

## NEUROSYSTEMS

# Two crossed axonal projections contribute to binaural unmasking of frequency-following responses in rat inferior colliculus

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## Abstract

Frequency-following responses (FFRs) are sustained potentials based on phase-locked neural activities elicited by low- to medium-frequency periodical sound waveforms. Human brainstem FFRs, which are able to encode some critical acoustic features of speech, can be unmasked by binaural processing. However, the underlying unmasking mechanisms have not previously been reported. In rats, most neurons in the inferior colliculus (IC) exhibit binaural responses which are affected by axonal projections from both the contralateral dorsal nucleus of the lateral lemniscus (DNLL) and the contralateral IC. The present study investigated whether the contralateral DNLL and the contralateral IC modulate binaural unmasking of FFRs recorded in the rat IC. The results show that IC FFRs to the rat pain call (chatter) were enhanced by local injection of the excitatory glutamate receptor antagonist kynurenic acid (KYNA) into the contralateral DNLL but were reduced by KYNA injection into the contralateral IC. Introducing a disparity between the interaural time difference (ITD) of the FFR-eliciting chatter and the ITD of the masking noise enhanced IC FFRs. Moreover, the ITD-disparity-induced FFR enhancement was weakened by injection of KYNA into either the contralateral DNLL or the contralateral IC when the ipsilateral chatter preceded the contralateral chatter. Thus, binaural hearing can improve IC FFRs against noise masking. More importantly, both inhibitory projections from the contralateral DNLL and excitatory projections from the contralateral IC modulate IC FFRs and play a role in forming binaural unmasking of IC FFRs.

## Introduction

Frequency-following responses (FFRs) are sustained potentials based on precisely phase-locked responses to low- to medium-frequency periodical sound waveforms (Marsh *et al.*, 1970; Smith *et al.*, 1975). Human scalp-recorded FFRs reflect activities of brainstem neurons and are capable of encoding both spectra (Krishnan, 2002; Russo *et al.*, 2004) and pitch contours (Hall, 1979; Krishnan *et al.*, 2004) of speech. Interestingly, human FFRs can be modulated by both language experience (Galbraith *et al.*, 2004; Krishnan *et al.*, 2005; Xu *et al.*, 2006; Swaminathan *et al.*, 2008) and selective attention (Galbraith *et al.*, 2003).

Due to the presence of extraneous noises under everyday environments, several salient features of acoustic signals, particularly for life-threatening acoustic signals, such as predator calls (Hendrie *et al.*, 1998) and species-specific pain calls (Dennis & Melzack, 1983), must be precisely retained in neural coding by certain unmasking mechanisms. It is well known that signal detection against interfering background noise is improved by binaural hearing (e.g. Hirsh, 1948). Indeed, both binaural unmasking and spatial unmasking

have been demonstrated in both humans (Saber *et al.*, 1991; Gilkey & Good, 1995; Shinn-Cunningham *et al.*, 2001) and animals (Hine *et al.*, 1994; Dent *et al.*, 1997). In particular, human brainstem FFRs can also be unmasked by binaural processing (Wilson & Krishnan, 2005).

Although the corresponding physiological correlates of binaural/spatial unmasking have been found in the auditory midbrain, inferior colliculus (IC), of guinea-pigs (e.g. Caird *et al.*, 1991; McAlpine *et al.*, 1996; Jiang *et al.*, 1997; Palmer *et al.*, 2000), chinchillas (e.g. Mandava *et al.*, 1996), cats (e.g. Lane & Delgutte, 2005) and frogs (e.g. Ratnam & Feng, 1998; Lin & Feng, 2001, 2003), the neural pathways that are critically responsible for the formation of binaural unmasking of neural activity in the IC remain to be determined.

