Default mode functional connectivity altered by 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 normal connectivity between functionally related areas of the brain. Previous studies have identified a resting state network associated with the posterior cingulate (the "default mode" network) that is thought to be associated with self-awareness, and negatively correlated with external focus [3,4]. The effect of anesthetic agents on cortical activity and awareness is neither fully characterized nor completely understood. Preliminary work has investigated the motor network [5], and used single sedative levels of thiopental or midazolam sedation [6-8]. In this study, we extend the prior work by employing gradations of sevoflurane anesthesia during fMRI scanning to examine the effect of anesthetic influence on baseline task-independent connectivity of the default mode network.

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 ten 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. Simultaneous acquisition of the cardiac rhythm was done in each scan using a pulse oximeter.

Anesthesia

Following informed consent, 6 right-handed, male volunteers aged 22 to 24 were scanned 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

One subject was excluded from further analysis due to gross head motion. Functional connectivity maps were formed for the remaining subjects using a seed ROI in the anatomically-defined posterior cingulate. The timecourse of this ROI in the resting-state data was then averaged together, and low-pass filtered < 0.08 Hz to avoid aliasing of the respiration and cardiac harmonics into the frequency band of interest, while keeping the frequencies shown to contribute to functional connectivity [9]. This low frequency reference was then correlated with the low-pass filtered resting-state data to form functional connectivity correlation maps. 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 ($r > 0.5$) for each anesthetic level, summing over all slices, and normalizing by the amount in the Awake state. This method was repeated for every subject.

RESULTS

Results for a representative subject are shown in Figure 1. In the Awake and the Light state, the connectivity maps exhibited significant activation in areas associated with the default mode (posterior cingulate, medial frontal areas, and parietal areas) [3,4]. However, in the Deep anesthetic state, functional connectivity was virtually absent.

This pattern of anesthetic influence was consistent for all subjects (see Table 1), with a significant decrease in number of significant voxels ($r > 0.5$) in the Deep state compared to the Awake state (paired t-test, $p<0.001$) and a significant increase in the Light state compared to the Deep state ($p<0.01$). Additionally, there is an increase comparing the Light state to the Awake state ($p<0.05$), that may be due to the subjects having less external distractions.

The recorded primary cardiac frequency in each condition was verified to not alias into the low-frequency band of interest, and did not significantly vary between the three states (Awake: 0.93(±0.16) Hz, Deep: 0.93(±0.09) Hz, Light: 0.93(±0.14) Hz; $p > 0.9$). Thus, the cardiac rhythm is unlikely to be a confound.

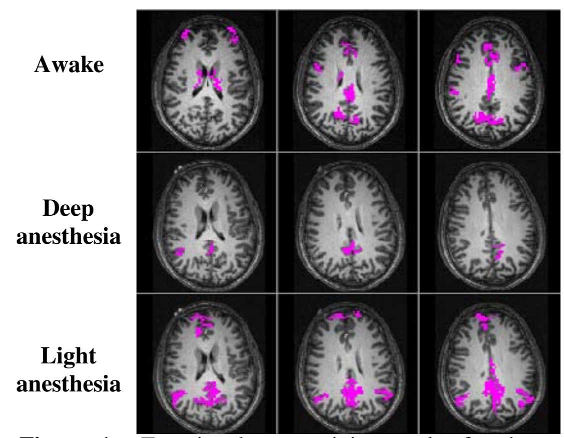

Figure 1. Functional connectivity results for three contiguous slices in a representative subject, for each anesthetic state. Significant voxels were thresholded at $r > 0.5$, and contiguity thresholded > 5 voxels.

Subject	Deep	Light
1	0.07	1.12
2	0.01	1.64
3	0	0.80
4	0.44	2.68
5	0	2.14
Mean(Std)	0.10(0.19)	1.68(0.76)

Table 1. Amount of significant voxels (r>0.05), normalized to the amount in the Awake state.

CONCLUSIONS

Sevoflurane anesthesia significantly reduces functional connectivity associated with the posterior cingulate in the deep anesthesia state, compared to focal reductions seen under midazolam sedation [6], with significant default mode activity subsequently recovered under light anesthesia. Future studies of how anesthetic concentrations affect cortical activity will help to fully characterize brain physiology and function.

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