Functional connectivity in the Mouse brain detected under different dosages of Medetomdine

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Introduction

Spontaneous fluctuations of the blood oxygen level-dependent (BOLD) functional MRI signal at resting state have been shown to reveal intrinsic brain network [1]. Highly organized bilateral connectivity in various sensory and motor cortices, subcortical areas like the hippocampus, as well as default mode network have been detected. Most of these networks have been consistently identified across species, in humans, monkeys, rats. With most transgenic models of neurodegenerative diseases are only available in mouse, efforts have been made to detect the resting-state networks in mice. Recently, one study reported resting state fMRI in the mouse brain [2]. However, despite anatomical similarities between the mouse and rat brain, this paper reported unilateral connectivity in the mouse compared to the bilateral connectivity in the rat brain. Since medetomidine has been shown to suppress connectivity in the rat brain at high dosages [3], the reported unilateral connectivity may be due to the higher dose used. To allow more robust and reliable functional connectivity mapping in the mouse brain under medetomidine sedation, we compared the effect of two dosages of medetomidine on somatosensory activation and functional connectivity.

Methods

Animal study was approved by the local Institutional Animal Care and Use Committee. C57BL/6 mice (27 ± 3 g) were first anesthetized with isoflurane (3%) after which medetomidine was injected and isoflurane was turned off. A bolus of 0.3 mg/kg medetomidine (Dormitor, Pfizer) was administered by i.p. and then sedation was maintained with 0.1, or 0.6 mg/kg/hr infusion (n = 4 for each dosage group).

MRI measurements were performed using a 9.4T Varian scanner. For functional activation, two pairs of electrodes were introduced into the skin of the right and left forepaws of the mouse for activating the somatosensory cortex. BOLD fMRI were measured using a single-shot gradient-echo EPI (TR 2 sec, TE 15 msec, 0.5 mm slice thickness, 64x64 matrix size, and FOV 2.0x2.0 cm). Stimulation was given by a block design with 20 sec resting and 10 sec stimulation alternately repeated four times and adding 20 sec of resting at the end. Electrical pulses of 6 Hz with 0.3 ms, and 0.5, 0.75, and 1 mA current were applied to either left or right forepaw. Cross-correlation analysis was used to detect the activation.

Resting state fMRI was conducted using the same sequence parameters At one hour after the start of medetomidine infusion under 0.1 mg/kg/h dosage, and 2 hours in the case of the 0.6 mg/kg/h dosage. The processing of the resting state data included high-pass filtering at 0.01Hz, low-pass filtering at a cutoff frequency of 0.1 Hz, and spatial smoothing with a FWHM of 0.6x0.6 pixel. The average signals from the ventricles were regressed out to reduce contributions from physiological noises. A 2x2 pixel ROI was chosen as the reference point from each of the SI forepaw, Caudate Putamen (Cpu), SII cortical area, Hippocampus (Hip), Thalamus (Thal), and Visual cortex (VC), whose average time course was then correlated with every voxel time course in the brain. In both studies, a correlation coefficient higher than 0.2 was considered significant and clusters smaller than 4 pixels were rejected.

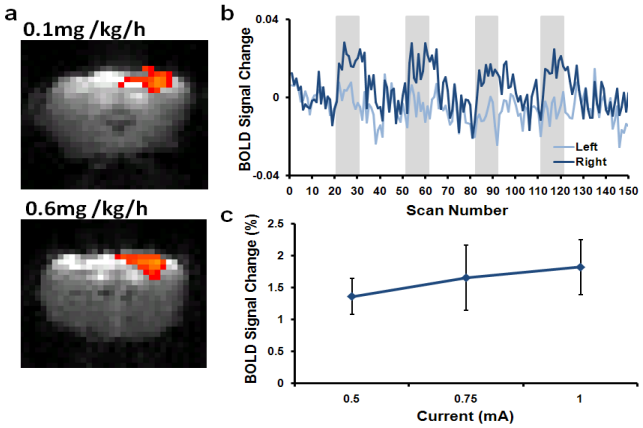

Fig. 1. (a) Activation maps under 0.1 and 0.6 mg/kg/h medetomidine show similar activation. (b) BOLD signal change in right(dark blue) and left (light blue) forepaw area (c) signal change in SI increases with stimulation currents.