Most neurons in the IC exhibit binaural responses, which can be shaped by GABAergic axonal projections from the contralateral dorsal nucleus of the lateral lemniscus (DNLL) (Burger & Pollak, 2001; Faingold *et al.*, 1993; Kelly & Li, 1997; Kidd & Kelly, 1996; Li & Kelly, 1992; Van Adel *et al.*, 1999; Zhang *et al.*, 1998; for a review see Li & Yue, 2002). The rat IC, which has a cytoarchitecture similar to that of the cat IC (Loftus *et al.*, 2008), also receives crossed axonal projections from its counterpart, the contralateral IC (Irvine, 1986; González-Hernández *et al.*, 1996; Saint Marie, 1996;

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Zhang *et al.*, 1998; Hernández *et al.*, 2006) with both divergent and point-to-point wiring patterns (Malmierca *et al.*, 2009). The intercollicular commissure plays a role in modulating both binaural responses and frequency-response areas in the IC (Malmierca *et al.*, 2003, 2005). However, it is unknown whether inputs from the contralateral DNLL and/or those from the contralateral IC affect binaural unmasking in the IC.

To provide an initial understanding of why FFRs recorded in humans, which are based on synchronized activities of a sufficiently large population of neurons in the auditory midbrain, can be unmasked by binaural hearing, we used here a segment of the rat tail-pain chatter that consists of harmonics (Jourdan *et al.*, 1995) to investigate: (i) whether the chatter-evoked FFRs recorded in the rat IC are affected by binaural processing and even unmasked by introducing a disparity between the interaural time difference (ITD) of the chatter and that of the masking noise, and (ii) whether chemical blockade of either the contralateral DNLL or the contralateral IC by kynurenic acid (KYNA), a broad-spectrum glutamate receptor antagonist, affects FFRs and/or binaural unmasking of FFRs in the IC.

## Materials and methods

### Animal preparation

Forty-eight young-adult male Sprague–Dawley rats (age 10–12 weeks, weight 300–350 g) were used and treated in accordance with the Guidelines of the Beijing Laboratory Animal Center and the Policies on the Use of Animals and Humans in Neuroscience Research approved by the Society for Neuroscience (2006). Procedures of this study were approved by the Committee for Protecting Human and Animal Subjects, the Department of Psychology at Peking University. Rats were divided into four structure/injection-agent groups: (i) DNLL/KYNA ( $n = 14$ ), (ii) DNLL/Locke's solution ( $n = 10$ ), (iii) IC/KYNA ( $n = 14$ ), and (iv) IC/Locke's solution ( $n = 10$ ).

Rats were anaesthetized with 10% chloral hydrate (400 mg/kg, i.p.) and the state of anaesthesia was maintained throughout the experiment by supplemental injection of the same anaesthetic. Stainless steel recording electrodes (10–20 k $\Omega$ ) insulated by a silicon tube (0.3 mm in diameter) except at the 0.25-mm-diameter tip (Zheng *et al.*, 2008) were aimed at the IC on either side in all the 48 rats and injection guide cannulae (C317G guide cannula; Plastics One Inc., Roanoke, VA, USA) were aimed at either the contralateral DNLL or the contralateral IC (relative to the recorded IC). Based on the stereotaxic coordinates of Paxinos & Watson (1997) and referenced to Bregma, IC coordinates were: AP, -8.8 mm; ML,  $\pm 1.5$  mm; DV, -4.5 to -5.0 mm, and DNLL coordinates were: AP, -8.3 to -8.7 mm; ML,  $\pm 2.9$  mm; DV, -6.5 to -6.8 mm.

### Acoustic stimulation and recording

A train of tail-pain chatter (simply termed 'chatter') was recorded from one rat in response to tail-clamping pain in a soundproof chamber and digitized at 44.1-kHz sampling rate and 16-bit resolution. A 150-ms stimulus section without any amplitude-modulation or frequency-modulation was isolated from one selected chatter burst and tapered with 5-ms linear onset/offset ramps. The spectrum of the chatter shows a fundamental frequency (F0) at 2.1 kHz and two harmonics at 4.2 (h2) and 6.3 kHz (h3), respectively. The relative size of each of the three frequency components has been reported in our previous study (Du *et al.*, 2009), showing that F0 and h2 of the chatter are

approximately equal in amplitude and h3 is about 16 dB lower in amplitude.

The masker was a burst of broadband white noise (0–10 kHz) with a duration of 750 ms (including 5-ms linear onset/offset ramps). It was started 500 ms before the onset of the chatter.

