Cortical Activations to Transient Tracheal Obstruction in the Rat Using BOLD fMRI

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Introduction

Airway obstruction produces a distressing respiratory sensation common to many respiratory diseases such as emphysema and asthma. Elucidating the neural mechanisms involved in respiratory sensation may lead to better treatment strategies for patients with respiratory diseases. Recent studies suggest a role for suprapontine structures and the cerebral cortex in generating respiratory sensations. Functional imaging studies in humans show activations in the sensorimotor cortex as well as fear-eliciting areas of the limbic cortex to respiratory stimuli that produce distressing respiratory sensations. To clarify the role of higher brain structures in respiratory sensation generation, an animal model is needed so that invasive techniques necessary to study these neural pathways may be utilized. We have developed a model of transient tracheal obstruction in the rat to reproduce the respiratory sensations experienced by patients. The purpose of this project was to assess brain activations in the rat during tracheal obstruction using functional magnetic brain imaging. We hypothesized that the sensorimotor and limbic cortices reported to be activated in humans will also be activated in rats, thus verifying the transient tracheal obstruction protocol in the rat as an appropriate animal model to study the mechanisms of respiratory sensory distress. To achieve this goal, our first task was to develop the blood oxygen level detection (BOLD) functional imaging technique to image rat brain activity at the AMRIS facility. Once we developed a functional imaging sequence that produced images free of artifacts and a good signal to noise ratio, we used this sequence with our tracheal obstruction model. While a great deal of time and effort was spent developing this sequence, in this report we present the resulting preliminary data from our tracheal obstruction experiments in rats.

Experimental

Tracheal Obstruction. An occluder cuff was placed around the trachea of four anesthetized male Sprague-Dawley rats. The tube connecting the cuff was filled with water and connected to a syringe. The cuff was inflated and deflated by pushing in and pulling back on the syringe, respectively. Respiratory rate was assessed using a pressure sensitive pillow placed under the rat's abdomin. A hose blowing warm air into the magnet bore kept the rat's body temperature close to normal.
BOLD fMRI. The anaesthetized rats were positioned in an MRI-compatible sterotaxic head holder and placed into a 4.7 T magnet (Bruker Inc.). An echo planar imaging (EPI) sequence was used to image brain activity to tracheal occlusion (TR:1000 ms, TE: 17.68 ms, FA: 90, Matrix: 64 x 64, in plane resolution: 0.60 x 0.60, slice thickness: 2 mm, scan time: 5 min). The trachea was occluded for 2-3 scans (4-6 sec) and unoccluded for 3-4 scans (6-8 sec). Each scan corresponded to one brain volume. Images were analyzed using NeuroLens (Mac). Voxels with an activation threshold of $p<0.05$ were considered significant.

Results and Discussion

We observed significant activations in neural relay areas (thalamus: 5%) that gate sensory afferent information into the cortex, sensory areas (somatosensory cortex: 4.4% increase in signal activity) that detect respiratory stimuli from peripheral receptors, and motor areas (caudate putamen: 5%) that increase motor output to respiratory muscles. We also saw activations in limbic structures involved in generating aversive sensations such as fear and anxiety, namely the amygdala (4.3%), lateral hypothalamus (4.4%), hippocampus (4.9%), piriform cortex (7.1%) and mostly notably the agranular insular cortex (18%). Activation of these structures is in agreement with previous work in humans, thus our preliminary data support our hypothesis. We will complete this data set using the same protocol but increase the scan duration to 10 min to increase signal intensity and include experimental controls to account for non-respiratory sensory brain activations. In future studies we will investigate the cortical structures that are essential in generating respiratory sensation using BOLD fMRI.

Conclusions

We have successfully developed a functional MRI sequence to image brain activity in the rat. Using this sequence we report activations in the sensorimotor and limbic cortices during transient tracheal obstruction thus supporting our hypothesis.

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