Regional alterations between different anaesthesia protocols effects on the mice brain using resting-state fMRI

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Purpose: Resting-state fMRI (rs-fMRI) in mice is a growing area given the wide range of studies on transgenic mice models of human brain diseases. The use of anaesthesia is an integral part of most rs-fMRI mice studies, therefore it is important to understand how anaesthetic agents influence patterns of spontaneous brain activity. Because the brain as a whole is not influenced to the same degree by agents, this study attempts to examine intra-regional alterations in endogenous networks induced by different anaesthesia protocols and aims to refine the framework of understanding anaesthetic effects on functional correlations. Regional homogeneity (ReHo) is a local measure of the temporal similarity between a given voxel and its closest neighbours. While independent component analysis (ICA) and seed-based analysis provide information on inter-regional synchronization of spontaneous fMRI signals, ReHo provides information on the local oscillations.

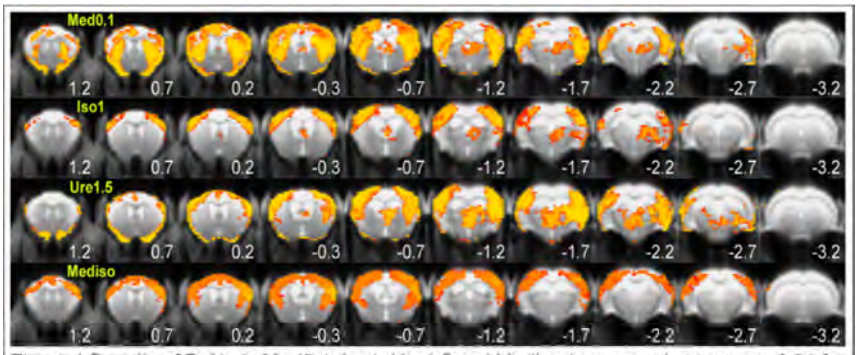

Figure 1 Results of ReHo in Med0.1, Iso1, Ure1.5 and Mediso (one-sample t-test; p<=0.01 for Med0.1, Iso1 and Ure1.5, p<=0.05 for Mediso). Distances relative to bregma are shown in the bottom of the images.

Methods: Data were collected by Grandjean, Schroeter et al. 2014, where a detailed acquisition procedure is provided. Briefly, mice were mechanically ventilated, paralysed with pancuronium, and either anesthetised with propofol (pro30), isoflurane (iso1), urethane (ure1.5), medetomidine (med0.1 and med0.05) or medetomidine and isoflurane (mediso) combination. Rs-fMRI was acquired on a 9.4T scanner (Bruker) equipped with a receiver only 2x2 phased array cryogenic coil. Echo planar imaging (EPI) were acquired with TR/TE/FA = 1000 ms/10 ms/90°, 360 repetitions, MD = 90 x 60, in-plane voxel dimension 263 x 233 µm. Images were processed as in [1] and further regressed out blood vessel signals. ReHo was performed using Data Processing Assistant for Resting-State fMRI (DPARSF) toolbox. Statistics were performed using FSL, t-tests were performed on each pair of groups. Image overlays indicate p<=0.05 for two sample unpaired t-test, overlays indicate p<=0.01 or p<=0.05 for one-sample t-test, with threshold-free cluster enhancement correction.

