BOLD fMRI Study of Rat Inferior Colliculus Activated by An Oddball Paradigm

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INTRODUCTION: Sudden change of the environment could signify danger for an individual. Therefore, rapid detection of sudden changes of external sensory stimulation is crucial for survival. In auditory neuroscience, how novel sounds are processed in different auditory structures has been studied in both humans and animals, usually by adopting an oddball paradigm [1, 2]. To date, most human studies were focused on the cortical regions [1, 3]. Recently, electrophysiological studies on animals revealed that neurons in low-level subcortical regions also respond to novel stimulus [4, 5]. Compare to electrophysiological methods, BOLD fMRI is noninvasive and can examine a larger field of view, therefore can significantly improve our understanding of the functions of different auditory structures. In this study, we investigated the role of rodent inferior colliculus (IC) in processing novel sounds using an oddball paradigm and fMRI.

METHODS:

***Animal Preparation*:** Adult Sprague-Dawley (SD) rats (320-350g, N=5) were examined. They were anesthetized with 3% isoflurane for induction and maintained at 1% throughout imaging. During MRI, warm water was circulated, and heart rate, respiration rate, oxygen saturation level and rectal temperature were monitored.

Acoustic Stimulation: Stimulation during fMRI was transmitted from a high frequency speaker (MF1, TDT) and through a custom-built tube to the animal's left ear. For the oddball paradigm, a sequence of 300 stimuli was generated. The duration of each stimulus was 0.2s and inter-stimulus interval (ISI) was 0.8s (Fig. 1). Among the 300 stimuli, 291 were identical normal balls. For normal balls, the amplitude linearly ramped up and the frequency spectrum was a band-limited noise while the identical but temporally reversed waveform was used as oddballs (Fig. 2). Oddballs were pseudo-randomly distributed and were apart from adjacent oddballs by at least 20 normal balls. For comparison to this oddball paradigm, the normal ball and oddball stimulation were also separately presented to an animal using a 20s-on-40s-off block design paradigm.

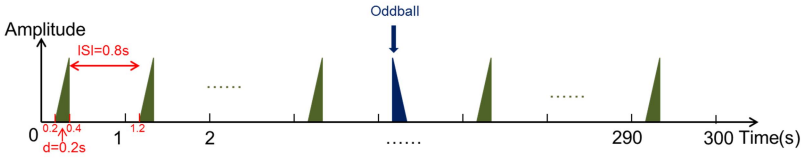

Fig. 1: Acoustic stimulation paradigm used in this study. 9 oddballs (1 shown in the figure) were pseudo-randomly distributed among 291 normal balls. Duration of each ball was 0.2s and inter-stimulus interval (ISI) was 0.8s, as shown for the initial 2 balls.

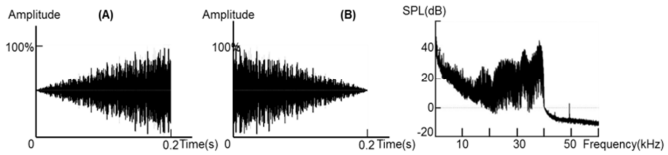

Fig. 2: Temporal waveforms of normal ball (A) and oddball (B, the temporal reversal of waveform A). Both the normal balls and oddballs had the identical frequency spectrum as shown in (C).

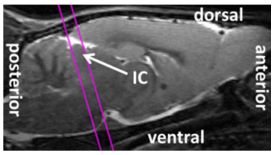

Fig. 3: Slice position covering whole IC.

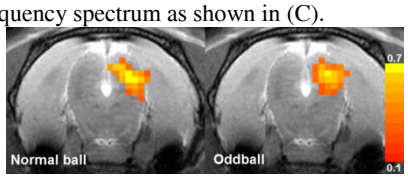

Fig. 4: CC map showing activation by individual normal ball and oddball stimulation.