All sound waves were processed by a TDT System II (Tucker-Davis Technologies, Alachua, FL, USA), and presented through two ED1 earphones. A 12-cm TDT sound-delivery rubber tube was connected to each ED1 earphone and inserted into rat's ear canal. Both chatter in quiet and chatter in noise at the tube end were calibrated using a Larson Davis Audiometer Calibration and Electroacoustic Testing System (AUDit™ and System 824; Larson Davis, Provo, UT, USA). The sound-pressure level (SPL) of chatter in quiet was 59 dB when each earphone played alone. Under conditions with masking noise presentations, the chatter intensity was held constant at this level while the whole-spectrum intensity of the white noise was adjusted to produce two signal-to-noise ratios (SNRs): -4 and 4 dB.

Neural potentials were recorded in a sound-attenuating chamber, amplified 1000-fold, bandpass filtered at 200–10 000 Hz, and averaged 50 times per condition. Online recordings were processed with TDT Biosig software, finally digitized at 16 kHz and stored on disk for offline analysis.

### Drug injection

Drug administration was made through the guide cannula which was connected to a 5.0- $\mu$ L micro-syringe via polyethylene tubing (inner diameter: 0.38 mm, outer diameter: 1.09 mm; Clay Adams, division of Becton and Dickinson Company, Parsippany, NJ, USA). Either the broad-spectrum antagonist KYNA (2 mM in Locke's solution; Sigma-Aldrich, St Louis, MO, USA) or Locke's solution was injected slowly into the contralateral DNLL (1.0  $\mu$ L) or the contralateral IC (2.0  $\mu$ L) over a period of about 1 min. Recording started 10 min after injection.

### Experimental procedures

Before injection, rats were first adapted to the chatter presented to both ears for 10 min, then the following stimuli were presented: (i) monaural chatter (ipsilateral, I; contralateral, C) in quiet, (ii) binaural chatter in quiet with the following ITDs: -0.1 ms (ipsilateral chatter leading, I/C), 0 ms (binaurally simultaneous, ST), and +0.1 ms (contralateral chatter leading, C/I) and (iii) binaural chatter in interaurally correlated noise.

Under conditions with co-presentation of masking noise, when the ITD for chatter was -0.1 or +0.1 ms, and the ITD for noise was -0.1, 0 or +0.1 ms, there were three absolute ITD disparities between signal and noise ( $|ITD_{S+N}|$ ): 0 (no ITD disparity), 0.1 (smaller ITD disparity) and 0.2 ms (larger ITD disparity). Note that the ITD value of 0.1 ms was shorter than the maximum ITD due to the head size of rats (0.13–0.16 ms, Koka *et al.*, 2008). Thus we assume that for awake rats when  $|ITD_{S+N}|$  is zero, no position separation is perceived between signal image and noise image; when  $|ITD_{S+N}|$  is 0.1 ms, signal is perceived at one ear and noise is perceived at the centre of the head (smaller perceived signal/noise separation); when the  $|ITD_{S+N}|$  is 0.2 ms, signal is perceived at one ear and noise is perceived at the other ear (larger perceived signal/noise separation).

The onset-to-onset inter-stimulus interval (ISI) was 800 ms for signals presented in quiet and 1000 ms for signals presented in noise. FFRs in quiet were recorded for a duration of 200 ms beginning at signal onset, while FFRs in noise were recorded for a duration of 800 ms

beginning at noise onset. Recordings were carried out before and after microinjection of KYNA or Locke's solution for each of the groups.

