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Auditory midbrain processing is differentially modulated by auditory and visual cortices: An auditory fMRI study

Patrick P. Gao [a,c,1], Jevin W. Zhang [a,c,1], Shu-Juan Fan [a,c], Dan H. Sanes [b], Ed X. Wu [a,c,d,e,*]

[a] *Laboratory of Biomedical Imaging and Signal Processing, The University of Hong Kong, Pokfulam, Hong Kong SAR, China*
[b] *Center for Neural Science, New York University, New York, NY 10003, United States*
[c] *Department of Electrical and Electronic Engineering, The University of Hong Kong, Pokfulam, Hong Kong SAR, China*
[d] *Department of Anatomy, The University of Hong Kong, Pokfulam, Hong Kong SAR, China*
[e] *Department of Medicine, The University of Hong Kong, Pokfulam, Hong Kong SAR, China*

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ABSTRACT

The cortex contains extensive descending projections, yet the impact of cortical input on brainstem processing remains poorly understood. In the central auditory system, the auditory cortex contains direct and indirect pathways (via brainstem cholinergic cells) to nuclei of the auditory midbrain, called the inferior colliculus (IC). While these projections modulate auditory processing throughout the IC, single neuron recordings have samples from only a small fraction of cells during stimulation of the corticofugal pathway. Furthermore, assessments of cortical feedback have not been extended to sensory modalities other than audition. To address these issues, we devised blood-oxygen-level-dependent (BOLD) functional magnetic resonance imaging (fMRI) paradigms to measure the sound-evoked responses throughout the rat IC and investigated the effects of bilateral ablation of either auditory or visual cortices. Auditory cortex ablation increased the gain of IC responses to noise stimuli (primarily in the central nucleus of the IC) and decreased response selectivity to forward species-specific vocalizations (versus temporally reversed ones, most prominently in the external cortex of the IC). In contrast, visual cortex ablation decreased the gain and induced a much smaller effect on response selectivity. The results suggest that auditory cortical projections normally exert a large-scale and net suppressive influence on specific IC subnuclei, while visual cortical projections provide a facilitatory influence. Meanwhile, auditory cortical projections enhance the midbrain response selectivity to species-specific vocalizations. We also probed the role of the indirect cholinergic projections in the auditory system in the descending modulation process by pharmacologically blocking muscarinic cholinergic receptors. This manipulation did not affect the gain of IC responses but significantly reduced the response selectivity to vocalizations. The results imply that auditory cortical gain modulation is mediated primarily through direct projections and they point to future investigations of the differential roles of the direct and indirect projections in corticofugal modulation. In summary, our imaging findings demonstrate the large-scale descending influences, from both the auditory and visual cortices, on sound processing in different IC subdivisions. They can guide future studies on the coordinated activity across multiple regions of the auditory network, and its dysfunctions.

Introduction

Sensory cortices contain extensive descending projections to subcortical nuclei (Winer, 2006), as well as widespread connectivity between different sensory modalities (Falchier et al., 2002). It is hence plausible that subcortical nuclei integrate cortical feedback from multiple sensory modalities, for the purpose of enhancing detection, identification, or localization of external objects. Specifically, in the auditory system, besides the ascending projections that transmit information from the ear to higher levels for perception (Malmierca, 2003), there are extensive descending projections from the auditory cortex (AC) to nuclei of the auditory midbrain, called the inferior colliculus (IC) (Bajo and Moore, 2005; Bajo et al., 2007; Coomes et al., 2005; Schofield and Motts, 2009; Schofield et al., 2011), which is a compulsory relay for all ascending auditory information from multiple brainstem nuclei (Malmierca, 2003) and the origin of several important auditory processing properties (Nataraj and Wenstrup, 2005; Woolley et al., 2005). At the same time, cortices of other sensory modalities, such as the visual cortex (VC), send direct projections to both the AC (Budinger et al., 2006; Campi et al., 2010) and the IC (Cooper and Young, 1976; Dong, 2008). However, until recently, the relative influence of AC and VC projections on auditory processing within the IC has not been investigated.

