Spontaneous activity in the delta band drives the resting state MRI (rsMRI) signal: A combined rsMRI and electrophysiological study in rat whisker barrel cortex

Hanbing Lu[1], William Rea[1], Leiming Wang[1], Elliot A Stein[1], and Yihong Yang[1]
[1]*National Institute on Drug Abuse, Baltimore, Maryland, United States*

Purpose Spontaneous fluctuations in the resting state MRI (rsMRI) time courses have been shown to exhibit structured spatial and temporal patterns, and are modulated in a variety of diseases. However, the underlying mechanisms are still poorly understood. Several lines of evidence suggest the important role of spontaneous slow and infraslow EEG oscillation underlying the low-frequency blood oxygenation level dependent (BOLD) fluctuations (1-3). However, contrasting hypotheses emphasize the roles of higher frequency (gamma) activity. Mounting evidence supports the proposition that gamma enhancement reflects a state of high neuronal excitability and synchrony, and is involved in brain operations ranging from simple sensory perception, to perceptual binding, selective attention and memory. However, the amplitude of gamma activity is often coupled with the phase of lower frequency delta and theta oscillations. One approach to disentangle the relationship between electrophysiological and rsMRI signal is to investigate how evoked responses interact with ongoing spontaneous brain activity. To this end, we use a whisker barrel cortex (WBC) stimulation model to investigate this question.

Material and Methods An MRI-compatible apparatus was developed such that rat whiskers could be moved rostral-caudally by a comb controlled by computer. fMRI Experiments were performed on a Bruker 9.4T scanner. Rats (n=9) were anesthetized with a combination of dexmedetomidine and low dose of isoflurane, and received fMRI scans with and without ***continuous*** whisker stimulation (TR/TE=1000/15 ms, 11 slices, 1 mm slice thickness, 300 repetitions). A block design paradigm, consisting of 20s baseline followed by 3 cycles of 20 s ON and 40 s OFF, was also applied to identify the WBC.

Electrophysiological study: Under identical anesthetic conditions, multi-channel epidural EEG signals were recorded from a separate cohort of rats (n=10) using a Plexon system with semi-micro electrodes. Recording sites: bilateral WBC with the visual cortex serving as a control site. EEG mean power, power time correlation and raw EEG signal coherence between electrode pairs were computed using the complex Morlet Wavelet analysis method.

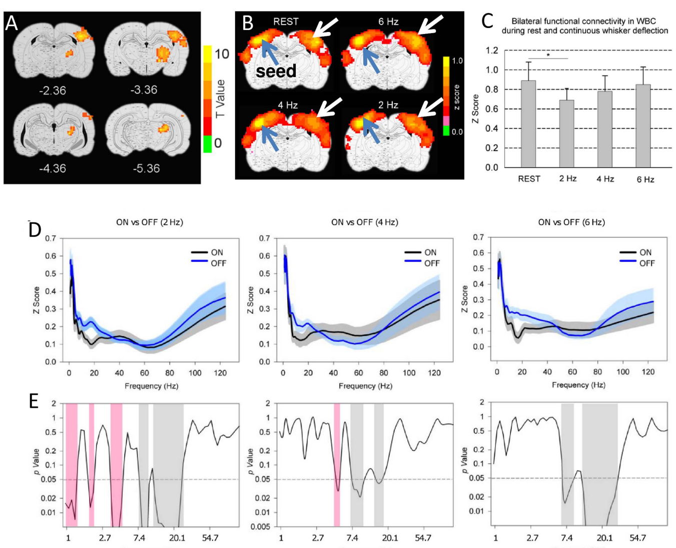

Figure 1. **A**: Group activation maps (n=9) induced by unilateral whisker deflection using the block-design paradigm. Activated areas include ventral posterior lateral and medial thalamus (VPL/VPM), primary barrel cortex (S1BF), and secondary somatosensory cortex (S2). **B**: Raw functional connectivity maps from one rat during the resting condition and during continuous unilateral whisker stimulation (2, 4 and 6Hz); white arrows=WBC; Blue arrows indicate seed voxels. **C**: Continuous unilateral whisker stimulation at 2 Hz, but not at 4 or 6 Hz, significantly reduces functional connectivity in bilateral whisker barrel cortex (N=9; *, *p*=0.001). **D:** Plots of power correlation (n=10) between bilateral WBC as a function of EEG frequency for each of the 3 whisker stimulations. **E:** Unilateral whisker stimulation significantly reduces power correlations in low frequency range (nctional connectivity in bilateral whisker barrel cortex (N=9; *, the complex r frequency delta and theta s (>4 Hz, gray shading) was reduced across all 3 stimulus condition (2, 4 and 6 Hz).

Results Robust BOLD response was seen in all rats with group activation maps shown in **A**. In comparison to the resting condition, continuous unilateral whisker stimulation significantly modulated bilateral functional connectivity only at the 2 Hz, but not the 4 or 6 Hz condition (**B & C**). Epidural EEG recording revealed that, in the high frequency ranges, power correlation in bilateral WBC was significantly modulated across *all* stimulation conditions. However, *only* in the delta frequency range was the power correlation significantly modulated at 2 Hz, but not at 6 Hz stimulus condition, *paralleling the fMRI findings*. Power correlation in other frequency ranges were similarly modulated irrespective of the stimulus conditions.

Discussion There have been substantial efforts to elucidate neuronal basis of spontaneous fluctuations observed by rsMRI. A number of studies reported that correlational activity in the high frequency band (gamma band) underlies the rsMRI signal. Several studies emphasize the role of alpha rhythm in temporal dynamics of rsMRI signal (4-6). Given the tight neurovascular coupling, it is conceivable that brain electrical activity at all frequency bands should have distinct hemodynamic signatures (7-9). The question, however, is to find the major driving force that underlies the rsMRI signal. While it is convenient to compare the correlational strength in LFP signal and rsMRI signal, spurious correlation could occur given that these are two fundamentally different measures.

We reason that if LFP signal in the high frequency bands are the major contributors, to the BOLD resting correlations, then by modulating brain electrical activity within these bands, one should expect modulations in corresponding fMRI functional connectivity coherence. This is not supported by our data: significant changes in power correlation were observed across all three stimulation conditions (2, 4 and 6 Hz), but only at the 2 Hz stimulation condition did we observed significant changes in functional connectivity. On the other hand, when the whisker stimulation induced power correlations in the delta band, we also observed changes in functional connectivity. These findings together support the view that spontaneous activity in the delta band drives the rsMRI signal as manifested in functional connectivity.

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