Alternating Phase Coherence of Spontaneous Hemodynamic Oscillation is Sensitive to Anesthesia Levels

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Introduction Coherent fluctuation of blood oxygen level dependent (BOLD) signals has been widely observed in human and animal brains, and it was hypothesized to reflect spontaneous brain activity and reflect a variety of "resting-state" brain networks [1–2]. Besides positive correlations, negative correlations have also been observed between spontaneous BOLD signals from different brain regions, for example the task-positive attention system and task-negative default mode network [3]. Although it was suggested later that such negative correlations may be caused by the global signal correction procedure [4], an electrophysiology experiment in cat did observe similar negative correlations between local field potential (LFP) powers of "task-on" and "task-off" brain regions [5].

In this study, we found that spontaneous cerebral blood flow (CBF) signals recorded from the cat primary visual cortex (V1) demonstrated very strong and slow oscillations at ~0.1 Hz, and their inter-hemispheric phase coherence varied with time and sometimes showed strong negative correlations. More importantly, the distribution of phase coherence strength is sensitive to the level of anesthesia with anti-correlations appearing more frequently under deeper anesthesia. Similar phenomenon was also observed on spontaneous BOLD signals acquired under the same condition. The findings suggest spontaneous hemodynamic coherence is a dynamic property, and its dynamics can be affected by brain states. This may provide new insights into the relationship between the resting-state connectivity reflected by BOLD coherence and the brain states.

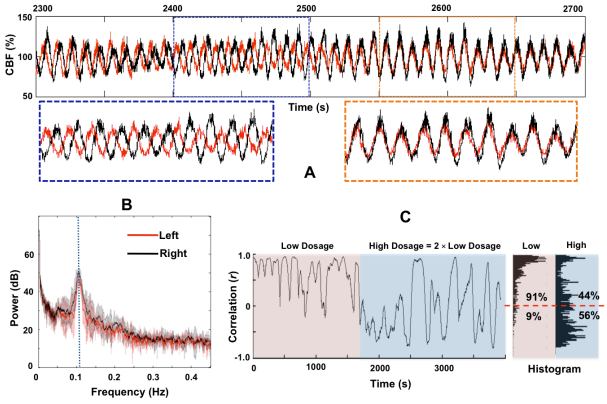

Fig. 1 A segment of CBF signals from the left (red) and right (black) visual cortex demonstrates the change of their phase coherence over time (A); the power spectra (the shadows represents 99% CI) show the ~0.1 Hz frequency of CBF oscillations (B); such inter-hemispheric phase coherence varied between positive and negative, and their relative proportions (histograms in the right side) changed significantly under different levels of anesthesia (C).

Methods Five cats were initially anesthetized with isoflurane (0.8-1.2%) and was then switched to alpha-chloralose anesthesia with initial dose of 25 mg/kg followed by continuous intravenous infusion of 25–50 mg/kg/hr. For a group of two cats, two Laser Doppler flowmetry (LDF) (Oxford Optronix, UK) probes were inserted into the bilateral V1 regions through two small holes opened symmetrically on the skull. The CBF signals were then recorded continuously over one hour at two different anesthesia levels: infusion rates of 25 mg/kg/hr (low dosage) and 50 mg/kg/hr (high dosage), respectively.

FMRI studies were performed on another group of three cats (with alpha-chloralose infusion rate at 25 mg/kg/hr) on a 9.4T horizontal magnet (Magnex Scientific, UK) interfaced with a Varian INOVA console (Varian Inc., Palo Alto, CA). The GE–EPI (FOV = 5×5 cm^2; TR/TE = 200/17.5 ms) was used to acquire 4 coronal fMRI slices (64×64 image matrix size; 2 mm thickness) covering both V1 and the lateral geniculate nucleus (LGN), part of thalamic-cortical visual network. The conventional block-design fMRI runs were first carried out to generate functional activation maps, then, spontaneous BOLD signals were acquired under the condition without stimulation. Based on this resting-state fMRI (rs-fMRI) data, correlation maps were calculated with respect to the BOLD time course from 2×2–voxel×voxel regions located in the right LGN and V1 areas, respectively, without using global signal correction.