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[*] Corresponding author at: Laboratory of Biomedical Imaging and Signal Processing, Departments of Electrical and Electronic Engineering, Anatomy and Medicine, The University of Hong Kong, Pokfulam, Hong Kong SAR, China. Fax: +852 2859 8738.
E-mail address: ewu@eee.hku.hk (E.X. Wu).

[1] These authors contributed equally to this work.

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In the auditory system, there are direct cortex-to-collicular or corticocollicular projections from several AC fields to all subdivisions of the IC (Bajo and Moore, 2005; Bajo et al., 2007; Schofield, 2009). There is also an indirect pathway from AC to cholinergic pontomesencephalic tegmentum neurons, which, in turn, project to the IC (Schofield et al., 2011). The direct and indirect projections are likely to have a profound impact on the sound-evoked response properties throughout the IC. However, previous electrophysiological studies investigating the functional implications of these projections could only sample a small fraction of IC neurons (Bajo and King, 2012). Although they indicate that the sensitivity of IC neurons to basic acoustic cues, e.g. frequency (Yan et al., 2005; Yan and Suga, 1998; Zhang et al., 1997), intensity (Yan and Ehret, 2002), duration (Ma and Suga, 2001), and location (Nakamoto et al., 2008), can be altered by electrically stimulating or cryogenically inactivating some AC neurons, the exact large-scale functional influences on the coordinated activity in different IC subnuclei is not easily extrapolated from single neuron recordings. Meanwhile, it is unclear how the corticocollicular projections modulate the IC responses to complex sounds, such as species-specific vocalizations, which can play important roles in communicating information or facilitating behavioral responses for many species (Portfors, 2007; Woolley and Portfors, 2013). In addition, there has been no attempt to differentiate the relative contribution of direct and indirect projections in modulating IC responses to different types of sounds. Lastly but more importantly, while evidence of the widespread connectivity from the VC to multiple levels of the auditory pathway has accumulated (Budinger et al., 2006; Campi et al., 2010; Cooper and Young, 1976; Dong, 2008) and interactions between the two sensory modalities at cortical level have been examined in many studies (Bizley and King, 2009; Finney et al., 2001; Lomber et al., 2010; Petrus et al., 2014; Wallace et al., 2004), how the visual feedback crossmodally influences IC auditory processing has not been investigated.

In this study, we employed blood-oxygen-level-dependent (BOLD) functional magnetic resonance imaging (fMRI) (Ogawa et al., 1990) to characterize the functional roles of cortical feedback throughout the auditory midbrain, particularly the differential contribution of auditory and visual modalities. BOLD fMRI is a non-invasive technique that can measure the hemodynamic responses (Kim and Ogawa, 2012) as neural correlates (Logothetis et al., 2001; Mukamel et al., 2005) throughout a processing area with relatively high spatial and temporal resolutions. BOLD fMRI has been successfully used to noninvasively measure stimulus-evoked activity in the auditory system of humans (Barton et al., 2012; De Martino et al., 2013; Ress and Chandrasekaran, 2013; Sigalovsky and Melcher, 2006) as well as animals, such as primates (Baumann et al., 2011; Kayser et al., 2007; Tanji et al., 2010) and songbirds (Boumans et al., 2008; Poirier et al., 2009; Van Meir et al., 2005; Voss et al., 2007). More recently, fMRI has been demonstrated as a powerful tool for investigating the auditory functions in small rodents (Cheung et al., 2012a; Lau et al., 2015b; Yu et al., 2009), particularly the processing of basic acoustic components in the midbrain (Cheung et al., 2012a,b; Gao et al., 2014, 2015; Lau et al., 2013, 2015a; Zhang et al., 2013a,b). To examine the influence of cortically originating descending projections on sound-evoked IC responses (both noise and species-specific vocalizations), BOLD imaging was performed in bilateral AC-ablated (ACA) and VC-ablated (VCA) rats with comparison to age-matched normal (NM) control animals. We also probed the potential role of the indirect cholinergic pathway in this descending modulation process by pharmacologically blocking it with systemic injection of atropine, an antagonist of muscarinic acetylcholine receptors (Habbicht and Vater, 1996). Loss of the AC led to a marked increase in sound-evoked responses and a diminished response selectivity to forward species-specific vocalizations (versus temporally reversed ones), indicating that the input normally exerts a suppressive influence on gain but a facilitative one on specific responses to natural vocalizations. In contrast, loss of the VC led to decreased sound-evoked responses and slightly decreased response selectivity, demonstrating that this modality normally increases gain and facilitates the specific responses. These results revealed a large-scale influence of descending projections on IC processing, both within and across sensory modalities.

