenon is due to anesthetic effect on underling neurovascular coupling. Rats were examined with fcMRI/fMRI using four medetomidine infusion sequences: a constant 100 µg/kg/hr in two successive time blocks, or a 100 µg/kg/hr time block followed by either: a 150, 200, or 300 µg/kg/hr time block. Each block lasted approximately 2 ½ hours. Two resting-state fcMRI acquisitions proceeded fMRI experiments. Rats were stimulated with electrical forepaw stimulation with a constant 2mA current, 3 ms pulse width and either: 3,5,7, or 10 Hz frequency. Stepwise increases in voxel activation area have been previously demonstrated using this frequency range (3). This stepwise increase in voxel area was used as a marker for neurovascular coupling. It has been previously demonstrated that electrophysiological local field potentials are directly correlated to voxel area in response to forepaw stimulation (4). In this work, data is presented that shows that medetomidine anesthesia dosage can directly affect this stepwise increase in BOLD activation area in response to rising stimulation frequency. Data also is presented that demonstrates resting-state functional connectivity is dependent upon anesthetic infusion rate.

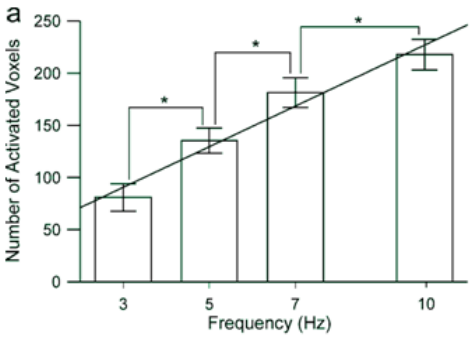

Figure 1: Stepwise increase in voxel activation area to forepaw stimulation of 3,5,7, 10 Hz during the initial 100 µg/kg/hr time block.

Methods: Six Sprague-Dawley rats (300 – 400 g) were used for each of the four infusion experiments. A Bruker AVANCE 9.4T small animal scanner was used for all experiments. Resting-state echo planar imaging (EPI) scans were acquired prior to fMRI electrical stimulation experiments. EPI parameters were: TE=18.76 ms, TR=2 sec, FOV=3.5 cm, and 1 mm slice thickness; 110 images were acquired for both fcMRI and fMRI.

Results: Figure 1 displays the increase in voxel area in response to larger stimulation frequencies. (*Denotes statistical significance between the columns) This stepwise increase is linear. Figure 2 demonstrates how this response to stimulation is attenuated for the 100/150 µg/kg/hr (Figs. 2a,b) secondary dosage. The stepwise dependence is maintained for the 200/300 µg/kg/hr (Figs. 2c,d) secondary dosages. Figure 3 displays attenuation of resting-state functional connectivity during constant 100 µg/kg/hr medetomidine infusion.

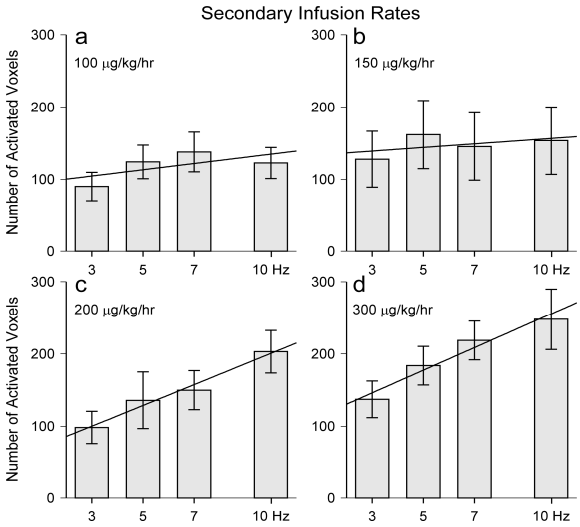

Figure 2: BOLD response to stepwise frequency stimulation at 3,5,7,10 Hz during secondary infusion time blocks: a) 100 b) 150 c) 200 or d) 300 µg/kg/hr

Discussion: This study provides evidence that anesthetic dose has an effect on BOLD response to forepaw stimulation frequency. This stepwise response has been previously shown to be tightly coupled in the neurovasculature (3). fcMRI data in the same animal under the same anesthetic conditions demonstrated changes in BOLD resting-state functional connectivity. This study provides evidence that the underlying mechanism of BOLD fcMRI and fMRI may be linked.

References: 1) Nature 447, 83-86. 2007 2) MRI 23, 531-37. 2005 3) Neuroimage 39, 248-60. 2008 4) JMRI 22, 483-91. 2005

Figure 3: Resting-state regional pairwise functional connectivity correlation matrices from the rat sensorimotor system during the initial 100 µg/kg/hr block (left), secondary 100 µg/kg/hr block (middle). Difference matrix demonstrating difference values between conditions (right).