Auditory Cortex Modulates the Midbrain Response Selectivity to Behaviorally Relevant Sounds

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INTRODUCTION Descending projections from cerebral cortex to subcortical nuclei are among the largest pathways in the brain. In the auditory system, the auditory cortex (AC) is the source of one of the largest inputs to the inferior colliculus (IC), the main auditory nucleus at midbrain [1]. The sensitivity of IC neurons to basic sound properties, such as frequency and intensity has been shown to change after manipulating the AC activities [2]. However, whether and how the IC response selectivity to behaviorally relevant sounds such as species-specific vocalizations is modulated by the AC has not been studied. In this study, BOLD fMRI was performed to examine the responses to forward and temporally inverted vocalizations in multiple nuclei simultaneously after bilateral or unilateral AC ablation.

METHODS *Experimental animals:* Sprague-Dawley male rats underwent bilateral or unilateral AC ablation surgery and fMRI experiments were performed after one month. Animals were anesthetized with 3% isoflurane for induction and maintained at 1% during the fMRI sessions. *Auditory stimulation:* Monaural sound stimulation was delivered to the ear canal via a 165cm long custom built tube. Rats were stimulated in a block design. 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 (Fig. 1). The 22kHz vocalization emitted by rat in aversive and dangerous situations was adopted [3, 4]. *MRI protocol:* Two 1.0mm thick slices (spaced 0.2mm apart) were positioned to cover the IC. BOLD fMRI were acquired with single-shot GE-EPI, with FOV=32×32mm^2, matrix resolution=64×64, TR/TE=1000/20ms, α=56°. *Data analysis:* General linear model analysis was performed. Activated voxels were determined by 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 and the averaged β values in each ROI were compared. The BOLD signal profiles were averaged across blocks (separately for forward and inverted vocalizations) and voxels within each ROI.

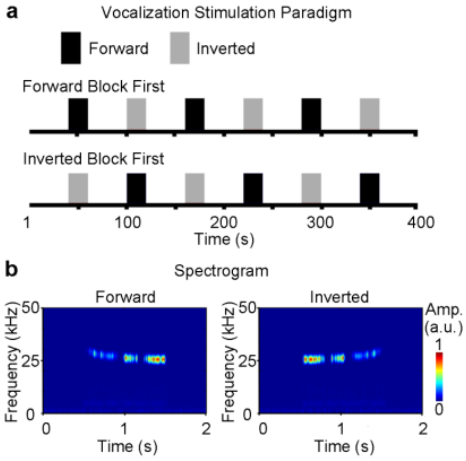

Fig. 1 (a) Stimulation paradigm of the interleaved forward and temporally inverted vocalizations. (b) The spectrogram of the forward and inverted 22kHz vocalizations.

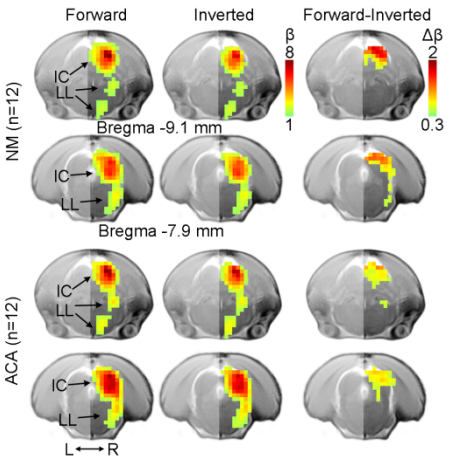

Fig. 2 The activation (β) maps for the forward and inverted vocalizations and the difference (Δβ) between them in normal (NM) and bilateral AC ablation (ACA) animals.