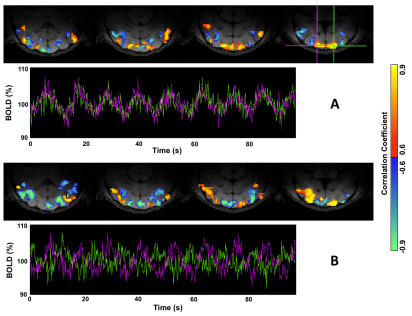

Fig. 2 Resting-state correlation maps with respect to the right V1 region (green cross) shows different phase coherence between the left and right V1 regions under two different runs A (positive) and B (negative). The corresponding BOLD signals demonstrate very similar oscillation as CBF signals

Result Figure 1A shows a segment (400 sec) of CBF signals recorded from bilateral V1 regions of a representative cat. The CBF signals clearly demonstrated very strong (~50% peak-to-peak) oscillations at ~0.1 Hz (Fig. 1B). Within this 400-sec time window, the inter-hemispheric phase coherence had a dramatic transition from strong negative (the segment in blue box in Fig. 1A) to strong positive (the segment in orange box). We calculated inter-hemispheric correlations within a sliding window (size: 30 sec, step: 3 sec) and obtained a curve describing CC values as a function of time (Fig. 1C). It is clear that under the low-dosage of anesthesia the inter-hemispheric phase coherence was maintained at a high level (highly skewed histogram with 91% CC curve points being positive). In contrast, after we doubled the dosage of anesthetics, the distribution of phase coherence changed significantly (Fig. 1C, right). The negative correlations appeared much more frequently (more uniform distribution with negative correlations appearing 56% of total time). This result suggests the strong influence of anesthesia depth on the inter-hemispheric phase coherence of CBF signals.

Figure 2 shows the rs-fMRI correlation maps with respect to the right V1 region (Fig. 2, green cross) from a representative cat. Figures 2A and 2B are two maps from the same cat but different runs. It is obvious that the left (magenta cross) and right V1 regions show quite distinct phase correlations under these two runs (positive for A, and negative for B). Based on BOLD time courses from these two regions, we can see that they both demonstrated strong (~5%) oscillations at ~0.1 Hz but with quite different phase coherence, which is very similar to those observed in the CBF experiment (Fig. 1A). More interestingly, the left and right LGN (identified by fMRI map shown in right panel of Fig. 3) also demonstrate the distinct phase coherence in two different rs-fMRI runs (see Fig. 3).

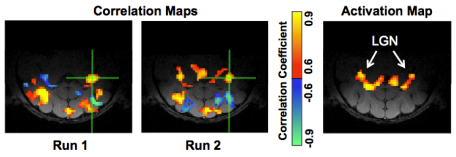

Fig. 3 The left and right LGN showed different phase coherence in two different rs-fMRI runs

Discussion and Conclusion Although we focused on different brain regions (left and right V1) and used a different anesthetics, the hemodynamic oscillations observed in our study share many common characteristics with the LFP power fluctuations observed in the previous electrophysiology experiment on cats [5]: ~0.1 Hz frequency and the change of signal phase coherence over time. They may originate from similar neural sources. The previous study also showed that the brain states (slow-wave sleep versus waking) could reduce the appearance frequency of anti-phase correlations, while our study demonstrated that the level of anesthesia could significantly affect the phase coherence distribution. The reduced inter-hemispheric coherence under deeper anesthesia may be due to reduced large-scale neuronal synchronization, which could happen at the stage as early as thalamic nuclei (LGN). A previous study on human subjects has shown that the resting-state connectivity reflected by spontaneous BOLD fluctuations is dynamic rather than static [6], and the finding of the present study supports this view. More importantly, our results further demonstrate that even the dynamics of spontaneous BOLD coherence (resting-state connectivity) will also change across different brain states.

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References 1. *Biswal B. et al. MRM 1995* 2. *Fox MD. et al. Nat Rev Nerosci 2007* 3. *Fox MD. et al. PNAS 2005.* 4. *Murphy K. et al. NeuroImage 2008* 5. *Popa D. et al. J Neurosci 2009* 6. *Chang C. et al. NeuroImage 2009*