#### *Data analyses*

For acoustically evoked potentials recorded in quiet, a 1000-Hz low-

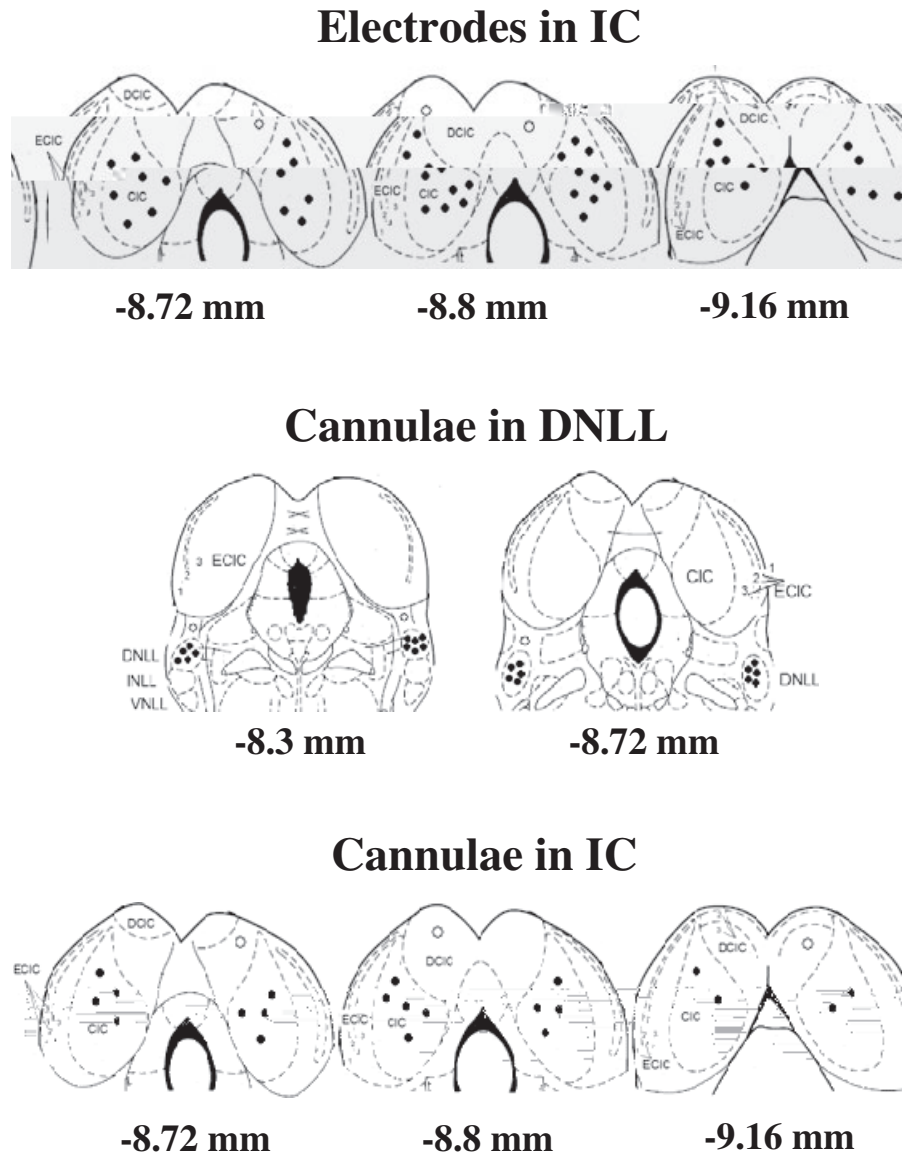


FIG. 1. Locations of recording electrodes and injection cannulae in all 48 rats. Electrodes were located precisely within the inferior colliculus (IC) area in 45 of 48 rats (filled circles), and injection cannulae were located precisely within the dorsal nucleus of the lateral lemniscus (DNLL) area in 21 of 24 rats, and within the IC area in 21 of 24 rats (filled circles). Incorrect locations of electrodes and cannulae are shown by open circles.

For the IC/KYNA group (Fig. 4C), a within-subjects, repeated-measures ANOVA reveals that F0 amplitude significantly decreased after KYNA injection ( $F_{1,11} = 18.303$ ,  $P < 0.01$ ), and the main effect of stimulation condition was significant ( $F_{4,8} = 74.447$ ,  $P < 0.001$ ), but the interaction between testing time and stimulation condition was not significant ( $F_{4,8} = 0.596$ ,  $P > 0.05$ ). This result suggests that blockade of glutamate transmissions in the contralateral IC by KYNA generally weakened IC FFRs across stimulation conditions.

By contrast, for the other two groups with Locke's solution injection (Fig. 4B and D), repeated-measures ANOVAs indicate that neither the main effect of testing time nor the interaction between testing time and stimulation condition was significant (all  $P > 0.05$ ), but the main effect of stimulation condition was significant (all  $P < 0.01$ ). Thus, injection of Locke's solution into either the contralateral DNLL or the contralateral IC did not affect FFRs recorded in the IC.

