Changes in functional connectivity with increasing concentrations of sevoflurane anesthesia

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INTRODUCTION

Low frequency (< 0.08 Hz) synchronized oscillations in resting state timecourses have been detected in recent fMRI studies [1,2]. These fluctuations are important as a potential signal of interest, which could indicate connectivity between functionally related areas of the brain. It has also been shown that the synchronized oscillations decrease in some spontaneous pathological states (such as cocaine injection) [3,4]. Thus, detection of these functional connectivity patterns may help to serve as a gauge of normal brain activity. The effect of anesthetic agents on cortical activity is neither fully characterized nor completely understood. This study assessed whether and how anesthesia affects temporal relations in activity between functionally related but anatomically separate cortical brain areas. In this work, we examined resting-state functional connectivity in fMRI at different concentrations of sevoflurane. By employing gradations of anesthetic influence, we were able to explore the effect of anesthesia on baseline, task-independent connectivity. In particular, changes in the functional connectivity of the motor network were analyzed.

METHODS

Acquisition

A series of fMRI experiments were performed on a 3 T Siemens Trio scanner. An EPI pulse sequence was used to acquire 280 images, with two 5 mm thick axial slices acquired in each run, with an in-plane resolution of 3.44 mm x 3.44 mm. Pulse sequence parameters were TR/TE/FA/FOV of 750 ms/35 ms/50°/22 cm.

Anesthesia

Following informed consent, 6 right-handed, male volunteers aged 22 to 24 were studied under three successive conditions: while breathing 0, 2.0 and 1.0% end tidal sevoflurane (Awake, Deep, Light state, respectively). Prior to induction of anesthesia, volunteers gargled with 4% viscous lidocaine. Anesthesia was induced with sevoflurane in oxygen, using the single breath technique. After placement of a laryngeal mask airway, sevoflurane concentration was held constant at 2% for 15 min to allow for effect site (brain) equilibration, after which scans were obtained. End tidal sevoflurane was then adjusted to 1% and again held constant for 15 min prior to scanning.

Analysis

Functional connectivity maps were then formed by using seed ROIs in the anatomically-defined motor cortices. The timecourse of this ROI in the resting-state data was then averaged together, and low-pass filtered < 0.08 Hz. This low frequency reference was then correlated with the low-pass filtered resting state data to form functional connectivity correlation maps. This is a common method for examining resting state functional connectivity [1-3]. Qualitative assessment of anesthesia level dependence was investigated by visually inspecting the resultant functional connectivity maps at different anesthesia levels. The dependence was quantitatively assessed by calculating the amount of significant voxels for each anesthesia level, summing over all slices, and normalizing by the amount in the awake state. This method was repeated for every subject.

Further assessment of bilateral/unilateral patterns in the functional connectivity maps was done for the awake and light states. First, the left and right hemispheres were anatomically identified and masked for each slice. Then, two connectivity maps for each condition (awake and light) were formed, using a seed in both the left and right motor cortex. The total number of significant voxels in each hemisphere was then normalized by the total number of significant voxels in the pattern, to give the fraction of the connectivity pattern in each hemisphere.

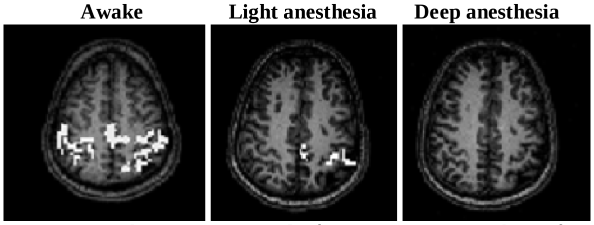

Figure 1. Functional connectivity results for a representative subject, for awake, deep anesthesia, and light anesthesia states. Significant voxels were thresholded at $p<2.5e^{-5}$, and contiguity thresholded > 4 voxels for viewing purposes.

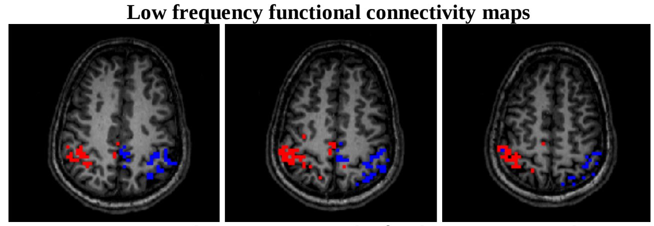

Figure 2. Functional connectivity results for three contiguous slices in a representative subject under light anesthesia, for left (red) and right (blue) seed ROIs. Significant voxels were thresholded at $p<2.5e^{-5}$.

RESULTS AND DISCUSSION

Results for a representative subject for all three conditions are shown in Figure 1. The connectivity maps exhibited significant activation in the motor-related areas (primary motor cortex, sensorimotor area, and supplemental motor area (SMA) in both hemispheres in the awake state. This is in agreement with previous functional connectivity studies[1-3]. The connectivity maps for light anesthesia exhibited reduced connectivity in the hemisphere opposite the seed cluster (Figure 2, Table 1). In the deep anesthetic state, functional connectivity was virtually absent. This pattern of functional connectivity change across the different anesthetic levels was consistent for all subjects. The amount of significant voxels decreased (compared to the awake state) in the deep and the light anesthetic state ($p<10^{-8}$, $p<10^{-5}$, respectively); and the amount increased comparing the light to the deep state ($p<10^{-2}$).

	Left hemisphere seed		Right hemisphere seed	
Subject	**Awake**	**Light**	**Awake**	**Light**
1	0.44	0.76	0.55	0.93
2	0.49	0.76	0.56	0.69
3	0.46	0.76	0.55	0.86
4	0.50	0.99	0.51	0.99
5	0.44	0.78	0.56	0.58
6	0.44	0.92	0.47	0.93
Mean	0.46(±0.03)	0.83(±0.10)	0.53(±0.04)	0.83(±0.16)

Table 1. Amount of significant voxels in the hemisphere containing the seed cluster, normalized by the total amount of voxels, for the awake and light anesthesia states.

Sevoflurane anesthesia significantly reduces low frequency functional connectivity in the motor network. Additionally, in comparing the awake state to that of light anesthesia, we observe a shift from bilateral to unilateral functional connectivity, which has not been previously reported. This has implications for how anesthetic concentrations affect cortical activity, and for characterizing functional connectivity in brain networks.

REFERENCES

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