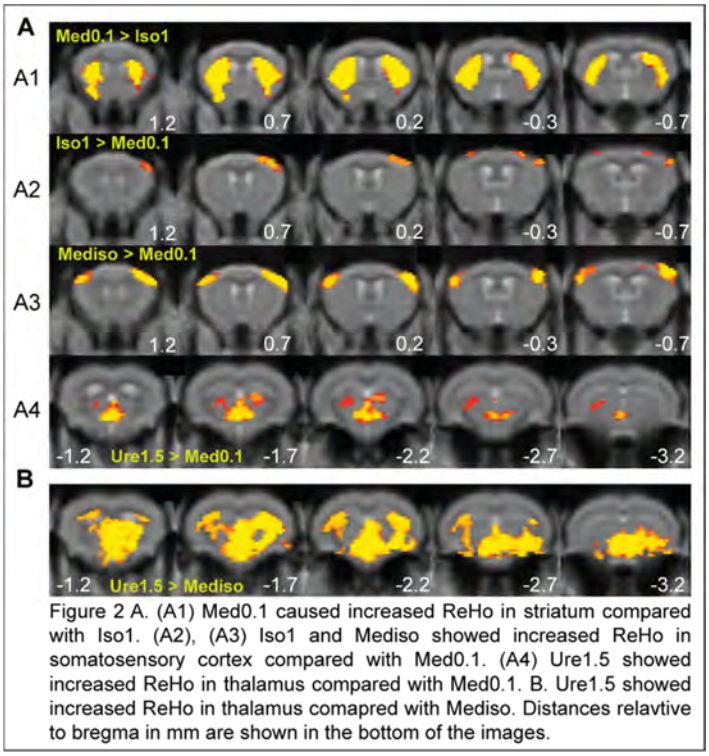

Figure 2 A. (A1) Med0.1 caused increased ReHo in striatum compared with Iso1. (A2), (A3) Iso1 and Mediso showed increased ReHo in somatosensory cortex compared with Med0.1. (A4) Ure1.5 showed increased ReHo in thalamus compared with Med0.1. B. Ure1.5 showed increased ReHo in thalamus comapred with Mediso. Distances relavtive to bregma in mm are shown in the bottom of the images.

Results: Changed ReHo values between groups were mainly located in thalamus, striatum and somatosensory cortex. One-sample t-tests showed visual impressions of ReHo (Fig.1) and analysis on both global signal regressed (GSR) and unregressed (UR) data revealed similar results. Significant results from both data after two-sample unpaired t-tests were in general located in similar areas while more highlighted GSR results were observed. Med0.1 displayed significantly increased ReHo in striatum compared to other groups (Fig 2. A1). Iso1 and Mediso caused higher ReHo than Med0.1 in sensory cortex (Fig1. A2 and A3), while Ure1.5 caused higher ReHo than Med0.1 in thalamus (Fig 2. A4). Ure1.5 also showed higher ReHo in thalamus compared to Mediso and Pro30 (Fig 2. B).

Discussion: Medetomidine caused increased ReHo in the striatum compared to other anaesthetics, possibly due to the low density of alpha2-adrenoreceptors in the striatum, which is the target of medetomidine, compared with the high level of GABAergic receptors in striatum, which is the main targets of isoflurane, propofol and urethane. Med0.1 showed locally decreased ReHo in the cortex and thalamus perhaps due to the relatively low alpha2-adrenoreceptors density in these areas. The observations are consistent with global FC analysis between remote areas using ICA and seed-based methods described in [1]. While inconsistent observations were reported in global FC analysis on GSR and UR data, altered ReHo located in similar areas from GSR and UR data indicates that GSR may not introduce significant changes to local similarity of time courses. Similar observations have been reported on human studies in [2]. Ure1.5 caused increased ReHo in thalamus implying that it might preserve more regional activations within thalamus. Somatosensory cortex is featured by ReHo in this study indicating this region may be more sensitive to local effects of different agents among cortex area. Regional neural activity revealed by ReHo emphasized brain areas targeted by different agents. This data-driven method does not rely on *a priori* knowledge and explores short-distance connectivity. The results demonstrate potential application of ReHo in mice rs-fMRI studies. In future, we are going to examine spontaneous brain activity changes between agents on a medium scale and a global level. Multivariate network analysis will be used to characterize the global network properties.

Reference:

1. Grandjean, J., Schroeter, A., Batata, I. & Rudin, M. Optimization of anesthesia protocol for resting-state fMRI in mice based on differential effects of anesthetics on functional connectivity patterns. *NeuroImage* **102P2**, 838-847 (2014).

2. Maximo, J.O., Keown, C.L., Nair, A. & Muller, R.A. Approaches to local connectivity in autism using resting state functional connectivity MRI. *Frontiers in human neuroscience* **7** (2013).