

Auditory Midbrain Encoding of Ultrahigh Frequency Sound

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INTRODUCTION Ultrahigh frequencies (UHF, e.g. higher than 40/60 kHz for rats/mice, respectively) are important for social communication in many species [1]. While lower frequencies are known to be represented as tonotopy in the auditory system [2, 3], the encoding and representation of UHFs are poorly understood. In the auditory pathway, the inferior colliculus (IC) is a midbrain nucleus targeted by both ascending and descending auditory projections, thus a key station for auditory information processing [4]. Previous electrophysiological studies have noticed that some IC neurons could respond to pair of tones if they are tuned to (i) the two frequency bands [5] or (ii) the quadratic distortion of the two tones generated at cochlear basilar membrane [6, 7]. It is yet unclear if/how these mechanisms are related to the encoding of UHFs. This study applied non-invasive BOLD fMRI method to investigate the underlying mechanisms of UHF encoding in the IC.

METHODS *Animal Preparation:* Imaging was performed on adult male Sprague-Dawley rats (~300g, N=6) that were anesthetized with 1% isoflurane. *Acoustic Stimulation:* Monaural stimuli were produced by a high-frequency magnetic speaker (MF1, TDT) and delivered through custom-made tubes into the right ear of animals. Animals were stimulated with a standard block design paradigm (Fig. 1). (i) Rat UHF vocalization (Fig. 2) with spectral content between 50 and 70 kHz, (ii) single UHF tones and (iii) pairs of UHF tones (e.g. 45 kHz and 55 kHz) interleaved with their quadratic distortion (e.g. 10 kHz) were presented in 9 different fMRI sessions. *MRI Procedure:* All fMRI data were acquired on a 7T Bruker scanner using single-shot GE-EPI (FOV=32×32 mm², matrix=64×64, TE/TR=20/1000 ms, 10 slices, thickness/gap=1.0/0.2 mm). *Data Analysis:* The GE-EPI images from each animal were realigned and co-registered using SPM8. Data from each fMRI session were then averaged across animals, smoothed and high-pass filtered. GLM was applied on the resulted image series to map the BOLD responses.

RESULTS The IC was strongly activated by UHF vocalization (Fig. 3) but not by single tones at similar UHFs. Meanwhile, pairs of UHF tones evoked robust activations in the IC (Fig. 4). A cluster of voxels (blue boundary) in the ventromedial side apparently exhibited strong responses whichever pair of tones was presented. This pattern was consistently observed in individual animals, strongly suggesting that neurons in these voxels are sensitive to the combination of different frequencies. Meanwhile, lateral to these voxels, secondary activation (green boundary) was observed to shift from dorsolateral to ventromedial side of the IC when the quadratic distortion of two tones shifted from 10 kHz to 30 kHz. Note that the activation for the corresponding distortion frequencies shifted from dorsolateral to ventromedial IC similarly.

DISCUSSION AND CONCLUSION Our results showed that UHF vocalizations are over-represented in the auditory midbrain compared to single tones at similar UHFs. Similar findings have been reported by previous electrophysiological studies on mice [8], suggesting that the encoding mechanisms of UHF sounds are likely shared across different species [9]. More importantly, our results nicely revealed the co-existence of two mechanisms for UHF encoding in the IC. Neurons in the tonotopic part of IC respond to the cochlear distortion of different UHFs while those in the ventromedial side of IC (where non-tonotopic inputs are integrated) are sensitive to combination of different frequencies. Strong BOLD responses in the combination sensitive voxels may suggest a primary role of neurons in this region in UHF sound processing. Such sophisticated mechanisms may have been developed by animals while they evolved to emit UHF vocalizations to avoid predation such that auditory neurons tuned to low frequencies can encode their social vocalizations [9].

References: [1] Portfors C.V. *JAALAS* 2007;46:28-34. [2] Cheung M.M., *NI* 2012;61:978-86. [3] Yu X., *Nat Neurosci* 2005;8:961-8. [4] Winer J.A. and Schreiner C., *The inferior colliculus: with 168 illustrations*, New York, NY: Springer, 2005. [5] Portfors C.V. and Felix R.A., *2nd Neuroscience* 2005;136:1159-70. [6] Abel C. and Kossli M., *J Neurophysiol* 2009;101:1560-74. [7] Robles L., *Nat* 1991;349:413-4. [8] Portfors C.V., *Neurosci* 2009;162:486-500. [9] Woolley S.M. and Portfors C.V. *Hear Res* 2013;305:45-56.

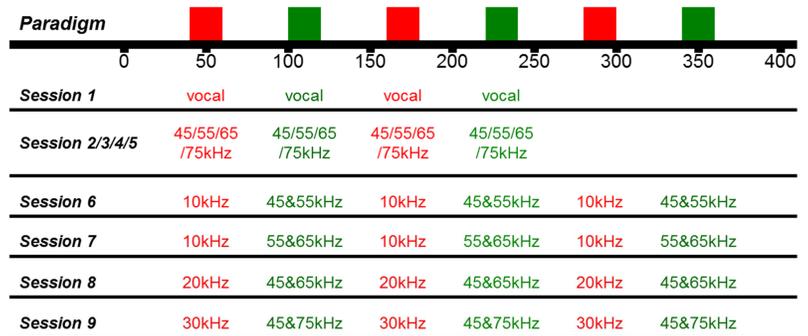


Fig. 1. Block design paradigm (20 s on and 40 s off) for acoustic stimulation used in this study. UHF vocalization, single UHF tones and pairs of UHF tones interleaved with their quadratic distortion were presented in 9 fMRI sessions.

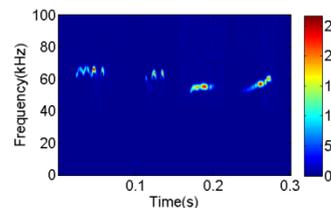


Fig. 2. Spectrogram of the UHF vocalization used in fMRI session 1.

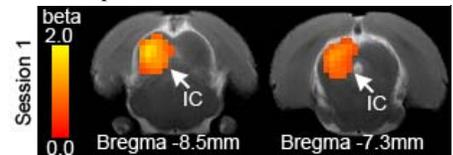


Fig. 3. Activation map for the UHF vocalization in session 1. Note that in sessions 2~5, single tones at similar UHFs did not activate IC.

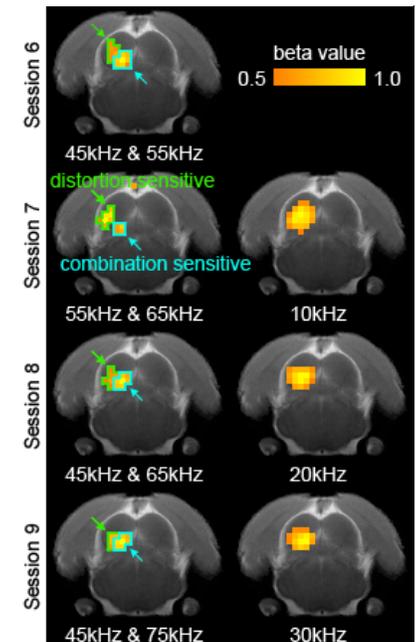


Fig. 4. Normalized activation maps for different pairs of UHF tones and their quadratic distortions. Strong activations were consistently observed in combination sensitive voxels in the ventromedial side of IC in all 4 sessions and all individual animals, while secondary activation in distortion sensitive voxels were observed to shift from dorsolateral to ventromedial IC.