Modulation of Coherent BOLD Fluctuation in Human Visual Cortex with Continuous Brain Stimulation

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Introduction The functional magnetic resonance imaging (fMRI) studies have demonstrated that at the resting-state low-frequency (< 0.1 Hz) fluctuation of the blood oxygen level dependent (BOLD) signals are temporally and spatially correlated within the human motor cortical areas[1], as well as other brain networks, such as the visual, auditory, language and default mode systems. It was hypothesized that such spontaneous coherence of BOLD fluctuation might indicate the underlying anatomical and functional connectivity between different brain regions. If this hypothesis is right, we would expect that the coherent BOLD fluctuation could be modulated (or re-synchronized) when the brain networks are engaged in certain tasks or activated by specific stimuli. Therefore, examination of coherent BOLD fluctuations under conditions other than resting-state would help us to better understand its underlying mechanism.

The purpose of the present study is to investigate the modulation of coherent BOLD fluctuations within human visual system under continuously-stimulated conditions. By examining the coherent BOLD fluctuations under three desired steady conditions: (a) resting-state (RS); (b) the condition with continuous half-field visual stimulus (CCHVS); and (c) the condition with continuous full-field visual stimulus (CCFVS), we found that (i) under continuously-stimulated conditions, the activated region formed its own coherent network while the inactivated regions of visual system still remained their temporal correlation similar to resting-state; (ii) the coherent network at RS covered the widest area of the visual cortex and included some regions which were not activated by full-field visual stimulus; and (iii) no significant differences in terms of coherence strength were found among the three steady brain conditions.

Method Five healthy subjects (two females) were scanned on a 4T/90 cm bore magnet (Oxford, UK) system with the Varian INOVA console (Varian Inc., Palo Alto, CA) and a RF surface coil. For the fMRI experiment, GE-EPI (FOV = 20×20 cm^2; TR/TE = 500/30 ms) was used to acquire 3 adjacent coronal image slices (64×64 image matrix size; 5 mm thickness) covering the calcarine fissure in the primary visual cortex based on the anatomical information.

The half- (right side of visual field) and full-field visual stimuli were the radial red-black checkerboard flashing at 8 Hz with a white cross-mark in the center. The first two runs of fMRI experiment were carried out in a block-design manner (two stimulated blocks were sandwiched by three control blocks with only the cross-mark) with the half- and full-field stimuli, respectively. Then, the fMRI signals were acquired under three steady conditions. Each condition had 2~4 fMRI runs which contained 550 image volumes. The fMRI datasets with serous motions were abandoned, and then motion-correction was done for the rest datasets. The fMRI data from the first two runs were used to create the activation maps for the half- and full-field stimuli by the period cross correlation method. For the fMRI data acquired under the steady conditions, first 20 image volumes were abandoned to guarantee the steady state; then a band-pass filter (0.005~0.1 Hz) was applied in time domain to remove the linear drift and the possible fluctuations induced by cardiac and respiratory pulsations. Based on the activation maps, two most activated 2×2-pixel regions (from left- and right-hemisphere, respectively) were chosen as the left and right reference regions. For each run, the time courses of all the pixels were cross-correlated with the average time courses of the reference regions to create two correlation maps, which then were transformed to two Z maps according to the well-established method[2].

To quantify the coherence strength, the activation regions in left and right hemisphere were defined as two Regions of Interest (ROIs). Then, the Z scores of **left** Z map (created based on left reference region) were averaged within these two ROIs to obtain statistics $\overline{Z}_{LL}$ and $\overline{Z}_{RL}$. The linear mixed model taking inter-subject variation as random effect was used to combine the results from all subjects and give the statistical inference.

Result The fMRI activation maps and Z maps from one representative subject are shown in Fig.1. The left and right Z maps in Figs.1. c, d and e were color-coded (red and green) and combined in the same map. Among three brain conditions, only the left and right Z maps for the CCHVS (Fig.1.c) have almost no overlaps. The left Z map (red) just covers the activated regions by the half-field stimulus, while the right Z map (green) covers the remaining inactivated regions (see Fig.1.a and c). In contrast, for the CCFVS (both hemispheres were activated) and RS (both hemispheres were not activated), the left and right Z maps (Figs.1.d and e) are largely overlapped. Comparing Z maps from these two conditions, we also note that Z maps of the CCFVS are much more similar to the fMRI activation map for the full-field stimulus (see Figs.1.b and d) than the Z maps of RS, which cover wider cortical regions including *cuneus* (delimited by white line in Fig.1.d). These results imply that the spontaneous coherent network of visual system at the resting-state covers wider regions than what can be activated by external stimuli.

