

fMRI Demonstrates Response Selectivity to the Behaviorally Relevant Sounds in the Midbrain

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INTRODUCTION Behaviorally relevant sounds such as species-specific vocalizations are important for conspecific aural communication throughout the animal kingdom [1]. The inferior colliculus (IC) is the major auditory midbrain nucleus and an obligatory relay center for all ascending information in the auditory pathway. Single neuron recordings have shown that the IC responds to specific acoustic features in conspecific vocalizations [2], yet it is unclear to what extent the IC preferentially responds to such vocalizations. This study aims to devise an fMRI method to detect the response selectivity to vocalizations, and characterize the large-scale responses to vocalizations throughout the IC. Previous study has reported that cholinergic neurons are involved in the 22kHz vocalization production [3]. Using fMRI, here we also aim to explore the effect of pharmacologically blocking cholinergic projections to the IC.

METHODS Normal SD rats (300g, n=12) were anesthetized with 3% isoflurane for induction and maintained at 1%. Monaural sound stimuli were delivered to the left ear canal via a 165 cm long custom built tube. Animals were stimulated in a block design paradigm (Fig. 1). The 22kHz vocalization emitted by rat in aversive and dangerous situations was adopted in our study [4]. During the 20s stimulation on period, sound unit was played every 2s. Forward vocalization (true vocalization) block and temporally inverted vocalization (non-vocalization) block were interleaved. Two 1.0mm thick slices (spaced 0.2mm apart) were positioned to cover the IC. BOLD images were acquired with single-shot GE-EPI, with FOV=32×32mm², matrix resolution=64×64, TR/TE=1000/20ms, $\alpha=56^\circ$. fMRI experiments as described above were also performed in normal rats (n=6) before and after injecting acetylcholine receptor antagonist, atropine (50 mg/kg, i.v.) [5]. General linear model analysis was performed. Activated voxels were determined using threshold of $t>3.13$ (equivalent to $p<0.001$) and cluster >2 . ROIs of central nucleus (CNIC), dorsal cortex (DCIC), external cortex (ECIC) of the IC and dorsal nucleus of the lateral lemniscus (DNLL) were defined by consulting the brain atlas. The averaged β values in each ROI were compared. The BOLD signal profiles were averaged across blocks corresponding to same stimulation and voxels within each ROI.

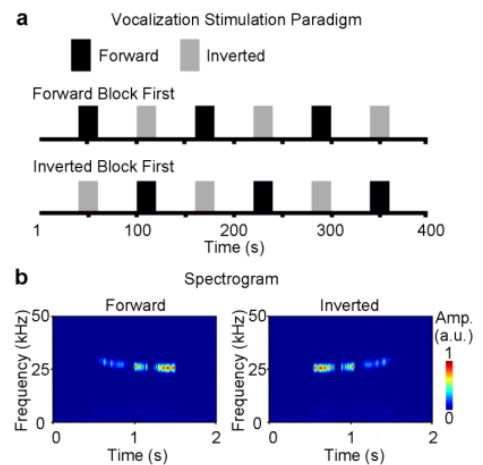


Fig. 1 (a) Stimulation paradigm of the interleaved forward and temporally inverted vocalizations. (b) The spectrogram of the forward and inverted 22kHz vocalizations.

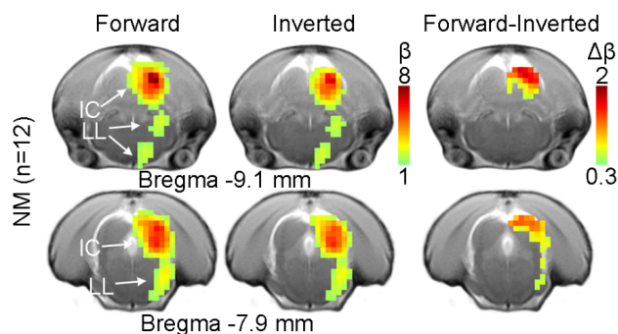


Fig. 2 The activation (β) maps for the forward and inverted vocalizations and the difference ($\Delta\beta$) between them in normal animals.

