

Resting-state Functional Connectivity Changes Induced by Sleep Deprivation

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INTRODUCTION

Sleep deprivation (SD) is known to diminish alertness and impair cognitive performance in humans [1]. Various functional neuroimaging techniques have been employed to investigate the effects of SD on learning and memory and to study the underlying neural changes [2-4]. However, not only the brain activations during task performance are altered after SD, but also it is possible that the intrinsic connectivity during resting-state can be modified by SD. Resting-state functional connectivity MRI (rsfMRI) has been increasingly used in the diagnosis of a variety of brain diseases including Alzheimer's, schizophrenia and autism [5]. Recent rsfMRI study showed a reduction of default mode network (DMN) connectivity after 24hr of total SD in humans [6, 7]. It is well known that rapid eye movement (REM) sleep plays a key role in memory consolidation [8]. The effects of REM SD on functional connectivity are of interest and may provide insights into the neurophysiological alterations underlying the neurobehavioral changes. In this study, we aim to use rsfMRI to examine the changes in functional connectivity induced by REM SD in a well-controlled rodent model.

MATERIALS AND METHODS

Animal Preparation: Male Sprague-Dawley rats (~8 weeks old, N=7) were subjected to REM SD and examined by MRI before and after the SD treatment. **Sleep deprivation** [9]: In the multiple small-platform technique employed, five platforms (each of 6cm diameter) were placed in the middle of a water tank. Platforms were spaced 9cm apart so that rats could easily move between them but could not lie down across any two. The water reached up to ~2 cm below the surface of the platform. Food and water were available *ad libitum*. All SD treatments lasted 72hr under a 12h day/night cycle. Video monitoring was performed throughout the training and was used for behavioral validation of SD later. **MRI Protocols:** All MRI experiments were conducted using a 7 T Bruker scanner with a surface coil. Six rsfMRI acquisitions were performed using a single-shot GE-EPI sequence with TR/TE=1000/18ms, flip angle=30°, FOV=32×32mm², 64×64 matrix, nine 1-mm-thick contiguous slices and a total of 280 data points. RARE T2W images were acquired using TR/TE=4200/36ms as an anatomic reference for EPI data. **Data Analysis:** All rsfMRI data was slice-timing corrected, co-registered, detrended and temporally low-pass filtered. Group independent component analysis (ICA) was performed using GIFT v1.3h Toolbox. Cross-correlation analysis based on the seed voxels selected from atlas was performed using the STIMULATE software. Statistical evaluation of the differences between the cross-correlation coefficients (ccc) before and after SD was performed using paired test with p<0.05 considered to be significant.

RESULTS AND DISCUSSION

In Fig. 1, the resting-state fMRI cross-correlation maps show that, after SD, the interhemispheric correlations in the hippocampus and visual cortex prominently diminished while the connection remained unchanged for the primary somatosensory cortex. Statistical evaluation of ccc confirmed that significant reduction of the interhemispheric correlations occurred in hippocampus and visual cortex but not in somatosensory cortex (Fig. 2). This was consistent with a recent human study that reported a significant reduction of the DMN [6] including the prefrontal cortex and hippocampus nodes. Hippocampus is an essential brain structure regulating learning and memory. Previous histological study showed that the cell proliferation in the dentate gyrus of hippocampus was suppressed by prolonged (72hr) SD. Using the same SD paradigm, neurophysiological study also found severely reduced neuronal excitability in CA1 area of hippocampus [9]. Therefore, the reduced connectivity of hippocampus possibly results from the neuronal loss or/and neuronal dysfunction after SD. On the other hand, it has been reported that decreased neural activity in visual cortex was correlated positively with the impairment in saccadic velocity after SD [10]. Furthermore, reduction in visual task-related activation [11] also suggests the visual cortex could be affected by SD, which was in line with our observation of the reduced intercortical connection in visual cortex. Lastly, the somatosensory network was found not strongly affected by SD in the current study, suggesting that the alterations were not occurring globally. In conclusion, our results demonstrated that SD could diminish the functional connectivity in hippocampus and visual cortex as detected by rsfMRI. Future longitudinal study remains to be performed to identify if these alterations are reversible.

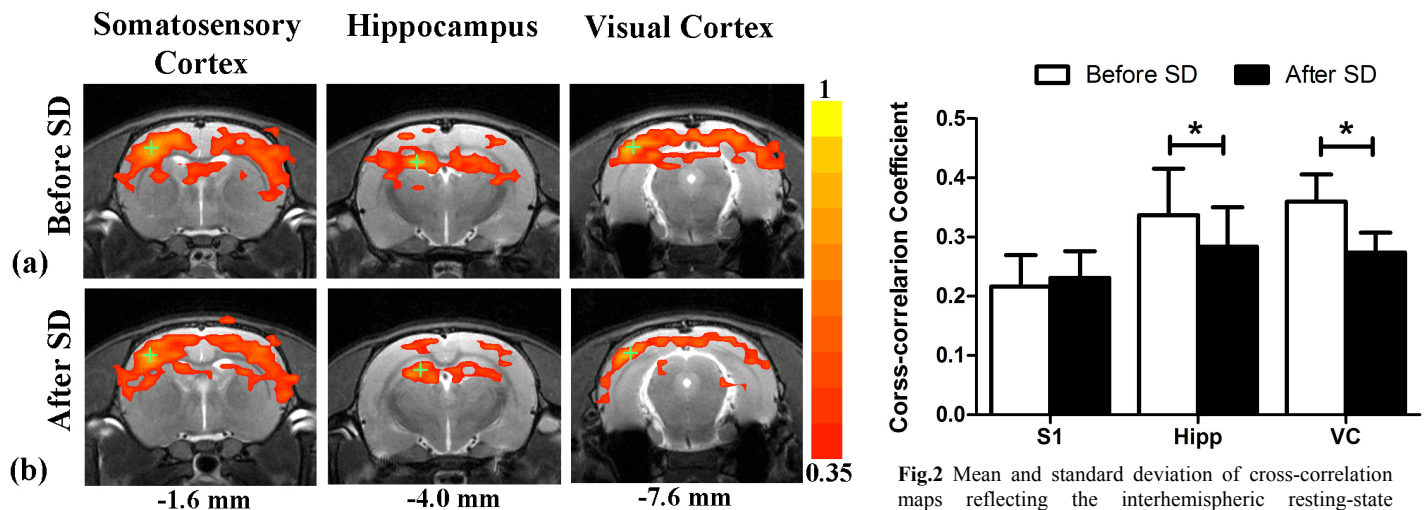


Fig.1 Typical resting-state fMRI cross-correlation maps with the seed voxels in left primary somatosensory cortex (left), hippocampus (middle) and visual cortex (right), for the same animal before (a) and after (b) sleep deprivation (SD) are overlaid on T2W images. Green crosses indicate the center of seed voxels. Distance to Bregma for each slice is labeled at bottom.

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