

# Isoflurane affects brain functional connectivity in rats 1 month after exposure

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## Introduction, aim and methods

#### Introduction

- Surgeries are commonly performed under general anesthesia
  - However, the long-term effects of general anesthesia on brain function are poorly understood
- Isoflurane can influence plasticity and gene expression several days or weeks after the initial exposure
  - No studies have been conducted to evaluate the long-term effects of isoflurane anesthesia on functional connectivity

#### <u>Aim</u>

To investigate the long-term effect of 1.8% isoflurane on brain function using functional magnetic resonance imaging (**fMRI**), electrophysiological local field potential (**LFP**) and gene expression (**mRNA-seq**) measurements **a month after the initial exposure**.



### Results - fMRI



### Results - LFP



- No change in any burst suppression parameters

#### Coherence



**Right DG – Right S1** Isoflurane 1.3% 1st Isoflurane 2.0% 0.8 Control Treated 0.0 0.4 0.2 alpha (beta) (beta) 0 10 20 25 10 15 20 25 30 1 5 15 30 5



#### LFP derived connectivity

Hilbert envelope of LFP signal

S1L

S1R DG

CA1

30

Hemodynamic response function convolution







LFP-predicted fMRI time courses



LFP, inter-channel correlation, isoflurane treated - control Isoflurane 1.3% 1st Isoflurane 2.0% Isoflurane 1.3% 2nd Isoflurane 3.0% \* \* \* S1L S1R DG CA1 S1L S1R DG CA1 S1L S1R DG CA1 S1L S1R DG CA1

## Results - gene expression



Involved in synaptic transmission

- Solute Carrier family 32 member 1 (*Slc32a1*) involved in GABA and glycine uptake into synaptic vesicles
- Bestrophin 1 (Best1) involved in astrocytic glutamate transportation
- Gap junction delta 2 (Gjd2)
  involved in synchronous
  electrical activity
- Sodium voltage-gated channel alpha subunit 9 (*Scn9A*) involved in generating and conduction of action potentials

### Discussion

- A single 3 h isoflurane exposure, deep enough to induce burst suppression in EEG, has a persistent effect on brain connectivity
- Because no change was seen in burst suppression pattern, observed alterations in functional connectivity likely reflect neural network plasticity changes rather than a change in the depth of anesthesia
- Differently expressed genes like gap junction delta 2 (*Gjd2*) and sodium voltage-gated channel alpha subunit 9 (*Scn9A*) suggest changes in synaptic transmission



### Conclusion

A typical single isoflurane anesthesia for a major surgery induces changes in brain functional connectivity and gene expression that last at least for a month.

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#### Main references

- Long li RP, Aroniadou-Anderjaska V, Prager EM, Pidoplichko VI, Figueiredo TH, Braga MF, 2016. Repeated Isoflurane Exposures Impair Long-Term Potentiation and Increase Basal GABAergic Activity in the Basolateral Amygdala. Neural Plast. 2016, 8524560.
- Uchimoto K, Miyazaki T, Kamiya Y, Mihara T, Koyama Y, Taguri M, Inagawa G, Takahashi T, Goto T, 2014. Isoflurane impairs learning and hippocampal long-term potentiation via the saturation of synaptic plasticity. Anesthesiology 121, 302–10.
- Joksovic PM, Lunardi N, Jevtovic-Todorovic V, Todorovic SM. Early exposure to general anesthesia with isoflurane downregulates inhibitory synaptic neurotransmission in the rat thalamus. Mol Neurobiol. 2015 Oct;52(2):952-8. doi: 10.1007/s12035-015-9247-6.
- Rammes G, Starker LK, Haseneder R, Berkmann J, Plack A, Zieglgänsberger W, Ohl F, Kochs EF, Blobner M. Isoflurane anaesthesia reversibly improves cognitive function and long-term potentiation (LTP) via an up-regulation in NMDA receptor 2B subunit expression. Neuropharmacology. 2009 Mar;56(3):626-36. doi: 10.1016/j.neuropharm.2008.11.002.
- Xie P, Yu T, Fu X, Tu Y, Zou Y, Lui S, Zhao X, Huang X, Kemp GJ, Gong Q. Altered Functional Connectivity in an Aged Rat Model of Postoperative Cognitive Dysfunction: A Study Using Resting-State Functional MRI. PLoS One. 2013; 8(5): e64820., May 30. doi: 10.1371/journal.pone.0064820



