Studying Coherent BOLD Fluctuation and Functional Connectivity of Cortico-thalamic Visual Network in Anesthetized Cat Brain and their Dependence on Anesthesia Depth

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Introduction The coherent fluctuations of blood oxygen level dependent (BOLD) signals have been widely observed in many brain networks at the resting-state. It was hypothesized that such spontaneous coherent BOLD fluctuation might indicate the underlying anatomical and functional connectivity between different brain regions; therefore it was also named as "resting-state functional connectivity"[1]. However, the underlying mechanism of this observation still remains elusive; and its neural origin is still in doubt[2]. To further investigate the coherent BOLD fluctuations, animal models some times provide better choices than human subjects. So far the coherent BOLD fluctuation has been observed in the anesthetized monkey[3] and rat[4] brains, but to our knowledge no related studies have been done on cats, which are widely used in neuroscience researches. Moreover, most studies in the literature were to address the resting connectivity among different cortical regions. It should be essential to explore if the resting-state functional connectivity also exists in the cortico-thalamic networks.

The purpose of the present study is to examine the coherent BOLD fluctuation at resting-state in the anesthetized cat brain with the focus on the visual system. We found that the spontaneous BOLD signals from the lateral geniculate nucleus (LGN), posteromedial lateral suprasylvian area (PMLS), area 18 and 19 were temporally correlated with that from the primary visual cortex (V1, area 17). We also observed that such coherence (temporal correlation) was much stronger at the light anesthesia condition (~0.4% isoflurane) than in the mild anesthesia condition (~1.0% isoflurane). These findings not only prove the existence of coherent BOLD fluctuation in the cat brain, but also provided evidence for supporting the neural origin of coherent BOLD fluctuation.

Methods Two cats were anesthetized with ~1.0% isoflurane in 70% N_2O/30% O_2 gas mixture. The head position of cat was fixed by a home-built head-holder with mouth-bar and ear-bars. All the fMRI studies were performed on a 9.4T horizontal magnet (Magnex Scientific, UK) interfaced with a Varian INOVA console (Varian Inc., Palo Alto, CA) and a surface coil. The multi-slice T_1-weighted anatomical images were acquired first for identifying the cat LGN and V1 for appropriately choosing fMRI image slices. Then, the GE EPI (FOV = 5×5 cm^2; TR/TE = 250/17.5 ms) was used to acquire 4 coronal fMRI slices (64×64 image matrix size; 2 mm thickness) covering both LGN and V1. To generate functional activation maps, the visual stimulus (2 Hz flickering red LED boards) was presented to the cats in a block-design manner (3 control and 2 task blocks in an interleaved way). All the other runs were acquired when the cats were in uniform darkness; we regard it as the resting-state. The resting-state fMRI BOLD time courses were acquired under light (~0.4% isoflurane) and mild (~1.0% isoflurane) anesthesia condition, respectively.

The functional activation map was generated by the period cross correlation method, and the most activated (having the highest correlation coefficient with the block-design paradigm) 2×2-pixel region was chosen inside V1 as the reference region. For each run of the resting-state dataset, the time courses from all the pixels were cross-correlated with the reference time course extracted from the reference region to generate a correlation map for each run.

Result Figure 1 shows the fMRI activation maps (Fig.1.a) and the resting-state correlation maps under light (Fig.1.b) and mild (Fig.1.c) anesthesia conditions. The activation was robustly observed in the left- and right-hemispheric LGNs and V1 as demonstrated in Fig.1.a. From the correlation map obtained under the light anesthesia condition (Fig.1.b), there is a clear and strong resting-state coherent network connecting to: i) the PMLS area, which is responsible for motion processing and homologous to the middle-temporal (MT) areas of primates; ii) the areas 17, 18, 19; and iii) a less extent to LGNs. The LGNs would disappear in the correlation maps if we increased the threshold of correlation coefficients from 0.2 to 0.3; but if we lowered the threshold to 0.15, the right LGN on the left slice could also show up.

