Supplementary Data

Duration Effect of 1% Isoflurane on the Functional Connectivity Between the Default Mode Network and Motor (M1) or Visual Cortex (V1)

These resting-state functional magnetic resonance imaging data sets were analyzed with the same data processing procedure (see details in the Materials and Methods section of the article) to investigate the duration effect of 1% isoflurane on the functional connectivity between motor/visual cortex (M1/V1) and the default mode network (DMN), including anterior cingulated cortex (ACC), posterior cingulate cortex (PCC), and dorsal/medial prefrontal cortex (DMPFC). The entire M1 or V1 region in the left hemisphere was used as a seed for regions of interest-based data analysis. It is found that the correlation degree (z score) of the M1-ACC connectivity was decreased ($p<0.05$) and that of the V1-ACC was increased ($p<0.05$) after a 3.5-h isoflurane administration. The reduction of the M1-DMPFC connectivity is nearly significant ($p=0.08$) (Supplementary Table S1). No obvious changes are seen in the connectivity, including the M1-PCC, V1-DMPFC, V1-PCC, and the interhemispheric connectivity of M1 and V1 regions.

The changes of the functional connectivity between DMN and M1 and V1 in an adult rhesus monkey are illustrated in Supplementary Figures S1 and S2, respectively. By comparing Supplementary Table S1 with Table 1, a substantial variation in the z scores and changes of different brain networks is observed. These preliminary results indicate that the duration effect of isoflurane administration is more sensitive in the spontaneous neuronal activity of some specific networks (PCC-ACC, PCC-DMPFC, M1-ACC, M1-DMPFC, V1-ACC).

The regional variation of isoflurane's effect on the functional connectivity of different brain networks has been previously demonstrated in a few studies. Hutchison et al. have reported dose-related effects in which a decrease or complete loss of interhemispheric cortical functional connectivity was seen in monkeys under 1.0% and 1.5% isoflurane (Hutchison et al., 2014). Also, Lv et al. (2016) demonstrated a dosage-related decrease or increase of cerebral regional activity and functional connectivity in monkeys under 1.0 to 1.6 minimum alveolar concentration (MAC) isoflurane.

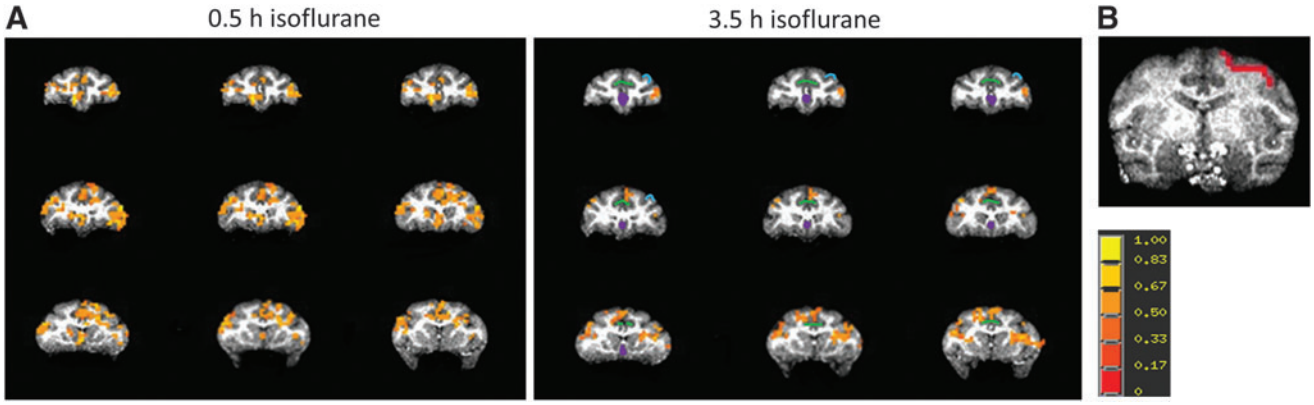
It is known that the suppression effect of isoflurane on neuronal activation is dose dependent, as seen in the isoflurane-induced burst suppression pattern (Ferron et al., 2009). But the neuronal substrate of the functional connectivity variation of isoflurane's effect (due to dosage and/or duration) on different brain networks remains poorly understood. Obviously, the isoflurane duration effects observed in the present study are closely associated with the applied dosage and duration of isoflurane administration, and further work is needed to investigate those effects of isoflurane on the functional connectivity in different brain networks.

