Adrenergic receptor agonist vs antagonist tuning functional connectivity in resting state

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Introduction

Resting state functional connectivity has been used to characterize multiple brain systems and alterations associated with mental illness and neurodegenerative diseases [1]. However, a better understanding of the possible signal sources that give rise to correlations between regions is required to understand and interpret connectivity. Experiments are beginning to address the spatiotemporal characteristics of spontaneous fluctuations using optical [2], electrophysiological [3], and functional imaging techniques [4]. The noradrenergic system plays a key role in modulating neurotransmission. We have demonstrated the alpha-2 adrenoreceptor agonist, medetomidine (Med), could suppress the functional connectivity in dosage and regional dependent manner [5]. To further understand the role of the adrenergic system in modulating functional connectivity, the alpha-2 adrenoreceptor agonist and antagonist, Med and Atipamezole (Atip), were applied under isoflurane anesethesia.

Methods

Animal study was approved by the local Institutional Animal Care and Use Committee. Male Wistar rats (290-360g) were anesthetized and prepared under 3% isoflurane. 1.5mg/kg bolus of pancuronium bromide was given after which the isoflurane level was decreased to 1.3%. Two drugs were tested in this study, Medetomidine (Dormitor, Pfizer), administered i.v. at a constant infusion rate of 0.1 and 0.3mg/kg/hr (n = 6 for each group), and Atipamezole (Antisedan, Pfizer), also administered i.v. at a constant infusion rate of 1.0 and 1.5 mg/kg/hr (n=6 for each group). Animal physiology including blood pressure were monitored throughout the course of the experiment.

MRI measurements were performed using a 9.4T scanner (Agilent, USA). For functional activation, two pairs of electrodes were introduced into the skin of the right and left forepaws of the rats for stimulating activity in the somatosensory cortex. BOLD fMRI data were measured using a single-shot spin-echo EPI sequence (TR 2 sec, TE 38 ms, 1 mm slice thickness, 64x64 matrix size, and FOV 2.56x2.56 cm) before and after drug infusion. Stimulation was given by a block design with 60 sec resting and 20 sec stimulation alternately repeated three times and adding 60 sec of resting at the end. Electrical pulses of 9 Hz, 0.3 ms duration, and 3 mA current wee used and cross-correlation was used to detect the activation.

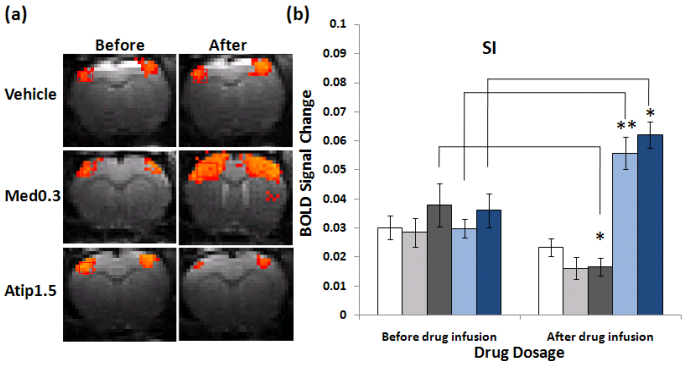

Fig. 1. (a) Activation maps at 3 mA before (right column) and after (left column) infusion of either vehicle (top), 0.3 mg/kg/hr Medetomidine (Med0.3, middle), or 1.5mg/kg/hr Atipamezole (Atip1.5, bottom). (b) signal change in SI before and after drug infusion, white bars represent vehicle, light and dark grey bars represent 1 and 1.5 mg/kg/hr Atip, respectively, and light and dark blue bars represent 0.1 and 0.3 mg/kg/hr Med, respectively.

Resting state functional connectivity was also measured using the same sequence with 1400 repetitions during the administration of either drug. The processing of the resting state data included slice timing correction, high-pass filtering at 0.01Hz, low-pass filtering at a cutoff frequency of 0.1 Hz, and spatial smoothing with a FWHM of one pixel. The average signals from the ventricles and skin were regressed out to reduce contributions from physiological noises. Time course of a 4x4 pixel ROI was chosen as the reference from the left SI forepaw region to correlate with the whole brain. Correlation coefficient higher than 0.25 was considered significant and clusters < 4 pixels were rejected.

