Odor- Induced Functional Imaging of Brain Activity in Conscious Animals

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Introduction

Individuals smell a wide variety of odors with or without awareness. Since olfactory cues are particularly salient to animals. We utilized a novel lemon odor to explore the feasibility of using both fMRI and manganese-dependent contrast to visualize cognitive and emotional responses to novelty. We hypothesize that the two methods can more clearly delineate stimulus specific responses to novelty odor under awake conditions. To test this hypothesis, the present study examined changes in BOLD signal and manganese-enhanced magnetic resonance imaging in the brain of fully conscious male rats in response to lemon scent in a novel paradigm.

Methods

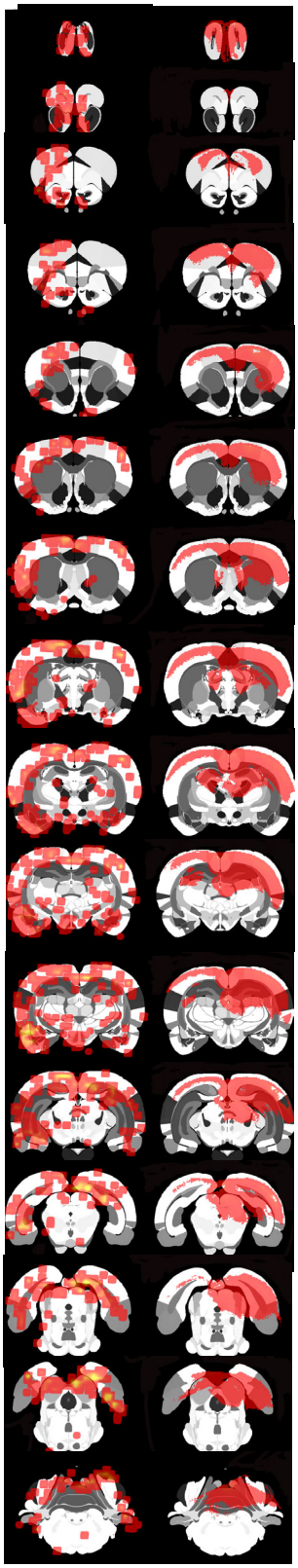
fMRI studies were conducted on acclimated adult male Sprague Dawley rats. During MR sessions, males were first lightly sedated with ketamine HCl (Ketaset, 2 mg) plus medetomidine (Domitor, 0.02 mg) and placed in the MR head and body restrainer. Once securely restrained, anesthesia was reversed with atipamezole (Antiseden, 0.1 mg). Males were fully conscious within 2-5 min upon anesthesia reversal; imaging began at least 30 min after reversal. A dual coil system consisting of a volume coil as transmitter and surface coil as receiver was used for imaging. The coils were built into a composite unit that included a head and body restrainer used for imaging conscious animals (Insight Neuroimaging Systems, Worcester, MA). All images were acquired using a 4.7T/40cm horizontal magnet (Bruker, Billerica, MA U.S.A). High resolution multislice anatomical data sets were acquired (Fast spin echo, TR = 2.0s, effective TE =12ms, Matrix = 256 x 256, FOV = 3.0cm x 3.0 cm, eighteen 1.0-mm slices.) at the beginning and end of each imaging session. Subtraction of these data sets confirmed there was no significant movement of the animal over the imaging session. Functional MRI imaging was performed at a resolution of 64^2 x 18 slices with the same FOV and slice thickness as the anatomical images with RARE sequence of TR = 2.5s, TE = 7 ms,16 echo train length, average =2, Number of Repetitions=30, total acquisition time=10 minutes. Lemon scent was presented one minute after baseline.

For Manganese contrast studies: Male Sprague-Dawley rats (300-400g) were anesthetized with 2%-isoflurane for surgery. Polyethylene catheters (PE-50) were placed in the femoral vein and the right common carotid artery (CCA). Mannitol could later be administered from the severed CCA toward the internal carotid artery (ICA) and the brain but not toward the heart. After surgery, isoflurane was discontinued and the animals were returned to cage awake. Rats were infused in the femoral vein with 120mM MnCl2 at a rate of 2 ml/hr for a total of 30 minutes. Ten minutes after starting the infusion, a bolus of 20% mannitol (at 4°C, dissolved in 0.1M PBS, pH 7.4) was given into the carotid artery at a concentration of 5 ml/Kg. Mannitol was injected at a constant rate over one minute to break the blood brain barrier (BBB). One minute after the mannitol injection, rats were presented with lemon scent until the end of the infusion time. After the infusion, rats were secured in a MR compatible restrainer similar to that used in the fMRI studies. T1-weighted images were completed 45-50 minutes after the MnCl2 infusion ended by using a gradient echo sequence (TR=300ms; TE=4.2ms; FOV=2.5x2.5cm; matrix=256x256; slice thickness=1.0mm; number of slices=18; averages=12).

Statistical comparison of control periods to olfactory stimulus periods was carried out using Student's t-test. Activation maps were generated using a statistical threshold of $P < 0.05$. CWBench software was used to register, segment and analyze the data.

Results

All males tested with olfactory odor showed significant BOLD signal in the cortex, hippocampus, thalamus and olfactory system. Figure A shows a composite (n=5) lemon-elicited brain activation maps of positive BOLD signal. Figure B shows a composite (n=5) T1W images throughout the brain exposed to lemon scent. Areas in which the signal intensity increased significantly are shown in color. Comparing the two types of imaging, we can visually trace the smell pathway.



A B

Discussion:

Using fMRI and manganese contrast we found that rats respond to a novel odor with neural activation in brain regions implicated in both animal and human responses to novelty. In addition, this study demonstrates rapid processing speed from stimulus onset in several brain regions. Since olfactory cue processing is vital to an organism's assessment of its environment the intense response to novelty is not surprising. Finally, this study demonstrates that it is feasible to address cognitive and emotional paradigms using fMRI and manganese contrast in fully conscious rats. Such studies provide a unique opportunity to map response latencies, synchronicity of activation, and neural sites involved in novelty assessment.

References:

Lahti K, Ferris CF, Li F, Sotak CH, and King JA. (1999). Comparison of evoke cortical activity in conscious and propofol anesthetized rats using functional MRI. *Magnetic Resonance in Medicine* 41, 412-416.

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