Supplementary References

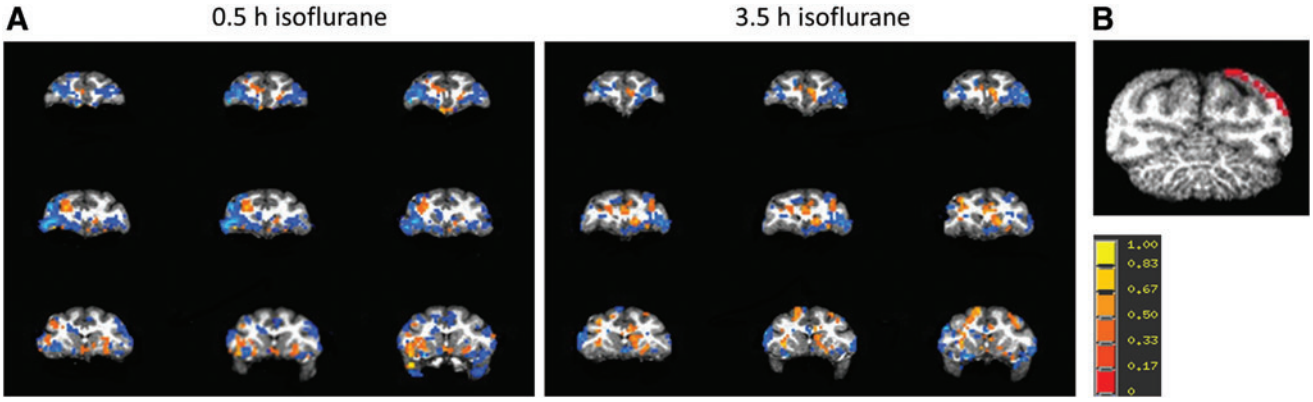
Ferron JF, Kroeger D, Chever O, Amzica F. 2009. Cortical inhibition during burst suppression induced with isoflurane anesthesia. J Neurosci 29:9850–9860.

Hutchison RM, Hutchison M, Manning KY, Menon RS, Everling S. 2014. Isoflurane induces dose-dependent alterations in the cortical connectivity profiles and dynamic properties of the brain's functional architecture. Hum Brain Mapp 35:5754–5775.

Lv P, Xiao Y, Liu B, Wang Y, Zhang X, Sun H, et al. 2016. Dose-dependent effects of isoflurane on regional activity and neural network function: A resting-state fMRI study of 14 rhesus monkeys: An observational study. Neurosci Lett 611:116–122.



SUPPLEMENTARY FIG. S1. The representative changes of DMN with primary motor cortex (M1) in an adult rhesus monkey maintained with 1% isoflurane exposure. **(A)** The activation coronal maps were generated by using the left M1 as seed. The color bar represents the magnitude of the regression coefficient (z score threshold $p<5\times10^{-11}$, cluster threshold = 203 mm^3/overall). **(B)** The seed with M1 is highlighted as red. ROIs: light blue covered regions represent dorsal prefrontal cortex; purple covered region represents medial prefrontal cortex; DMPFC region is marked with light blue and purple region; and green region represents ACC. ACC, anterior cingulate cortex; DMN, default mode network; DMPFC, dorsal/medial prefrontal cortex; ROI, regions of interest.



SUPPLEMENTARY FIG. S2. The representative changes of DMN with primary visual cortex (V1) in an adult rhesus monkey maintained with 1% isoflurane exposure. **(A)** The activation coronal maps were generated with left V1 as seed. The color bar represents the magnitude of the regression coefficient (z score threshold $p < 6.3 \times 10^{-7}$ plus cluster threshold 203 mm^3/overall). **(B)** The seed with V1 is highlighted as red. ROIs are referred to Supplementary Figure S1.

SUPPLEMENTARY TABLE S1. THE z SCORE CHANGES BETWEEN LEFT MOTOR/VISUAL CORTEX (M1/V1) AND DEFAULT MODE NETWORK (ACC, PCC, AND DMPFC) OF ADULT MONKEYS MAINTAINED WITH 1% ISOFLURANE EXPOSURE

	M1-ACC	*M1-DMPFC*	*M1-PCC*	*V1-ACC*	*V1-DMPFC*	*V1-PCC*
0.5 h isoflurane (baseline)	0.23 ± 0.06	0.23 ± 0.08	0.19 ± 0.04	−0.07 ± 0.04	−0.03 ± 0.04	−0.02 ± 0.02
3.5 h isoflurane	0.12 ± 0.06[a]	0.02 ± 0.08[b]	0.18 ± 0.03	0.07 ± 0.03[a]	0.07 ± 0.04	0.07 ± 0.06

Data are reported as means ± SEM.
[a] $p < 0.05$.
[b] $p = 0.08$, compared to the baseline.
ACC, anterior cingulate cortex; DMPFC, dorsal/media prefrontal cortex; PCC, posterior cingulate cortex.