

Differential effect of medetomidine on functional activation and connectivity: electrophysiology validation

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Introduction

Functional connectivity MRI has been used to study the intrinsic brain network [1]. However the underlying neural mechanism is still not clear [2]. Pharmacological manipulation could help to elucidate the neural receptor system related to this phenomenon. Previously, we showed that functional connectivity in the primary somatosensory cortex (S1) can be suppressed by an α 2-adrenergic receptor agonist, medetomidine, while the neural activation remained the same [3]. Since a drug may change the hemodynamics and neurovascular coupling, knowledge of these aspects is of utmost importance in interpreting neuroimaging findings. Here we conducted electrophysiological measurements of somatosensory evoked potential (SEP) and resting electroencephalography (EEG) to correlate with the BOLD signal.

Methods

All experimental procedures were approved by the local Institutional Animal Care and Use Committee. Male Wistar rats (290–360g) were first anesthetized with isoflurane (3%) after which a bolus of 0.05 mg/kg medetomidine (Dormitor, Pfizer) was administered by i.p. and isoflurane was turned off. Then three dosages of medetomidine were studied by i.p. infusion with 0.1, 0.2, or 0.3 mg/kg/hr infusion rate ($n = 6$ for each dosage group). Activity at resting state and under stimulation was measured by fMRI and EEG. For functional activation of the S1, two pairs of electrodes were inserted into the skin of the right and left forepaws. Electrical pulses of 9 Hz and 0.3 ms duration was used with current varied from 1, 2, 3, to 4 mA and randomized among the rats.

For EEG and SEP measurement, the rat's head was secured in a stereotaxic frame, the skull exposed and two holes were drilled at 3.5mm lateral, 1mm anterior of the bregma and electrodes were inserted at 1mm below dura. Another electrode was inserted at 10mm posterior to the right hole as the reference. Resting EEG was recorded for 600 sec with a high pass filter at 0.01Hz (MP150, Biopac, USA). SEP was recorded under a 30sec resting followed by 20 sec stimulation. The average SEP over the 20 sec stimulation was obtained. Integral of the negative wave (N1) magnitude was calculated. For resting EEG, we compute the coherence between both sides of the S1 as well as the power distribution in different frequency bands.

MRI measurements were performed using a Varian 9.4T scanner (Agilent, USA). BOLD fMRI were acquired using single-shot spin-echo EPI (TR 2 sec, TE 38 ms, 1 mm slice thickness, 64x64 matrix size, and FOV 2.56x2.56 cm²). 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. Cross-correlation > 0.2 was used to detect the activation. Resting state functional connectivity was measured using the same sequence with TE increased to 45 ms and 305 scans were collected. The processing of the resting state data included slice timing correction, band-pass filter from 0.01Hz to 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. A correlation coefficient higher than 0.25 was considered significant and clusters smaller than 4 pixels were rejected.

Results

Similar to fMRI, evoked potential didn't change under different dosages of medetomidine (Fig. 1a, b). A linear relationship is observed between fMRI signal change and the integral of SEP N1 signal (Fig. 1c). The functional connectivity map shows a loss in synchrony between the left and right S1 regions when medetomidine dosage increases (Fig. 2a). The resting EEG shows similar signal under different medetomidine dosages (Fig. 2b). The coherence in most bands didn't change, except the Gamma band (Fig. 2c). No significant change in the power distribution was observed (Fig. 2d).

Discussion and conclusion

Neural activity is not suppressed by increased dose of medetomidine as evident in SEP results. The linear relationship between the BOLD signal and SEP shows that neurovascular coupling remains the same and indicates that the BOLD fMRI can reflect neural activities in this study. We also found that the loss of synchrony in S1 region at higher medetomidine dosage may be related to change in coherence in the Gamma band (30 to 49 Hz). However, no significant change is found in power distribution in each band. The link between the neural synchrony and the correlated fMRI fluctuation has yet to be determined.

Acknowledgement

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References

[1] Fox MD & Raichle ME. Nat Rev Neurosci 2007; 8:700-711 [2] He BJ, et al. PNAS 2008; 105:16039-44. [3] Nasrallah FA, et al. Proc ISMRM. 2010.

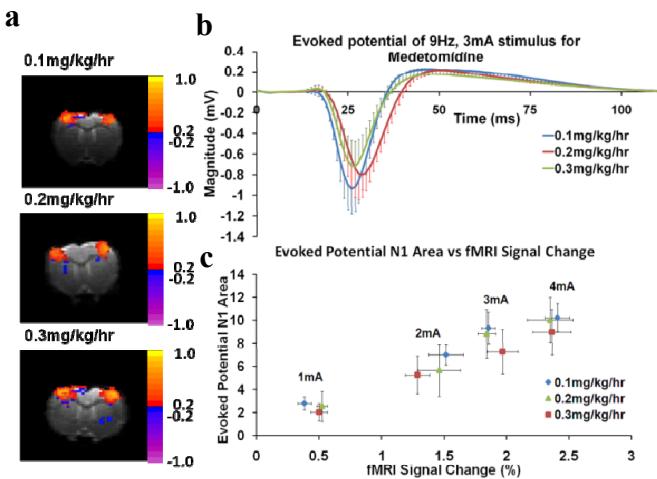


Fig. 1. (a) Activation maps and (b) SEPs at 3 mA stimulation show similar activation at different dosages of medetomidine. (c) fMRI signal change and SEP activities show similar correlation across dosages.

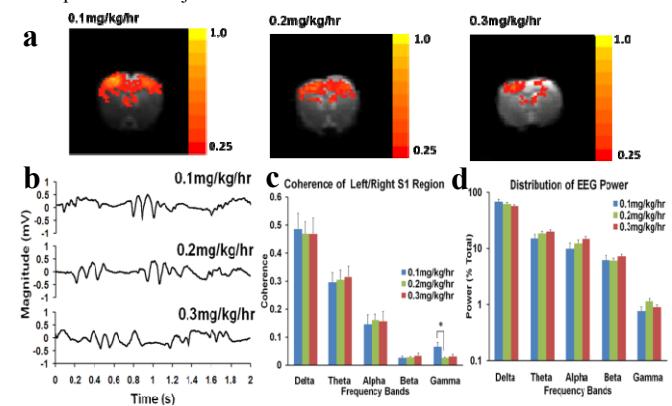


Fig 2. (a) Functional connectivity maps show a loss in connectivity between left/right S1 regions but (b) resting EEG shows similar signal as drug dosage increases. (c) Significant decreased coherence was found in Gamma band (30 to 49Hz). (d) No significant changes in power distribution with medetomidine dosages.