Results

With forepaw stimulation, signal change of BOLD activation was increased after Med infusion while a significant suppression in BOLD signal activation was seen after Atip administration. There was no change in BOLD signal intensity in the vehicle control (saline) infusion (Fig. 1a,b). Contrary to the results seen with the activation, the resting-state functional connectivity was suppressed with the agonist Med while enhanced with that of the antagonist Atip (Fig. 2 a). The effects are significant at higher dosage but not in lower dose (Fig. 2 b). No significant change in blood pressure was detected with either of the drugs used. A spectral analysis of correlation in different frequency bands showed a shift to lower frequency (0.01-0.04Hz) with Atip while suppression of higher frequency (0.07-0.1Hz) with Med (Fig. 2 c).

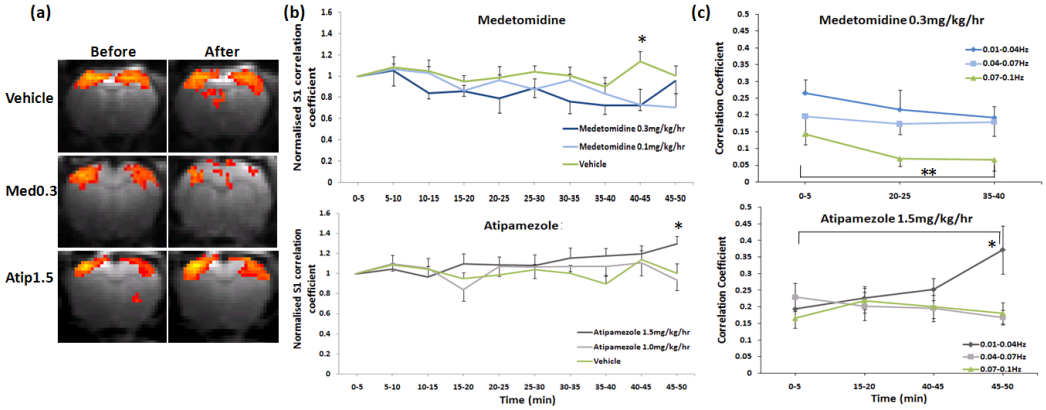

Fig. 2. (a)) Resting state connectivity maps in SI region before (right column) and after (left column) infusion of either vehicle (top), 0.3 mg/kg/hr Medetomidine (Med0.3,middle), or 1.5mg/kg/hr Atipamezole (Atip1.5,bottom). (b) Representation of the SI correlation coefficient analyzed in 5 min intervals across the timecourse of 0.1 or 0.3 mg/kg/hr Medetomidine infusion, respectively (top) and that with 1 or 1.5 mg/kg/hr Atipamezole infusion, respectively (bottom). (c) Correlation coefficient in different frequency bands under Medetomidine (top) and Atipamezole (bottom).

Discussion

Our results show that, by specific targeting of the α2-adrenergic receptor, functional connectivity can be modulated to reflect increases or decreases in receptor activity. While Med increased and Atip decreased BOLD activation, this could mainly be due to their vasoconstrictive versus vasodilatory effects, respectively. Consistent with our previous finding, Med caused a loss of functional connectivity in SI, which is further supported by increased connectivity under Atip. Since baseline BOLD signal and functional connectivity didn't have significant correlations with blood pressure, therefore the change in connectivity wouldn't be due to the vascular effects. This up and down regulation of synchrony indicates a role of adrenergic system in modulating the functional connectivity.

References: [1]Fox MD & Raichle ME. Nat Rev Neurosci 2007; 8:700-711. [2]Arieli et al. J Neurophysiol 1995 ; 73 :2072-2093. [3] Leopold DA & Logothetis NK. Rev Neurosci 2003;14:195-205. [4]Biswal, B et al. Magn Res Med 1995; 34:537-541. [5] Nasrallah et al. Proc. Intl. Soc. Mag. Reson. Med. 2010.