BOLD fMRI Investigation of Tonotopic Changes in Normal and Injured Auditory Systems

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Introduction Rodents share similar anatomical, physiological and behavioral features in the auditory system with humans and have proven useful in hearing studies[1]. Activations in major structures along the rat ascending auditory pathway can be revealed by block-design BOLD fMRI[2]. The inferior colliculus (IC) is a large ellipsoidal structure in the midbrain that serves as a relay center for all ascending inputs in the mammalian auditory system (Fig. 1). In this study, tonotopic changes in normal animals with increased sound pressure level (SPL) and in animals injured by post-natal noise exposure (NE) are investigated using a novel fMRI paradigm that integrates distortion-free MRI and continuous frequency sweeping.

Methods ***Noise rearing:*** A litter of rat pups (n=8) along with their mother were placed in a separate cage for seven consecutive days. They were continuously exposed to broadband noise trains at a SPL of approximately 100dB inside the cage. The noise exposed (NE) rats were returned to normal housing and scanned after five months. ***Animal preparation:*** Normal (n=4) and NE animals were anesthetized using isoflurane and kept warm with 37ºC water throughout the experiment. Vital signs were monitored. ***Auditory stimuli:*** Monaural stimuli were produced using an ultrasound loudspeaker driven by a power amplifier and a waveform generator. Sound waves were delivered to the rat ear canal via a 1m-long delivery tube. The continuous auditory frequency sweeping stimulation paradigm consisted of two 880s scans with different frequency sweeping directions (Fig. 2). Frequency was swept linearly from 1 to 40kHz in the first scan and 40 to 1kHz in the second scan with a period of 40s and repeated 22 times. An additional pair of scans with SPL increased by 12dB was performed on the normal animals. ***MRI protocol:*** Experiments were performed using a Bruker 7T scanner. Fieldmap-based shimming was applied prior to fMRI scans. 2D distortion-free balanced steady state free precession (bSSFP) functional images consisting of one coronal slice covering the entire IC were acquired with TR/TE= 3.8/1.9ms, FA=30^0, phase advance=180^0, FOV=32x32x120mm^3, data matrix=64x64 (zero-filled to 128x128), and NEX=4 (temporal resolution=1s). ***Data analysis:*** Data in the first 40s of each scan were discarded. The remaining fMRI time series were co-registered before further analysis. Fourier transform of the fMRI time series were performed on a voxel-by-voxel basis to obtain the coherence, which is derived from the magnitude[3], and phase at the cycling frequency (0.025Hz=1/40s). The average coherence map of the two sweeps was computed. In Fig. 2, the phase information is affected by both the characteristic frequency (t_F) of the voxel and the hemodynamic delay time t_H. The tonotopic map (1-40kHz) was therefore obtained by computing the difference between the phases of two scans to eliminate the hemodynamic time delay.

Results Fig. 3a shows a representative tonotopic map from a normal animal using the fMRI paradigm described above while Fig. 3b depicts the iso-frequency lines measured in the eight normal animals. Neurons sensitive to lower frequencies (LF) are located in the dorsolateral side and those sensitive to high frequencies (HF) are located in the ventromedial IC. Fig. 4 shows the effect of increased SPL on the tonotopy maps in the four animals studied. Voxels in the middle of the IC showed prominent increases in encoded frequency while those in the dorsal and ventral IC showed less prominent increases and decreases, respectively. Fig. 5 presents the coherence and tonotopic maps from normal and NE animals. The coherence of NE animals is stronger in the ventromedial IC and there is no observable activation in the dorsolateral region that is normally sensitive to lower frequencies. Of the eight rats exposed to noise, six showed a similarly homogeneous tonotopic maps and the remaining two showed maps similar to those of normal animals.

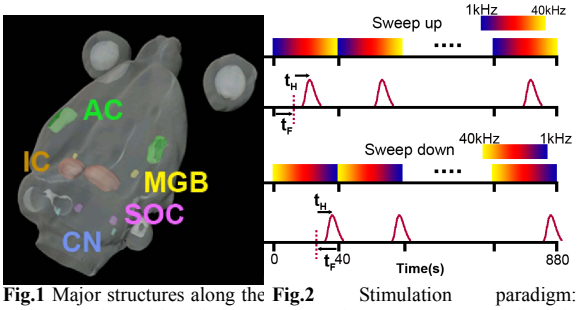

Fig.1 Major structures along the auditory pathway identified on a 3D rendered brain built from high resolution MRI anatomical images covering the entire brain. CN: cochlear nucleus; SOC: superior olivary complex; IC: inferior colliculus; MGB: medial geniculate body; AC: auditory cortex[2].