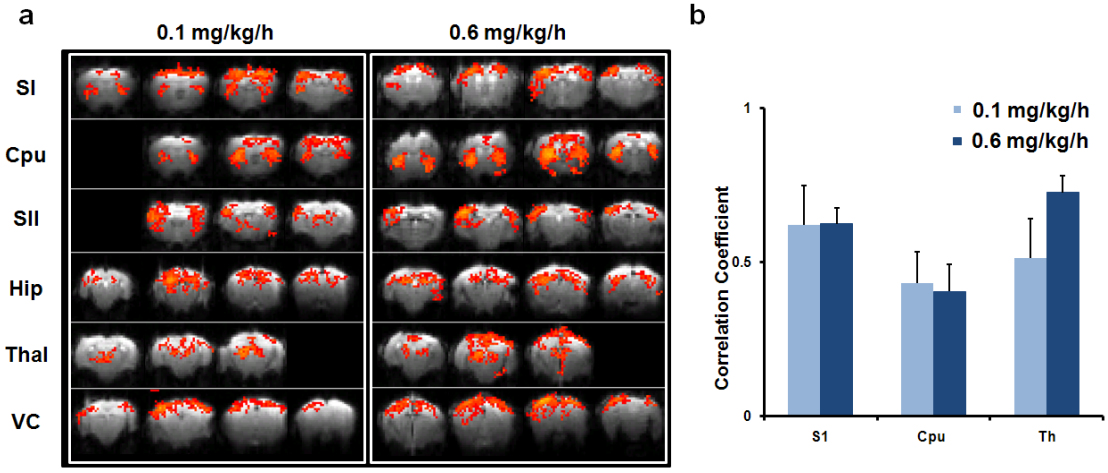

Fig. 2. (a) Resting state connectivity maps in SI, Cpu, SII, Hip, Thal, and VC regions. (b) Correlation between the left and right SI, Cpu, and Thalamic areas was unchanged with medetomidine dosages.

Results

With forepaw stimulation, robust BOLD activation was detected in the contralateral SI area under 0.1 and 0.6 mg/kg/h medetomidine dosages with signal change increased with stimulation current (Fig. 1). Interestingly, while high doses of medetomidine had no effect on the intensity of the signal observed (Fig. 1a), the detection of robust BOLD signal was delayed up to 2 hours compared to that of the 0.1 dose where reliable activation was detected 1 h from the start of infusion. (Fig. 2). Robust bilateral connectivity was detected in all the areas inspected -- SI, Cpu, SII, Hip, Thal, and VC.-- at both medetomidine dosages (Fig.2). Contrary to our observation in rats, resting-state functional connectivity was unchanged with increased dosages of medetomidine. There was no difference in correlation coefficients between the left and right SI, Thal, or CPu at high and low dosages of medetomidine.

Discussion and conclusion

Resting state functional connectivity measures have provided valuable insight into the functional organization of the brain and how such networks are disrupted in disease states. In this work we show that, similar to rats, consistent resting state networks can be detected in the mouse brain under the α2 adrenoreceptor agonist medetomidine. We show that connectivity can be detected bilaterally in the mouse brain as opposed to what is shown previously (Jonkers 2011). We also demonstrate that functional connectivity in all the main networks are fully preserved under high dosages of medetomidine compared to what has been reported in the rat. The capability to map such functional networks in vivo in both humans and mouse models will enhance our understanding of brain function and disease progression.

References: [1]Biswal et al. 1995 ; 34 :537-41, [2] Jonkers E et al. 2011; 6 :e18876, [3] Nasrallah FA et al. 2012 ; 60 :436-46.