Effects of Different Anesthesia on the Resting-State Networks in Rodents

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Abstract

Functional imaging in animal models is difficult to perform, and although awake experiments have been reported, results are scattered. The most convenient way to assess brain function is to perform resting state fMRI with the animal under anesthesia. We investigated the effects of three commonly used anesthetic (isoflurane, medetomidine and ketamine) in rodent experiments and their effects on brain function. Functional neuroimaging of the resting-state of animals has gained increased interest during recent years, especially functional Magnetic Resonance Imaging (fMRI) [1]. These studies of the resting-state place special demands on what kind of anesthesia drug are being used, which may affect the outcome of the activations of the resting-state networks. Previous works are mostly concentrated or compared in one or two anesthesia drugs [2]. No previous study has compared isoflurane, medetomidine and ketamine together. The aim of this study is to investigate the effects of these three different anesthesia drugs to the resting-state networks.

Method

Animals and Anesthesia:

14 wild type mice were used in this study. Ketamine was mixed with Xylazine and saline as a Ketamine/Xylazine cocktail at 100/10 ratio. The volume of the cocktail was administered to mice as 0.1 ml per 10 g of the weight of the mouse. Medetomidine (Domitor) was prepared in two concentrations for bolus dose and infusion.

Procedures:

For isoflurane, anesthesia was delivered by a SurgiVet anesthesia machine (Smiths Medical ASD Inc., Dublin, OH) with 3% isoflurane mixed with oxygen. Once the mouse was prepared, secured on the scanner bed and inserted into the magnet for imaging, isoflurane was reduced to 1.5%. This isoflurane level remained throughout the image acquisition.

For ketamine, anesthesia was delivered with intramuscular injection with the premixed ketamine/xylazine cocktail. When the animal was down, it was secured on the scanner bed. Then the animal was ready for imaging.

For medetomidine, 3% of isoflurane was delivered to sedate the mouse before intramuscular injection of the bolus medetomidine. When the mouse was sedated on the scanner bed, the isoflurane was reduced to 1.5%. A catheter was inserted into the back of the mouse, which was connected to long tubing to the control room. Medetomidine was then continuously infused into the mouse through a syringe pump (New Era Pump Systems Inc., Wantagh, NY). Isoflurane was reduced to zero within 5 minutes after the pump was started. Imaging commenced at this point.

A respiratory monitor (SA Instrument Inc., Stony Brook, NY) was used, and maintained all the mice's respiration within the similar range as best we could.

Imaging:

Imaging was performed using a BioSpec 7T MRI (Bruker-Biospin, Ettlingen, Germany). fMRI data were acquired using an EPI-acquisition (TR=2000ms, TE=27ms, FOV=12.8mm, matrix =96x96, 14 slices, thickness=0.8mm). Each fMRI run images were acquired over 20 min while the mouse was resting in the scanner. Mice were systematically randomized for each anesthetic method. Each mouse was scanned for one kind of anesthesia a day, and would not be scanned the following day. One day of rest was given to make sure the previous anesthesia was out of its system.

Acquired functional images were analyzed with FSL (Analysis Group, FMRIB, Oxford, UK) and in-house software. Brain extractions were created manually masked and implemented with the in-house software. A brain template was created by averaging all brain extractions. No motion correction was used in preprocessing. The created brain template was used to co-register with the functional images (FLIRT). Single-session and multi-subject independent component analysis (ICA) and MELODIC [3] were used to identify 18 unique networks of the resting-state activities. Dual-regression analysis was implemented with two-sample paired t-test (medetomidine vs. isoflurane) and two-sample unpaired t-test (medetomidine vs. ketamine and isoflurane vs. ketamine).

Results

Figure 1 shows the dual-regression t-test map with medetomidine vs. isoflurane. It indicates that the mice with medetomidine have a higher activation than isoflurane in the sensory motor network (indicated in red).

Conclusions

Several networks were found to have increased coactivation with medetomidine as compared with the ketamine or isoflurane alone. This is consistent with the fact that isoflurane and ketamine are NMDA inhibitors and may therefore decrease the signaling process, whereas medetomidine is an alpha2-adrenergic agonist. Investigations into the neurochemical effects of medetomidine show a dose dependent brain activity [4].

Reference

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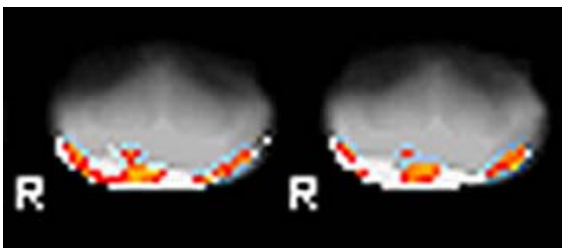

Fig 1: The dual-regression t-test map of the sensory motor network (Med vs. Iso).