Fig.2 Stimulation paradigm: frequencies were swept linearly between 1kHz and 40kHz in a cycle of 40s for 880s. The stimulation paradigm consists of two scans with different sweeping directions.

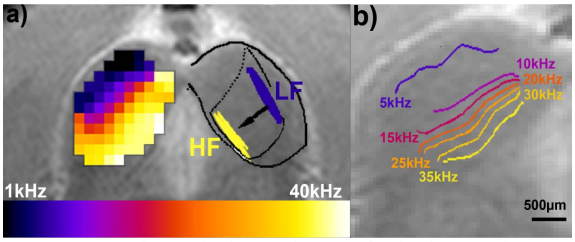

Fig.3 a) Tonotopic map in the IC of a normal animal. **b)** Iso-frequency contour lines of the averaged normal animals (n=8).

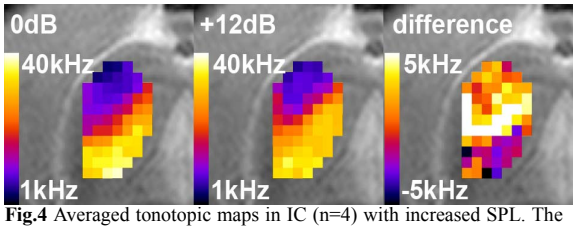

Fig.4 Averaged tonotopic maps in IC (n=4) with increased SPL. The difference of the two maps is plotted on the right.

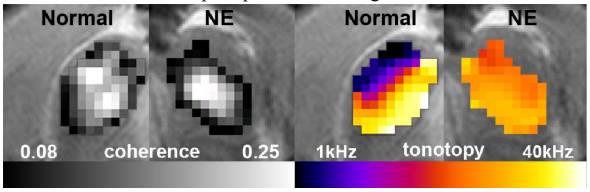

Fig.5 Coherence and tonotopic maps from representative (left) normal and (right) post-natal noise exposed (NE) animals.

Discussions The BOLD signal change could be assumed to be additional activation to the baseline caused by the scanner noise[2]. ***Probing local auditory neuronal characteristics with SPL:*** The response time obtained after Fourier transformation in a single scan was determined by not only the characteristic frequency (CF), but also frequency sweeping duration and mode (linear or logarithmic) and the complexity of the frequency tuning curves of neurons. Most of the frequency tuning curves are V-shaped and often asymmetric[4], and it is expected that the neurons respond to a broader bandwidth of stimuli at higher SPL. However, there is significant heterogeneity among the tuning curve shapes of different neurons in the IC[5,6]. The general increases of encoded frequency in Fig. 4 likely reflect the fact that neurons operated in the peripheral regions of their tuning curves. Neurons with lower CFs have more area under the tuning curve at frequencies above the CF and hence results in a positive shift in the measured response time, and vice versa in the neurons with higher CFs. By manipulating SPL and the stimulation paradigm, this technique could probe the tuning curve characteristics in local neurons. ***Disrupted tonotopic organization in NE rats:*** Intense noise exposure disrupts the tonotopy in IC[7]. Invasive studies have shown that the banded pattern of tonotopy in IC exists before onset of hearing and extensive refinement of frequency encoding occurs over the proceeding 2 to 5 weeks[8]. The loss of low frequency encoding observed in Fig. 5 was likely due to the NE during this critical period of development. The fact that NE could disturb the tonotopy also support the claims that experience dependent activity is essential for tonotopic refinement[9].

Conclusions This study demonstrated the capability of the proposed novel auditory fMRI paradigm to study subtle shift and alteration in the tonotopy. This technique can potentially characterize the auditory neuronal response and facilitate investigation of auditory information processing in cortical and subcortical structures.

References 1. Malmierca MS, et al. In: The Rat Nervous System, 2004. 2. Cheung MM, et al. Neuroimage (In Press). 3. Lee JH, et al. Nature 2010. 4. Ehret G, et al. In: The Inferior Colliculus, 2005. 5. Egorova M, et al. Exp Brain Res 2001. 6. Ehret G, et al. Neuroreport 2003. 7. Pierson M, et al. Brain Res 1994. 8. Bures Z, et al. Eur J Neurosci 2010. 9. Kandler K, et al. Nat Neurosci 2009.