Differential effect of Adrenoceptor on Functional Activation and Connectivity

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Purpose

Functional MRI (fMRI) has been used in detecting task-related hemodynamic responses following neuronal activation. Spontaneous low frequency fMRI signal fluctuations at resting state have emerged as another means to study brain function (1). The mechanism underlying these fluctuations in the brain has remained elusive and its neural origin still debatable. A major concern in studying the mechanism in rodents is the use of anesthesia. The alpha 2-adrenoreceptor agonist, medetomidine, has recently been used for functional activity and resting state studies because it allows longitudinal fMRI studies (2, 3). To understand the effect of medetomidine on resting state fluctuations, we studied the functional activation of the rat brain induced by forepaw stimulation and resting state functional connectivity under various dosages of medetomidine.

Methods

Animal study was approved by the local Institutional Animal Care and Use Committee. Male Wistar rats (290-360g) were first anesthetized with isoflurane (3%) after which medetomidine was injected and isoflurane was turned off. A bolus of 0.05 mg/kg medetomidine (Dormitor, Pfizer) was administered by i.p. and then sedation was maintained with 0.1, 0.2, or 0.3 mg/kg/hr infusion rate (n = 5 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 rats for stimulating activity in the somatosensory cortex. Functional MRI was typically started after the influence of initial isoflurane anesthesia was considered to be negligible. BOLD fMRI data were measured using a single-shot spin-echo EPI sequence (TR 2 sec, TE 38 msec, 1 mm slice thickness, 64x64 matrix size, and FOV 2.56x2.56 cm). 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 with 0.3 ms duration, was stimulated with 1, 2, 3, and 4 mA current randomized among the rats. Cross-correlation analysis was used to detect the activation.

Resting state functional connectivity was also measured using the same sequence with TE increased to 45 ms. 305 scans were collected without any external stimulation at 45 minutes after the administration of medetomidine. 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 were regressed out to reduce contributions from physiological noises. A 2x2 pixel ROI was chosen as the reference point from the left SI forepaw region whose average time course was then correlated with every voxel time course in the brain. In both studies, a correlation coefficient higher than 0.25 was considered significant and clusters smaller than 4 pixels were rejected.

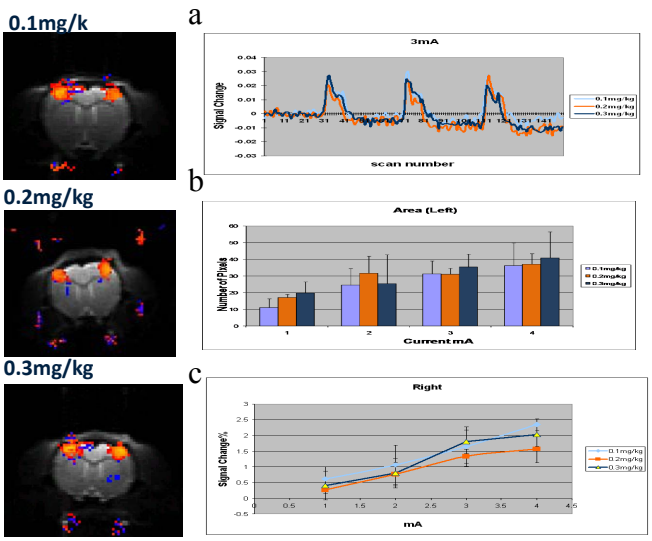

Fig. 1. (a) Activation maps at 3 mA show similar activation at different dosages of medetomidine. (b) Activated area size and (c) signal change in SI increase with stimulation currents.

Results

With forepaw stimulation, both signal change and area of BOLD activation increased with increased intensity of the stimulation (Fig1b,c). Interestingly, the signal change and area size were very similar across different dosages of medetomidine in both the left and the right SI areas (Fig1a).

Contrary to the unchanged activation, the resting-state functional connectivity was suppressed with increased dosages of medetomidine (Fig. 2). The correlation between the left and right SI forepaw regions at resting state decreased with increased dosages as shown from the reduced correlation coefficient and area size (Fig2b). The amplitude of the fluctuations, as measured by temporal standard deviation divided by the mean, remains unchanged across different medetomidine dosages with slight reduction (though insignificant) at the highest dosage (Fig 2c).

Discussion and conclusion

Previous studies using different dosages of anesthesia like alpha-chloralose and isoflurane showed that both functional activation and resting-state connectivity are reduced by increased anesthesia (4,5). Our results showed a strong dependency of resting-state BOLD fluctuations but not functional activation on medetomidine dosages. It is known that medetomidine is a vessel constrictor which reduces blood flow. The unchanged BOLD activation under forepaw stimulation implied a proportional reduction in oxygen consumption, which indicates reduced neural activation under the sedation. The unchanged resting-state fluctuation amplitude corresponds to this unchanged BOLD activation. However, the loss of correlation under resting state suggests a loss of inter-hemispheric temporal synchronous activity. This differential effect between the activation and resting state indicates a role of adrenergic system in modulating the functional connectivity.

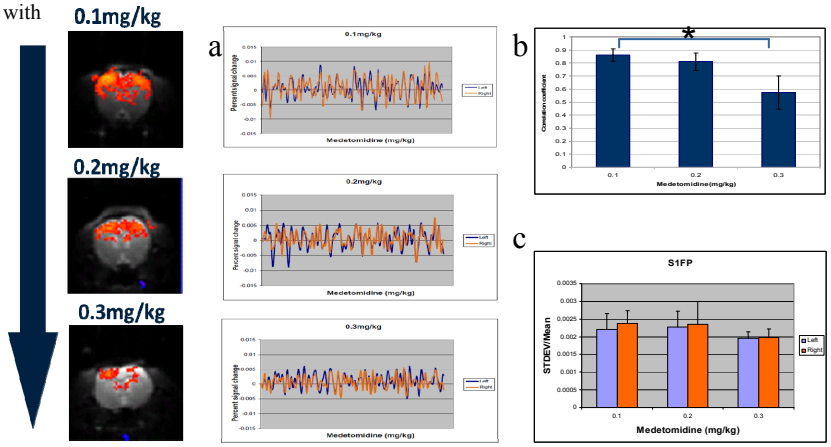

Fig. 2. (a) Resting state connectivity maps in SI region and the fluctuation time-course from the left and right forepaw areas. (b) Correlation between the left and right forepaw areas decreased with medetomidine dosages. (c) The amplitudes of fluctuation remained unchanged.

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