Compared with the light anesthesia condition, the coherence strength of BOLD fluctuation within the visual system decreased dramatically under the mild anesthesia condition. The LGNs could not appear in the correlation map (Fig.1.c). In addition, not many regions showed significantly negative correlations with the V1 reference.

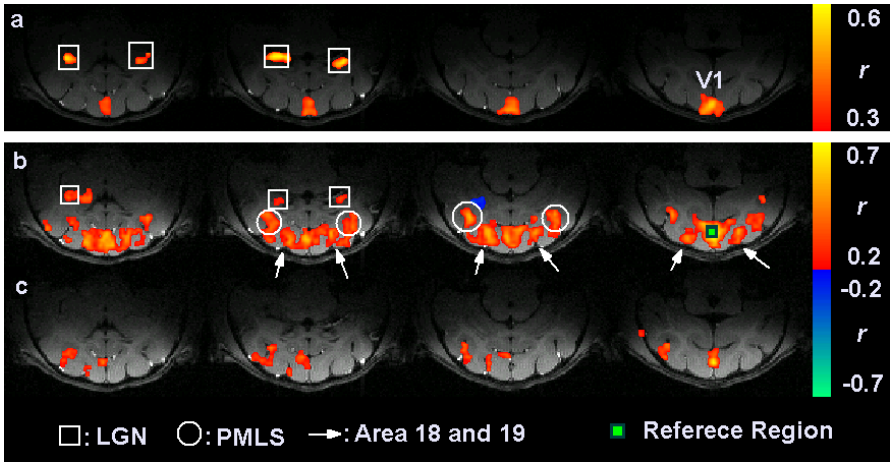

Fig.1. Functional activation map (a) indicating the evoked regions to visual stimulus, and the correlation maps for the low anesthesia condition (~0.4% isoflurane) (b) and the high anesthesia condition (c). The correlation coefficients (r) for activation map indicate with the block-design task paradigm, while the r for correlation maps indicate the correlation with the reference region (green square).

Discussion and Conclusion The coherent BOLD fluctuation between LGNs and V1 observed in the present study provides a piece of strong evidence against the argument[2] that coherent BOLD fluctuations could originate from vessel-dynamic regulations rather neural activity, since the blood supply to the LGN and V1 regions are unlikely to be homologous. Regarding the relatively weak correlation between the LGNs and V1 areas (their connections through the radiation fibers are very well-known), there are at least two possible explanations. First, the use of surface coil in the present study decreased the signal to noise ratio (SNR) in the thalamus area. An alternative one is that the cortico-thalamic network coherences are not as strong as the cortico-cortical network coherences. The further experiments are needed to verify this possibility.

The strongest coherence observed in our study is between the V1 area and PMLS area, which was some times also activated by the external visual stimulus[5] but not robustly. This finding was consistent with the result of the previous study[3] which observed the coherence BOLD fluctuation between MT and V1 areas in the anesthetized monkey brain. Also, the neuron recording experiment[6] has demonstrated that PMLS neurons can fire synchronously with the neurons from V1 at the frequency band of 40~60 Hz (gamma-band) upon visual stimulations. Their study observed the synchronization at cell level under stimulations, while our study found the coherence at system level at resting-state; this might provide us some clues about the neural origin of coherent BOLD fluctuation. Similar synchronizations were observed between neurons from the areas 18 and 19 and those from the area 17[7], and the BOLD signals from those regions also fluctuated coherently in our study.

We also observed that the coherence strength of BOLD fluctuations decreased dramatically when the anesthesia depth increased. This is probably one of reasons why most of studies concerning coherent BOLD fluctuations were carried out on waked human but not anesthetized animals. It also implies that the alertness might be an important factor affecting the strengths of coherent BOLD fluctuation and the resting-state functional connectivity. Therefore, the spontaneous neural activity associated with the coherent BOLD fluctuations may have an important role in maintaining consciousness and normal brain function.

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