Dose-dependent effects of sevoflurane on temporal distribution of BOLD responses to somatosensory stimulation in rats

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Target audience: Researchers and clinicians with interest in fMRI with anesthesia

Purpose

Sevoflurane is one of the most used volatile anesthetics in the clinical MRI studies[1]. However its influence in rodent functional MRI (fMRI) remains poorly explored. We aimed to investigate the dose-dependence of sevoflurane on the blood oxygenation level dependent (BOLD) responses in the upper layer (layer 1-3) and in the lower layer (layer 4-6) of the somatosensory cortex to electrical stimulation in the hindpaw.

Methods

(1) ***MRI scanning***: MRI experiments were performed on a 9.4 T imaging system (Bruker, Ettlingen, Germany) with volume coil for transmission and 4 channel rat brain array coil for reception. Nine male Wistar rats were used in this study. They were anesthetized with 4% sevoflurane during the setting. The concentration of sevoflurane was changed from 3% to 5% in the same rat randomly. An interval of 5 min was allowed after a change in the anesthetics concentration. BOLD images were acquired using a gradient echo EPI sequence (TE/TR = 12/1,000 ms, matrix size = 70 x 70, FOV = 21 x 21 mm, slice thickness = 0.8 mm, 3 slices. Anatomical images were acquired for spatial correction using multi-slice rapid acquisition with relaxation enhancement (RARE): TE_{eff}/TR = 60/2500 ms, RARE factor = 8, matrix size = 256 x 256, FOV = 21 x 21 mm, slice thickness = 0.8 mm, 3 slices. The scanning was continuously performed for 5.5 min (total 330 volumes). Two stainless electrodes were inserted under the skin of hindpaw and the protocol consisted of 5 blocks of hindpaw electrical stimulation (5 mA, 5 Hz, 0.3 ms duration, 10 seconds) followed by a 50 seconds resting: total 5.5 min.

(2) ***Analysis***: After the spatial correction by SPM8 (Welcome Trust Center for Neuroimaging, UK), the time-course of the signal changes were calculated using a script written in Matlab (Mathworks, MA) in region of interests (ROIs) in the upper and lower layers of the somatosensory cortex. The peak value of the BOLD signal response and full width at half maximum (FWHM) were calculated from time-courses (Figure 1a). The hemodynamic response function (HRF) during 10 s stimulation was estimated using the double gamma function[2]:

HRF=F1−F2, $F_i = fi \cdot \frac{\lambda_i{}^{\alpha_i}}{\Gamma(\alpha_i)} \cdot t^{\alpha_i - 1} \cdot e^{-\lambda_i t}$ i = 1,2 T, time; $\Gamma(\alpha_i)$, gamma function.

Results

The BOLD responses to the hindpaw electrical stimulation in the upper layer were significantly larger than those in the lower layer (Figures 1 and 2). The peak amplitude in the upper layer with 4% sevoflurane was larger than that that with 3% (Figure 2a and b). In the upper layer, FWHM under 3% sevoflurane was significantly higher than that under 4% sevoflurane in upper layer (Figure 2b). There was no significant difference in FWHM between the upper and lower layers at any sevoflurane dose examined. The estimated HRF was similar between upper and lower layers (data not shown). The estimated HRF in the upper layer is shown in Figure 3. The time-to-peak and the time-to-return-to-baseline were smaller than those in the canonical HRF in all doses. Time-to-peak was similar in all doses, while time-to-return-to-baseline with 3% was longer than 4% and 5%.

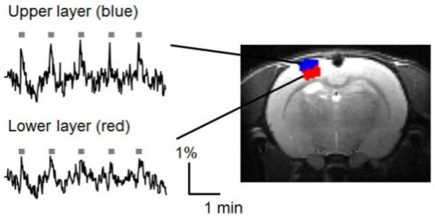

Fig. 1 ROIs in the upper and lower layers in the somatosensory cortex and BOLD response in a representative animal. Grey line, stimulation period.

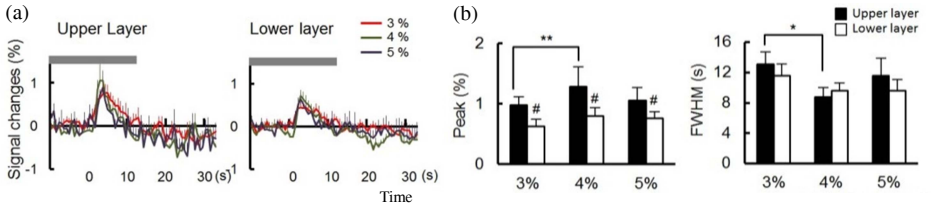

Fig. 2 (a) Averaged BOLD responses in the upper and lower layers in all animals. (b) The peak and FWHM of BOLD response with each dose of sevoflurane. Grey line, stimulation period. * p<0.05; **p<0.01; #p<0.05 vs upper layer

Discussion

These results show that the peak amplitude of BOLD response in the somatosensory cortex was essentially dependent on the layer. This conclusion is consistent with the previous studies using other anesthetics like alpha-chloralose[3]. Unlike isoflurane, a volatile anesthetic also frequently used in animal fMRI studies, peak amplitude was not proportional to the sevoflurane concentration (peak value with 4% was greater than those with 3% and 5% in both layers). In the previous study, the peak value of the BOLD response was increased in proportional to the concentration of isoflurane[4]. Importantly, the estimated HRF was distinct in all doses, indicating the disturbance of the neurovascular coupling by sevoflurane dose-dependently.

Conclusion

Sevoflurane would influence BOLD signals by affecting gliovascular networks and this effect is largely dependent on the dose used. The interpretation of the data, especially when calculating the activation map using HRF model, should be carefully made when sevoflurane is used as anesthesia.

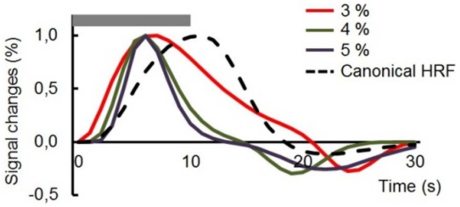

Fig. 3 Estimated HRF by somatosensory stimulations in the upper layer of the somatosensory cortex. Grey line, stimulation period.

References

1. Bernal B, Grossman S, Gonzalez R et al. FMRI under sedation: what is the best choice in children? J Clin Med Res. 2012; 4: 363-702.
2. Aso T, Urayama S, Poupon C et al. An intrinsic diffusion response function analyzing diffusion functional MRI time series. NeuroImage. 2009;47:1487-95.
3. Yu X, Wang S, Dodd S et al. Direct imaging of macrovascular and microvascular contributions to BOLD fMRI in layers IV–V of the rat whisker–barrel cortex. NeuroImage. 2012; 59: 1451-60.
4. Tsurugizawa T, Ciobanu L, Le Bihan D. Water diffusion in brain cortex closely tracks underlying neuronal activity. Proc Natl Acad Sci U S A 2013; 110: 11636-41.