Neurophysiological and neuroenergetic basis of spontaneous BOLD signal fluctuations in resting-state fMRI connectivity maps

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TARGET AUDIENCE. Neuroscientists interested in the metabolic/neural basis of resting-state fMRI connectivity maps.

PURPOSE. Resting-state fMRI (R-fMRI) is a popular way to measure brain-wide networks in humans. Spontaneous fluctuations in BOLD signal, based on the degree of co-variation across regions, are associated with gray matter networks and are referred to as functional connectivity maps[1]. However a lack of understanding in neurophysiological and neurometabolic basis of spontaneous BOLD signal fluctuations has made translation of R-fMRI to clinical settings difficult. The spontaneous BOLD signal fluctuations can either originate purely from hemodynamic variations, or oscillations in metabolic/neural activities, as well as combinations of these components[2]. Task-evoked responses have been shown to be dependent on the absolute level of baseline activity (i.e., in higher metabolic/neural baseline state the functional response is smaller but delocalized, whereas lower metabolic/neural baseline state shows higher amplitude localized responses)[3]. Other studies have shown that spontaneous fluctuations in BOLD signal seem to be important in local variability or trial-to-trial reproducibility of the functional responses[4]. Together these results suggest that the absolute metabolic/neural baseline state may be an important factor in interpreting R-fMRI data. This study was designed to understand the relationship of absolute baseline neurophysiological and neurometabolic activity to the spontaneous BOLD signal fluctuations in functional connectivity mapping. In two anesthetized states (α-chloralose – low baseline, medetomidine – high baseline), rats underwent multi-modal recordings of blood flow by laser-Doppler, absolute rates of glutamatergic neurotransmission ($V_{cyc(tot)}$) and neuronal glucose oxidation ($CMR_{glc(ox),N}$) by MRS, multi-unit activity (MUA) and local field potential (LFP) from extracellular signal, and R-fMRI derived functional connectivity maps from seed-based correlations and correlation density mapping.

METHODS. ***Animal preparation:*** Sprague-Dawley rats were tracheotomized and artificially ventilated (70% N_2O, 30% O_2). The anesthesia was switched to i.p. α-chloralose (40 mg/kg/hr) or i.v. medetomidine (0.1mg/kg/h) from isoflurane (1-2%) after the surgery. A femoral arterial line was used for monitoring blood pressure, acid-base balance and blood gases throughout the experiment. ***R-fMRI (n=10):*** All fMRI data were obtained at 11.74T using a ^{1}H resonator/surface coil. All images were acquired with gradient echo EPI (TR/TE=200/12.53 ms, NR=4200). ***CBF, MUA, LFP (n=18):*** Rats were placed in a stereotaxic holder and tiny burr holes were made above left and right somatosensory regions (S1). Tungsten microelectrodes were inserted together with laser Doppler probes for CBF recording. The MUA and LFP were extracted from the raw extracellular signal with electronic filters. ***^{13}C MRS (n=14):*** Proton-observed carbon-edited (POCE) MRS data were acquired at 11.7T using continuous infusion of [1,6-^{13}C]-labeled glucose through femoral vein to measure absolute rates of $V_{cyc(tot)}$ and $CMR_{glc(ox),N}$, where absolute CMR_{O2} was derived from $CMR_{glc(ox),N}$. ***Analysis:*** The temporal fluctuations of neural activity signals (denser and rarer regions in the MUA or LFP) was estimated using the spike rate and UP state[5] time of the signal. The fluctuations of CBF signals were estimated by their standard deviation (SD). POCE data were analyzed by the CWave program to calculate neuronal glucose oxidation ($CMR_{glc(ox),N}$) and glutamate-glutamine cycling rate ($V_{cyc(tot)}$). Fluctuations of the BOLD signals were estimated using voxel by voxel SD. In each state, we used the SD fluctuations of CBF and BOLD signal to derive the variance of CMR_{O2}. The R-fMRI data were used to calculate functional connectivity maps in two ways: seed-based correlations or correlation density mapping, where Pearson's correlations on low-pass filtered (≤1Hz) BOLD signals were used to create functional connectivity density (FCD) maps[6]. Finally, the SD measures were used to depict the magnitude of fluctuations of each signal in relation to the absolute level of metabolic/neural activity for each state.