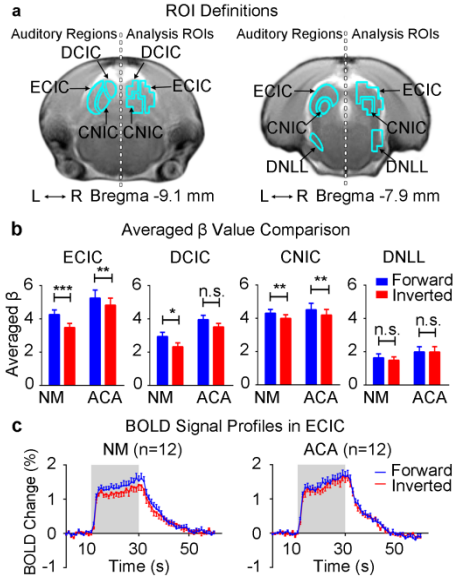

Fig. 3 (a) Analysis ROI definitions (right) based on an atlas (left). (b) Comparison between the averaged β values (mean ± SEM) and to forward and inverted vocalizations in each ROI. *p<0.05, **p<0.01, ***p<0.001 and n.s. not significant (c) BOLD signal profiles in ECIC.

RESULTS Fig. 2 shows that the BOLD response in the IC was stronger to the forward than to the inverted vocalization in normal animals, demonstrating response selectivity in the IC. Specifically, the averaged β values for the forward vocalization were higher than the inverted one in all three IC subdivisions, but most significantly in the relatively large ECIC (Fig. 3b). In the DNLL, the averaged β values for the two vocalizations were nearly identical. After bilateral AC ablation, the BOLD response difference between the two vocalizations in the IC was diminished (Figs. 2 and 3b) and the BOLD signal profiles for the two vocalizations in ECIC became similar (Fig. 3c), indicating that specific response selectivity requires descending feedback that originates in the AC. In the unilateral (right side) AC ablation animals, the BOLD response difference between the two vocalizations in the ablation (right) side was negligible while the contralateral (left) ECIC still showed a stronger response to the forward vocalization (Fig. 4).

DISCUSSION AND CONCLUSION Our large-scale fMRI findings showed that the IC in normal animals exhibits stronger BOLD response to forward species-specific vocalizations than to the temporally inverted one, clearly indicating that species-specific vocalizations are efficiently encoded at the early midbrain level. More importantly, our findings from the bilateral and unilateral AC ablation animals demonstrated that the AC descending projections mediate the IC response selectivity to behaviorally relevant sounds. Such top-down cortical feedback modulates the ipsilateral IC more, likely as a result of the extensive cortical to colliculus projections within ipsilateral side. Our findings also demonstrated that AC input exerts its greatest effect on vocalization response selectivity in the ECIC, consistent with the prominent corticocollicular projection to ECIC [5, 6]. Together, responses selectivity to behaviorally relevant sound is present in midbrain but it requires AC inputs. This knowledge provides insights into the interactions between ascending and descending auditory pathways, and will guide future study of coordinated auditory network and processing across multiple regions.

REFERENCES [1] Winer JA. The IC. 2005. [2] Suga N. J Comp Physiol A. 2008. [3] Wöhr M. Cell Tissue Res. 2013. [4] Litvin Y. Behav Brain Res. 2007. [5] Bajo VM. J Comp Neurol. 2005. [6] Schofield BR. Neuroscience. 2009.

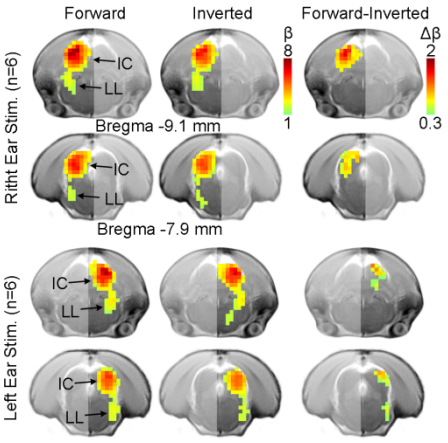

Fig. 4 The activation (β) maps for the forward and inverted vocalizations and the difference (Δβ) between them in unilateral AC ablation animals.