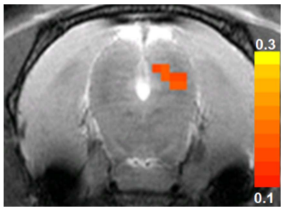

Fig. 5: Averaged CC map showing activation by the oddball paradigm.

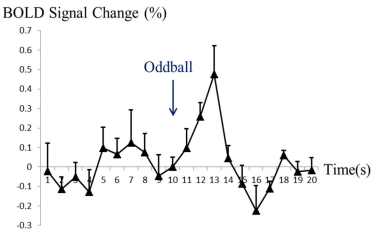

Fig. 6: Averaged 20s time course for all hot voxels and all 5 animals. Error bars indicate SEM for each point. Blue arrow indicates the oddball stimulus.

Image Acquisition: All MRI data were acquired using a 7T Bruker scanner with a receive-only surface coil. fMRI measurements were performed using GE-EPI sequence with FA=56°, TE=20ms, TR=1000ms, FOV=34×34mm^2 and matrix=64×64. A single axial 1.2mm slice was planned to cover whole IC (Fig. 3). Multiple slices were not used in order to reduce scanner noise. For each fMRI session using the oddball paradigm, 300 time points were sampled in synchronization with the stimulation sequence. Each session therefore lasted 5mins and 5-6 sessions were performed for each animal. For the block design paradigm, 300 time points (i.e. 5 on-off blocks) were acquired respectively for both normal ball and oddball stimulus.

Data Analysis: All GE-EPI images were registered, Gauss smoothed (FWHM=0.5mm) and detrended to remove linear drift. For the oddball paradigm, different EPI sessions from the same animal were averaged, such that there were 300 images for each animal. Then the 300s time course of each voxel was correlated with a boxcar function (0 for normal balls, 1 for odd balls with a delay of 3-4s) to identify regions activated by the oddball stimulus. Then for the activated voxels, 9 blocks were extracted and averaged. Each block contained 10 points before and 10 points after the onset of an oddball. Then the 20s time courses of all 5 animals were averaged and BOLD signal change was calculated. For the block design paradigm using individual normal ball or oddball stimulus, correlation coefficients were similarly calculated to examine activation.

RESULTS: Fig. 4 shows the activation maps by individual normal ball and oddball stimulation in one animal. Most area of IC was activated by both stimulations. Fig. 5 shows the activation map averaged for 5 animals in the oddball paradigm. Activated voxels were observed mainly in the ventral part of IC. Fig. 6 shows the 20s time course averaged for all activated voxels and all animals. BOLD signal change was 0.48%.

DISSCUSSION: Our results demonstrated for the first time that IC was activated when a novel sound stimulus was presented. This finding indicated that IC, a low-level subcortical structure, plays an important role in sensing sudden sound changes. Oddball effect in auditory cortex has been studied in both humans and animals by others. Yet the oddball was implemented by different frequency in those studies, which is not suited to subcortical structures that are highly tonotopic [6]. In this study, both normal balls and oddballs had identical broadband noise spectrum but temporally opposite order. Our fMRI results revealed that IC is involved in differentiating novel sounds, and it is sensitive to the change of amplitude patterns. More interestingly, our results indicated that the oddball effect is different in different parts of IC. This may suggest a topographical encoding of oddball information in IC, similar to the encoding of sound frequency and amplitude modulation [6, 7]. Our findings can help us better understand the sophisticated role of IC in auditory processing and may guide future studies of subcortical functional changes.

REFERENCES: [1]Liebenthal E. *et al*, Neuroimage, 2003; [2]Ilanovsky N. *et al*, Nat Neurosci, 2003; [3]Strobel A. *et al*, Neuroimage, 2008; [4]Malmierca M. S. *et al*, J Neurosci, 2009; [5]Anderson L.A. *et al*, J Neurosci, 2009; [6]Cheung M. M. *et al*, Neuroimage, 2012; [7]Langner G., Hear Res, 1992.