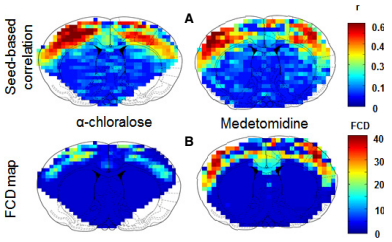

Figure 1. Maps by (A) seed correlation analysis and (B) FCD analysis.

RESULTS. R-fMRI derived seed-based correlation maps for the states failed to show significant difference (0.18±0.05 vs. 0.18±0.07, p=0.78, Figure 1A), whereas FCD maps showed significant alteration between the two states (6.11±3.66 vs. 21.95±5.02, p<0.001, Figure 1B). Figure 2A shows that deep anesthesia with α-chloralose and light anesthesia with medetomidine provided significantly different absolute rates of neuronal metabolism (p<0.002, 0.23±0.06 vs. 0.39±0.08 µmol/g/min, $CMR_{glc(ox),N}$) and glutamatergic neurotransmission (p<0.002, 0.21±0.07 vs. 0.32±0.08 µmol/g/min, $V_{cyc(tot)}$), in good agreement with absolute measures of neuronal activity as reflected by spike rate (from MUA, Δ=37.5%, p=0.003) and UP ratio (from MUA and LFP, Δ=61.7% and Δ=44.8%, respectively, p<0.001). Figure 2B shows that the SD of fluctuations for CMR_{O2} was greater in medetomidine because the SD of fluctuations for CBF and BOLD signals were all greater (p<0.004), in good agreement with other measures of magnitude of variance in metabolic/neural activities underlying R-fMRI connectivity maps. Thus regardless of the baseline state, the magnitude of these variations represented at most 5% of the total baseline metabolic/neural activities.

DISCUSSION. We characterized fluctuations of multi-modal neuroimaging signals at two different baseline levels, where larger fluctuations (i.e., larger SD) were observed when baseline energy was high. A plausible explanation of these results is that with light anesthesia and higher metabolic activity, the fluctuations in neural activity is larger due to higher frequency signaling. While the absolute energy fluctuations are different in baseline states and well correlated with the FCD maps, the relative energy fluctuations are baseline independent similarly to seed-based correlation maps, indicating that the R-fMRI networks exist in every energy state, but their degree of connectivity, the FCD map is baseline dependent. For clinical applications of R-fMRI it will be important to assess the energetic cost of connectivity maps in relation to total baseline for pathophysiology. These results signify the importance of FCD for R-fMRI and emphasize the need for absolute baseline for R-fMRI.

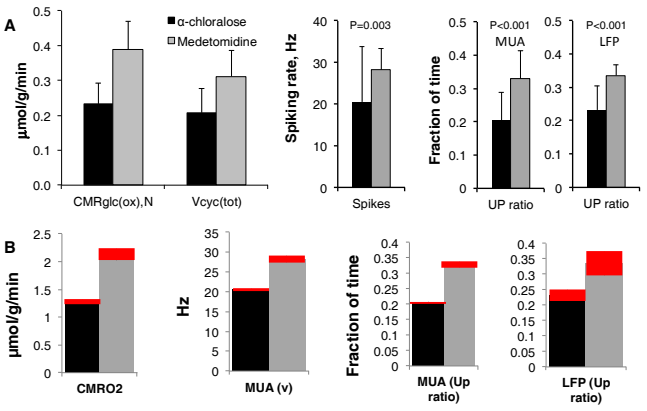

Figure 2. Quantitative metabolic and neural activities in terms of (A) absolute level for each state (black/gray) and (B) variation within each state (red).

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