The Relationship between States of Consciousness and Brain Connectivity: A Potential Biomarker for Discriminable States of Consciousness

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Introduction: Studying consciousness has plagued scientists for centuries due to its lack of definition and standardization. A relatively new tool, resting-state functional magnetic resonance imaging (rsfMRI), has been useful for characterizing and discriminating states of consciousness in humans (1,3) and animals (1,2,4). Using rsfMRI data, functional brain connectivity has been measured and compared during altered states of consciousness using a variety of anesthetic agents (1,5) as well as doses (1,3,4). Here we use rsfMRI to investigate functional brain connectivity at various doses of isoflurane anesthetic and correlate this with behavioral measures of anesthetic depth. Our findings can contribute to the systems-level mechanisms of anesthesia-induced unconsciousness as well as provide a potential biomarker for altered states of consciousness.

Method: Resting-state fMRI data from 12 male Long-Evans rats was acquired on a 7 T scanner interfaced with an Agilent console. We employed a 1-shot gradient echo EPI sequence with the following parameters: TR=1s, TE=13.78ms, flip angle=60º, matrix size=64 x 64, FOV=3.2 x 3.2cm, 20 1mm thick slices, in plane resolution=500um x 500um. Each rat was scanned at six different doses of isoflurane anesthetic: 0% (i.e. awake state), 0.5%, 1.0%, 1.5%, 2.0%, and 3.0%. Seven days prior to scanning, rats were acclimated to the scanning environment in order to reduce stress and motion during imaging. To attain a steady-state dose, each scan was initiated 5 minutes after increasing the isoflurane. rsfMRI data was preprocessed with conventional procedures including registration to a standardized brain atlas, motion correction, spatial smoothing, regression of motion parameters and white matter/ventricle signals, and band-pass filtering (0.0085-0.1Hz). We calculated the maximum number of connected ROI as a function of correlation threshold and found that a sigmoid function could be used to fit the data (Fig. 1). Furthermore, this measurement of connectivity was correlated with behavioral data obtained from the loss of righting reflex (LORR) paradigm. In this paradigm, a rat placed in a supine position will want to correct its position, flipping over onto its stomach. We measured the time it took the rat to correct its position at the six doses of isoflurane. A steady-state dosage was achieved before all behavioral measurements. If the rat did not correct its position within the first minute, it was regarded as completely unconscious. For each rat, three measurements were obtained at each dose and averaged. The average across rats per dose is shown in Fig. 4.

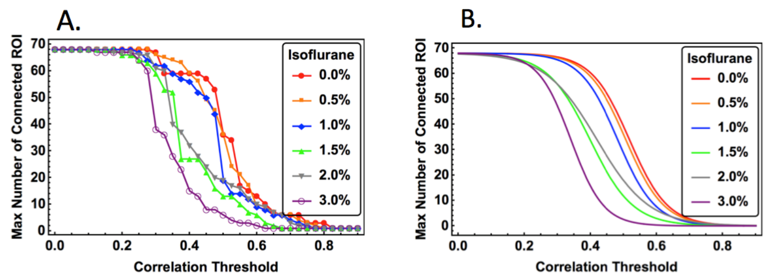
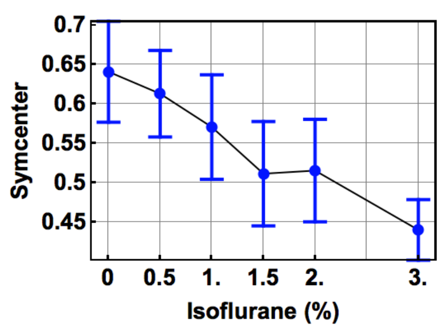


Figure 1. Maximum number of connected ROIs as a function of correlation threshold among six doses of isoflurane (A) the data from 1A was fitted with a sigmoid function (B).



P-value	0.0%	0.5%	1.0%	1.5%	2.0%	3.0%
0.0%	1.0	0.26	0.015	0.000073	0.000095	4.4×10^{-9}
0.5%	0.26	1.0	0.10	0.00049	0.00065	9.0×10^{-9}
1.0%	0.015	0.10	1.0	0.040	0.052	6.2×10^{-6}
1.5%	0.000073	0.00049	0.040	1.0	0.88	0.0039
2.0%	0.000095	0.00065	0.052	0.88	1.0	0.0023
3.0%	4.4×10^{-9}	9.0×10^{-9}	6.2×10^{-6}	0.0039	0.0023	1.0

Figure 2: Symmetry center of sigmoid curve at six doses of isoflurane (above) and table of associated p-values (below).

Results: Here we demonstrate that as anesthetic depth increases, the maximum number of connected ROIs decreases (Fig. 1, A & B). The deepest anesthetic states (1.5, 2.0, 3.0% isoflurane) showed decreased overall connectivity at lower thresholds compared to the awake states (0, 0.5, 1.0% isoflurane). These data were fitted with a sigmoid function (Fig. 1B). Furthermore, we demonstrated that the symmetrical center of the sigmoid curve in Fig.1B decreases almost linearly from the awake state (0% isoflurane) to the deeply anesthetized state (3.0% isoflurane) (Fig. 2). The symmetrical center of the sigmoid curve was also highly correlated with the behavioral measures of anesthetic depth obtained during the LORR paradigm (Fig. 3B, r=-0.937, p=0.006).

Conclusion/discussion: Consistent with previous literature (1-5), we show that anesthesia causes a reduction in global brain connectivity. Furthermore, the relationship between behavioral measures of anesthetic depth and the reduction in connectivity provides a novel use for rsfMRI data as a potential biomarker for discriminating states of consciousness as well as clinical application for the prognosis of complex disorders of consciousness. Additional voxel-wise analyses will provide a better understanding of the brain regions involved in these discriminable states of consciousness.

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References: 1. Alkire, Hudetz, Tononi, Science 322:876-880. 2. Vincent et al., Nature 447 (7140): 83–86. 3. Hutchinson et al., Human Brain Mapping 35(12):5754-5775. 4. Liang et al. J Neuroscience 32(30): 10183-10191. 5. Williams et al., Mag Res Imag, 28 995–1003.

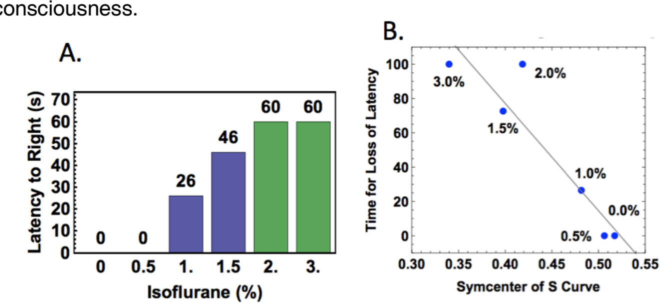

Fig. 3. Averaged latency for rats to right themselves at six doses of isoflurane (A) and the correlation between the latency and symmetry center of the sigmoid curve (B).