To quantify the above observations, the statistics were calculated from all subjects and summarized in Fig.2.b. At the significance level of 0.01, no significant differences were found among the three conditions in terms of the intra-hemispheric coherence strength (quantified by $\overline{Z}_{LL}$). However, inter-hemispheric coherence strength (quantified by $\overline{Z}_{RL}$) decreased significantly under CCHVS, in which case the inter-hemispheric coherence is equivalent to the coherence between the activated region and the inactivated region. For the RS and CCFVS conditions, in contrast, the intra-hemispheric and inter-hemispheric coherence are almost equal.

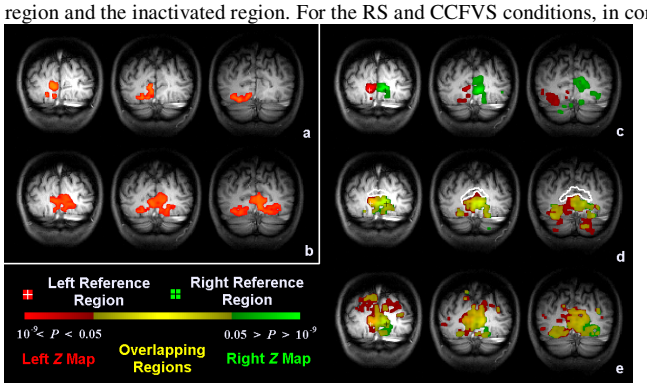

Fig.1. Typical multiple-slice maps from one representative subject. Functional MRI activation maps for half-field stimulus (a) and for full-field stimulus (b), as well as Z maps for CCHVS (c), CCFVS (d), and RS (e) are thresholded and overlapped on the anatomical images.

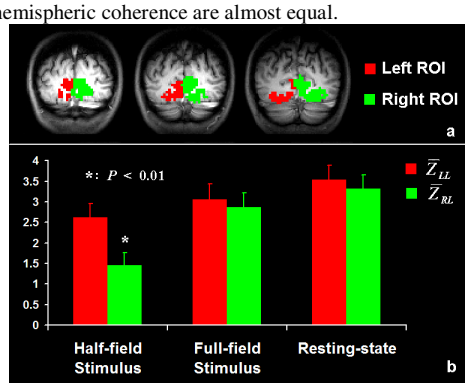

Fig.2. Statistics summary for all subjects. (a) An example of ROIs used to calculate the statistics. (b) The comparison between the statistics from the three steady brain conditions. The statistics for CCHVS and CCFVS were compared with those for RS, the significant changes were marked by stars.

Discussion and Conclusion Our results show that the spatial pattern of coherent BOLD fluctuation is significantly modulated under continuous stimulations: the activated region formed its own coherent network, which is distinct from the coherent network of the inactivated brain region. Taking into account the recent report about the relationship between resting-state BOLD fluctuation and simultaneous EEG signals[3], our findings could be explained by combining the cell assembly hypothesis[4] and the synchrony binding theory[5] at the system level: i.e., the dominant frequency of synchronized oscillator was shifted in the activated brain area (e.g., from alpha-band to gamma-band). The tight correlation between the hemodynamic response (recorded by optical imaging technique) fluctuation and the power of gamma-band EEG observed in the cat visual cortex under the constant stimulation[6] adds a strong support for this explanation, despite more experiments and investigations are needed to prove it. We also show that the coherence strength of BOLD fluctuation did not change significantly under continuous stimulations, and this is inconsistent with the former observations in the working memory network[7] and language system[8]. One of possible explanations is that the task paradigms used in those studies contained low-frequency and periodic task components, which might contribute to the increased strength of BOLD coherence. Our results suggest that majority of neurons might be characterized with strong and coherent interaction in the resting brain; the external stimulation would not increase this interaction strength significantly. These findings are helpful to better understand the underlying mechanism of coherent BOLD fluctuation in the human brain.

Acknowledgements NIH grants: NS41262, EB00329, EB00513, P41 RR08079 and P30NS057091; the Keck foundation and the MIND institute.

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