Neural Origin of Specificity Change of Functional Connectivity at Different Anesthesia Levels

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Introduction Spontaneous blood-oxygen-level-dependent (BOLD) fluctuation has been widely observed in both animal and human brains, and their correlations have been hypothesized to reflect brain "functional connectivity" [1] and imply many "resting-state brain networks" [2]. Spontaneous BOLD fluctuation is sensitive to the change of brain states. It has been reported previously that the specificity of functional connectivity changes with the depth of anesthesia: in the rat somatosensory system, multiple distinct resting-state BOLD coherent networks covering specific regions, e.g. the S1FL (primary somatosensory cortex, forelimb region) and S1BF (primary somatosensory cortex, barrel field), tend to merge into one with less spatial specificity as anesthesia level increased [3]. The interpretation of these results is, however, limited by the lack of electrophysiological recording. Although it is unlikely, it cannot be excluded that the specificity change of functional connectivity might arise due to some non-neuronal physiological modulations.

To understand whether the specific-to-less-specific transition of functional connectivity from light to deep anesthesia originates from the underlying spontaneous brain activity or from some other non-neuronal sources, the electroencephalography (EEG) signals were recorded from the rat somatosensory cortex at different anesthesia levels in this study. The power correlations of band-limited EEG signals between electrodes located at different brain regions were analyzed and compared to the results of the previous functional imaging study [3].

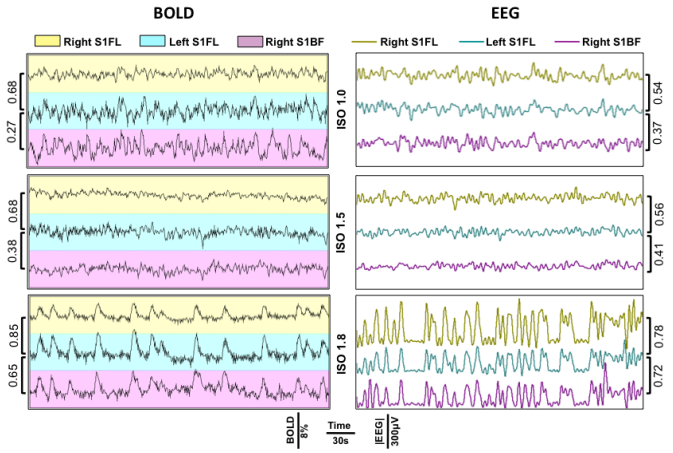

Fig. 1 BOLD signal (left) and EEG wide-band power (right) show similar changes over different anesthesia levels in terms of their fluctuation pattern and inter-regional correlations (from two representative rats). The numbers next to boxes give the correlation coefficient between different time courses.

Methods The EEG data were collected from six Sprague-Daley rats at the anesthesia level of ~1.0%, ~1.5%, and ~1.8% isoflurane (defined as ISO 1.0, ISO 1.5, and ISO 1.8 condition, respectively). An EEG electrode was inserted into the animal's nose as a ground, while three other electrodes were inserted into the rat brain through three small holes opened in the skull, located at the bilateral S1FL and the right S1BF, respectively. EEG signals were continuously recorded at least 20 min for each anesthesia condition. For data processing, the continuous EEG signals were first cut into 300 seconds segments, resulting 4~6 EEG segments for each anesthesia condition of each rat. For each segment, the EEG signal was band-pass filtered to obtained band-limited EEG signals in 6 different frequency ranges: wide (0.1–100 Hz), delta (1–4 Hz), theta (5–8 Hz), alpha (9–12 Hz), beta (13–30 Hz), and gamma (30–100 Hz). The Hilbert transformation was then applied to the band-limited EEG signals to extract their envelope amplitudes, which quantify the power of EEG signals (equivalent to square root of the power). Pearson's correlation coefficients were then calculated to quantify the EEG power correlation between different electrodes.

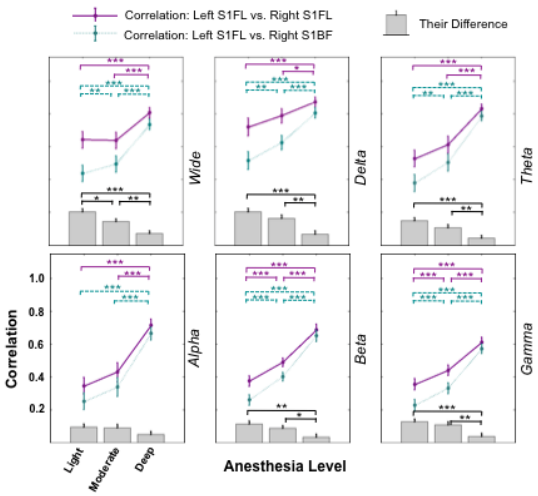

Fig. 2 Statistical summary of the data from all six rats. Stats represent the level of significance (*: $p < 0.05$; **: $p < 0.01$; and ***: $p < 0.001$)

Results The power fluctuation of wide-band (0.1–100 Hz) EEG acquired from a representative rat at different anesthesia levels were compared (Figure 1, right) to BOLD signals acquired under the same conditions (Figure 1, left; adapted from the previous study [3]). Both the BOLD signal and EEG power show big, aperiodic peaks at the ISO 1.8 condition, while the flattest pattern was observed under the ISO 1.5 for both modalities. At the same time, the EEG power correlations show similar anesthesia-level-dependency as the BOLD signal correlation. With regarding the correlation between the bilateral S1FL regions as the within-network correlation and that between the left S1FL and right S1BF regions as the inter-network correlation, the difference between them can be used as an index to quantify the spatial specificity of EEG power correlations. This index did decrease (from 0.17 to 0.15, and then to 0.06) as the anesthesia level increase, suggesting a specific-to-less-specific transition for the EEG power correlation. Moreover, the general level of correlation strength is also positively correlated with the anesthesia depth. Both tendencies are consistent with the previous observation on BOLD signals. EEG power correlations in different frequency bands were calculated and summarized for all six rats (Figure 2), and the results confirmed the above observation from the representative rat.

If the same analysis was applied to the EEG signal directly instead of its envelope amplitude (power), none of the above tendencies could be observed.

Discussion The results of this study strongly suggest that the increased global coherence and decreased spatial specificity of functional connectivity in rat brain at deeper anesthesia condition observed previously [3] reflect the change of spontaneous brain activity and its coherence across different anesthesia levels.

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