RESULTS Fig. 2 shows that in normal animals the BOLD response in the IC was stronger to the forward than to the inverted vocalizations, clearly demonstrating response selectivity. Specifically, the averaged β values and BOLD signal profiles showed the stronger response to forward vocalization in all three IC subdivisions (ECIC, DCIC and CNIC), but most significantly in the relatively large ECIC (ECIC: $p<0.001$, CNIC: $p<0.01$, DCIC: $p<0.05$) (Fig. 3). This selectivity was not observed in the LL. The response selectivity was nearly abolished following atropine injection (Fig. 4).

DISCUSSION AND CONCLUSION In this study, the IC was found to exhibit a stronger response to forward species-specific vocalization than to the temporally inverted one despite their identical frequency spectrum. Our previous study has shown that BOLD responses in the IC to a behaviorally irrelevant noise stimulus and its temporal inversion are the same [6]. Together, our present fMRI findings revealed the presence of strong and large-scale response selectivity to vocalizations in the midbrain, and that such selectivity is particularly prominent in the ECIC. Furthermore, no response selectivity was observed in the LL. This finding was consistent with the electrophysiological studies showing that the auditory midbrain is the first place in the ascending auditory pathway to display response selectivity to vocalizations [7]. Moreover, blocking cholinergic projections to the IC by atropine injection was observed to significantly reduce the IC response selectivity to the 22kHz vocalizations. This finding was in line with the previous reports that activating the cholinergic neurons induces an emission of 22kHz vocalizations [3], again highlighting the ability of fMRI in investigating the processing of behaviorally relevant sounds.

REFERENCES [1] Simmons AM. Acoustic Comm. 2003. [2] Suta D. J Neurophysiol. 2003. [3] Brudzynski SM. Neurosci Biobehav Rev. 2001. [4] Wöhr M. Cell Tissue Res. 2013. [5] Sutherland RJ. J Comp Physiol Psychol. 1982. [6] Gao PP. Neuroimage. 2014. [7] Woolley S. Hearing Res. 2013.

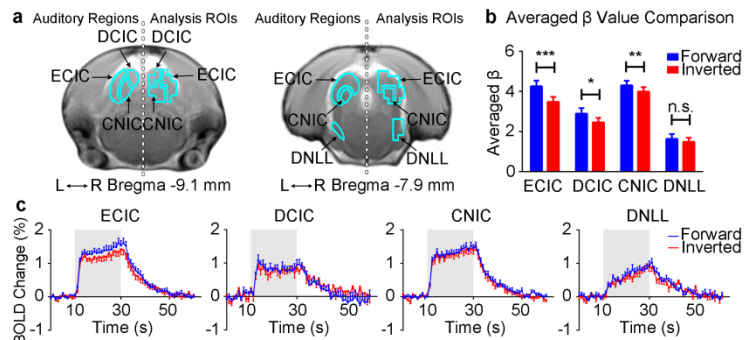


Fig. 3 (a) Analysis ROI definitions (right) based on an atlas (left). (b) Comparison between the averaged β values and to forward and inverted vocalizations in each ROI. * $p<0.05$, ** $p<0.01$, *** $p<0.001$ and n.s. not significant. (c) BOLD signal profiles in each ROI (mean + SEM for forward vocalization and mean - SEM for the inverted one).

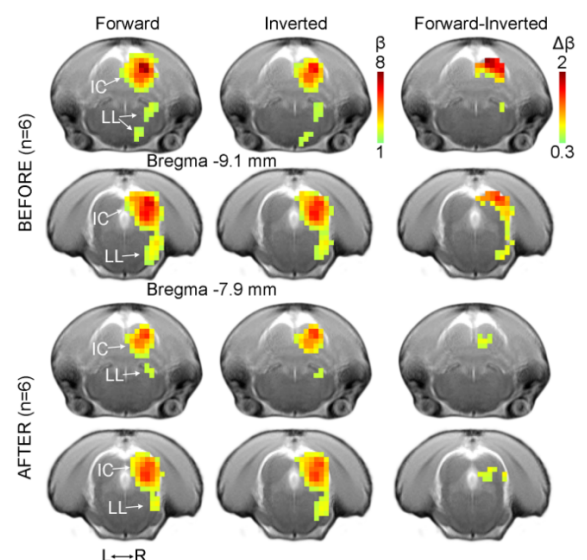


Fig. 4 The activation (β) maps for the forward and inverted vocalizations and the difference ($\Delta\beta$) between them in normal animals before and after atropine injection.