Large amplitude, spatially correlated fluctuations in BOLD fMRI signals during extended rest and early sleep

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Introduction

A number of recent studies of human brain activity using BOLD fMRI have reported the presence of spatio-temporal patterns of correlated activity in the resting state. Measurements performed in absence of external stimuli, with the subject at rest, have shown temporal signal fluctuations that correlate within apparent functionally related regions, including motor, visual, auditory cortex, and language areas. These correlations have been hypothesized to provide information about the "functional connectivity" of the brain [1-5]. In this study, we have tried to address whether the amplitude of these signals varies as a function of alertness, what their amplitude is relative to stimulus-evoked activity, and what their spatial extent is. For this purpose, we designed an experiment during which subjects were initially alert, and subsequently experienced increasing levels of drowsiness and fell asleep, while BOLD fMRI signals were continuously monitored.

Materials and Methods

BOLD fMRI was performed on 12 normal subjects (5 males, 7 females). In order to investigate signal fluctuations during the resting state at varying levels of alertness, an experiment with both active and resting conditions was designed (Fig. 1). The active period consisted of a visual task that alternatingly stimulated the central and the peripheral part of the visual field (30 seconds/block, 10 blocks), followed by an "eyes closed"-"eyes open" ("EOEC") paradigm (2 minutes/block, 4 blocks). After the active period, the subjects were instructed to close their eyes, relax and go to sleep. During the ensuing 27-minute rest period, room lights were dimmed, and no stimuli were presented to the subject. To minimize the contribution of thermal noise, intrinsic SNR was boosted by performing the experiments at relatively high field strength (3.0 Tesla, GE), and the use of a 16-channel receive-only detector array [6] (single shot EPI; 43 ms TE; 2 s TR; 90° flip angle; 1.7x1.7x3.4 mm^3 nominal resolution, 16 slices, 1200 volumes). To allow assessment of the influence of the cardiac and respiratory cycle on the fMRI temporal fluctuations, the timing of these physiologic cycles was recorded using a pulse oximeter and respiratory bellows. The temporal standard deviation (TSD) as a percentage of the image intensity was determined for all pixels at 2 minutes interval. To detect and characterize spatio-temporal patterns of correlated activity during the resting state (last 27 minutes of scan), we applied spatial ICA using MELODIC 2.0 (FSL3.1, FMRIB, University of Oxford) [7]. After ICA, inter-subject consistency of ICs was evaluated by determining their spatial overlap after spatial normalization. This was done on all subjects that were asleep at the end of the experiment.

Results and Discussion

Of the 12 subjects, 7 were asleep ("SLEEP subjects") at the end of the 40-minute fMRI scan, and 5 were awake ("NOSLEEP subjects"). Consistent with earlier studies, using brief rest periods, we found substantial correlated activity in absence of external stimuli. Furthermore, we found: 1) spatially independent patterns of correlated activity that involve all of grey matter, including deep brain nuclei; 2) many patterns that were consistent across subjects (Fig. 2); 3) average percentage levels of fluctuation in visual cortex and whole brain that were higher in SLEEP subjects (up to 2.29% and 1.56% respectively) than in NOSLEEP subjects (up to 1.56% and 1.18%), and were comparable to that of levels evoked by intense visual stimulation (up to 2.37% and 0.99%) (Fig. 1,3); 4) a higher fluctuation level in SLEEP subjects compared to NOSLEEP subjects; 5) no confirmation of correlation, positive or negative, between thalamus and visual cortex found in earlier studies; 6) little correlation (correlation coefficient < 0.3) was found at any temporal lag between BOLD fMRI signal, and either the cardiac or respiratory cycle, or their rates. Our results suggest a positive correlation of the amplitude of signal fluctuations with drowsiness and possibly depth of sleep. Among the possible origins of the observed phenomena is synaptic plasticity facilitated by sleep [8-10].

References

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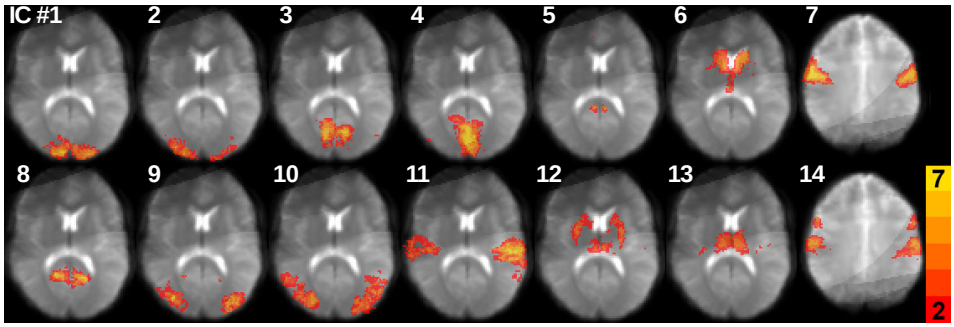

Figure 2: *Inter-subject consistency (overlap) of IC spatial distribution in SLEEP subjects. The color scale indicates number of subjects with IC in voxel.*

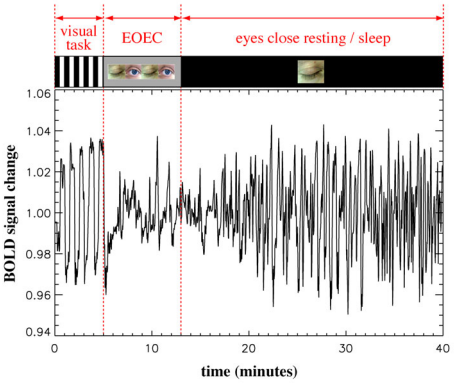

Figure 1: *Timeline of experiment and example signal time course of visual cortex in SLEEP subject*

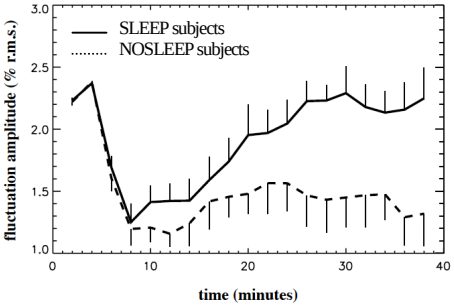

Figure 3: *TSD in visual cortex. The vertical bars indicate standard error.*