Altered functional connectivity of rhesus brain during increasing levels of sevoflurane: a resting-state fMRI study on 3T

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Purpose:

In spite of many years' research, the exact mechanism of how anesthetics modulate the cerebral function is still unknown. One possible mechanism is that anesthetics could influence the synchrony of neuronal networks as reflected by studies on rats, though the results were controversial [1, 2]. However, it is still unclear whether such effects would be observed in rhesus monkeys which are closer to human than rats. Moreover, most previous animal studies were performed at a single anesthetic dose rather than graded levels of anesthesia; the latter one can potentially reveal the dose-dependent alterations of functional connectivity (FC). Thus, present study aimed to investigate alteration of FC in rhesus monkeys at different concentrations of sevoflurane (1.0, 1.3, 1.6 MAC) using resting-state fMRI.

Methods:

14 rhesus monkeys between 5.6 and 6.5 kg in weight and 8–10 years old were scanned on a 3T MR system (Siemens Trio) using a single shot gradient echo EPI sequence (TR/TE = 2000/29 ms; slice thickness = 2.0 mm, matrix flip angle=85°, FOV=14cm, matrix=64×64) with 12 channel phase coil. After induction with and intubation, inhalation of sevoflurane in 100% oxygen was given to each monkey by anesthesia machine at three different concentrations, resulted in three levels of MAC, i.e., 1.0, 1.3 and 1.6 as reflected on the monitor placed outside scanning room. fMRI data were acquired for each of the three conditions after the stabilization of MAC for at least 20 munities. Simultaneous cardiac, blood SO_2 and respiratory recording were also acquired during scanning.

FC across brain regions was evaluated using a seed voxel correlation approach. We have selected brain stem, left cerebellum, bilateral thalamus, bilateral prefrontal cortex, anterior and posterior cigulate cortex as seeds. Seed voxel correlation approach included following steps: (1) Obtaining seed reference by averaging the fMRI time series of all voxels within the areas with ALFF alteration; (2) Temporally bandpass filtering (0.01–0.08 Hz) for each time series; (3) Correlation analysis of the seed reference with the rest of the brain in a voxel-wise manner using the realigned images, and subsequently individual relativity value (r-value) map was produced, and (4) the correlation coefficients were transformed to z-values using the Fisher r-to-z transformation to improve normality prior to averaging data across subjects. Changes in these measures at three levels of MAC were examined to characterize effects of sevoflurane on regional function and functional integration respectively. These analyses were performed across the whole brain using repeated measure analysis as implemented in SPM8 software. Inferences were made with a statistical threshold of $P < 0.05$ (corrected with FWE).

Results:

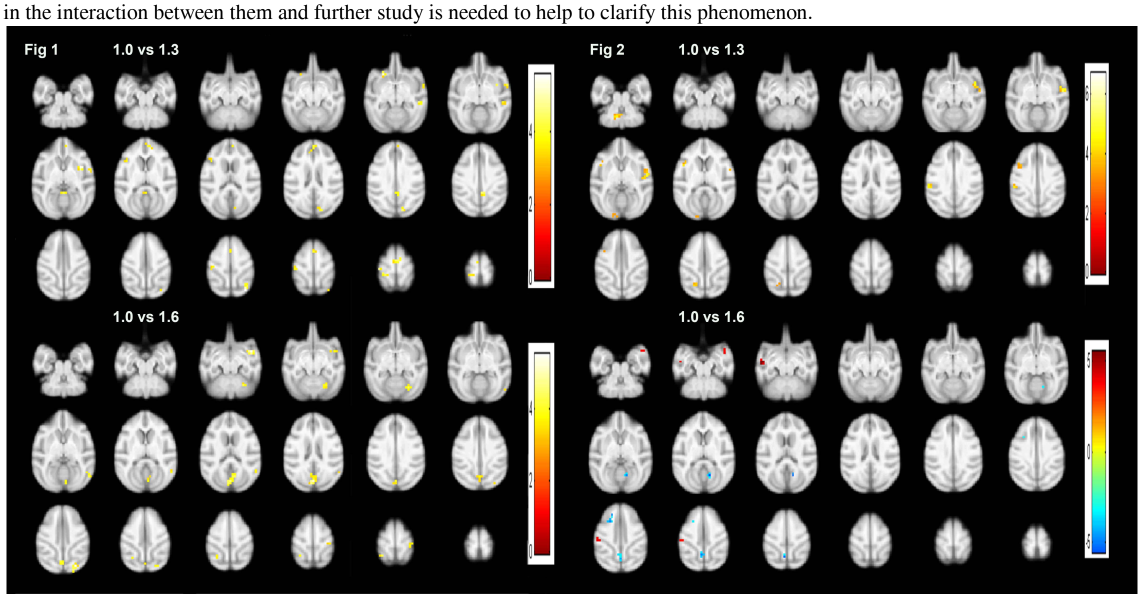
The heart rate, respiratory rate, blood SO_2 and CO_2 were stable during scanning for all monkeys. Using the standard seed-based correlation, two patterns of response to sevoflurane were found in the present study. The one response pattern was observed in the regions of default mode network (anterior and posterior cingulate cortices), frontal-parietal and visual areas. Compared with the state of low concentration of sevoflurane (1.0 MAC), FC of those regions was observed reduced in medial concentration (1.3 MAC) and remained reduced in high concentration (1.6 MAC) state (see Figure 1). In the contrary, the other response pattern occurred in regions of brain stem and bilateral thalamus. Compared with the state of low concentration of sevoflurane (1.0 MAC), FC between the thalamus and prefrontal cortex, somatosensory cortex, visual area as well as cerebellar vermis was observed reduced in medial concentration (1.3 MAC), but increased in high concentration (1.6 MAC) state (Figure 2).

Discussion:

The present study with a relatively large sample of rhesus monkeys revealed two patterns of response to the increasing concentrations of sevoflurane. The one response pattern which demonstrated reduced FC in high concentration was observed in widespread cerebral cortex regions. Thus, it revealed a dose-dependent globally disconnecting of cortex and could be considered an important phenomena in comprehensive study of central anesthetic action [3]. In the contrary, the other response pattern demonstrated increased FC in high concentration mainly in the subcortical-cortical regions. Though reason for the increased FC is presently unclear, it may be the result of homeostatic compensatory mechanism [4].

Conclusion:

Based on the findings, sevoflurane have been found to affect FC of distant regions of the rhesus brain in a dose-dependent way. Two different response patterns exist in the interaction between them and further study is needed to help to clarify this phenomenon.



References:1. Lu H, et al. PNAS. 2007; 104(46):18265-9.

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Figure 1&2: Sectiona Figure 1&2: Section images of comparisons of FC between different concentrations of isoflurane (1.0 vs 1.3, 1.0 vs 1.6 MAC). ($p<0.05$,corrected).