Materials and methods

Cortical ablation surgery

All animal experiments were approved by the Committee on the Use of Live Animal in Teaching and Research of the University of Hong Kong. Adult male rats (Sprague–Dawley strain, 250 g) underwent surgery. After induction of anesthesia using 2% isoflurane, skull windows were opened over the bilateral auditory or visual cortex. The tissue in the primary and secondary auditory cortex or the anterior part of the entire primary and partial secondary visual cortex was ablated without injuring the white matter underneath (Fig. 1). The ablated area was then filled with biodegradable hemostatic sponge (Surgicel®) and skin incision was sutured. The animals were allowed to recover at 37 °C before returned to the feeding cage. They underwent fMRI experiments 2 weeks later. Note that the ACA and VCA surgeries both involved more than 30 animals. The location and size of the ablated areas were verified in each animal using anatomical MRI and 12 animals whose ablated areas were bilaterally symmetric and restricted within the intended AC/VC region were employed in the following fMRI experiments. The resulted sample size was NM: $n = 12$, ACA: $n = 12$, VCA: $n = 12$ (Table 1).

Preparation for fMRI

Animals were prepared for fMRI experiments as described in our previous studies (Chan et al., 2010; Cheung et al., 2012a,b; Gao et al., 2014, 2015; Lau et al., 2013, 2015a,b; Zhang et al., 2013a,b; Zhou et al., 2014). Briefly, rats were initially anesthetized with 3% isoflurane and then mechanically ventilated via oral intubation. They were placed on a holder in the prone position with a tooth bar to restrict head motion. Throughout the course of MR scanning, light anesthesia was maintained with 1% isoflurane. Animal heart rate, respiration rate, oxygen saturation, and rectal temperature were continuously monitored by sensors (SA instruments) and kept in normal ranges (heart rate: 380–420; respiration rate: 56–60; oxygen saturation: >95%; rectal temperature: 36.5–37.5 °C).

fMRI data acquisition

All MR experiments were performed on a 7 T MRI scanner (PharmaScan 70/16, Bruker Biospin GmbH) using a transmit-only birdcage coil in combination with an actively decoupled receive-only surface coil. Two fMRI experiments were performed to measure the gain of response and the selectivity to species-specific vocalizations, respectively, in IC and a set of projection nuclei to the IC, the nuclei of the lateral lemniscus (LL, Fig. 2a) (Malmierca, 2003). Scout images were first acquired to determine the coronal and sagittal planes of the brain. Then in the response gain experiment, a single coronal slice with 1.0 mm thickness was positioned to cover the center of the IC (at Bregma −8.5 mm, Fig. 2b), while in the vocalization experiment, 8 slices with 1.0/0.2 mm thickness/gap were positioned, with the 3rd and 4th covering the full IC (at Bregma −9.1 mm and −7.9 mm, Fig. 2c). T2-weighted images were acquired as anatomical reference using a Rapid Acquisition with Refocused Echoes (RARE) sequence (FOV = 32×32 mm^2, data matrix = 256×256, RARE factor = 8, TE/TR = 36/4200 ms). In the response gain experiment, the fMRI measurements were obtained using a single-slice balanced Steady-State Free Precession (bSSFP) sequence (FOV = 32×32 mm^2, data matrix = 64×64, flip angle = 19°, TE/TR = 1.9/3.8 ms, average = 4, temporal resolution = 1000 ms, no. of time points = 880). In the vocalization experiment, they were obtained using a multi-slice single-shot Gradient-Echo Echo-Planar-Imaging (GE-EPI) sequence (FOV = 32×32 mm^2, data matrix = 64×64, flip