#### *Binaural unmasking of FFRs*

Figure 5 shows relative rSNRs of IC FFRs when the chatter was co-presented with white noise before injection manipulations with the ipsilateral chatter either leading or lagging behind the contralateral one by 0.1 ms. Clearly, when the ipsilateral chatter led the contralateral one, compared with the condition without ITD disparity ( $|ITD_{S+N}| = 0$  ms), introducing an ITD disparity (0.1 or 0.2 ms) markedly enhanced the rSNR. However, when the leading ear for chatter changed to the contralateral ear, the ITD-disparity-induced enhancement of rSNR decreased remarkably.

The binaural unmasking effect of ITD disparity between the chatter and noise masker was also quantified over the mean UIs under different ITD disparity conditions. UIs are displayed separately when the ipsilateral chatter either led (Fig. 6A) or lagged behind (Fig. 6B) the contralateral chatter. We found that the FFR SNRs significantly increased with increasing ITD disparity between

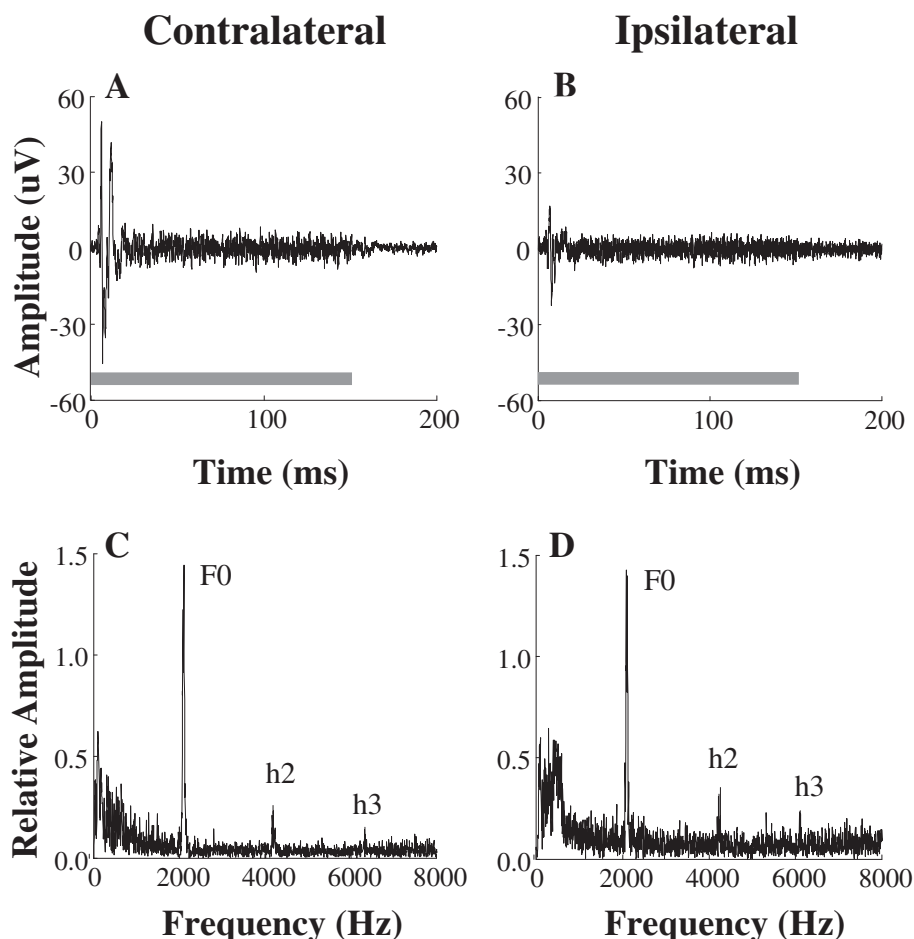


FIG. 2. Typical response waveforms to chatter (A and B) and fast Fourier spectral analyses of IC FFRs (C and D). Note that the recording site contralateral to the stimulated ear (A and C) exhibits a much larger onset-evoked potential than the site ipsilateral to the stimulated ear (B and D), but contralateral FFRs and ipsilateral FFRs exhibit similar F0 and h2 amplitudes. The horizontal bar in A and B represents the duration of the chatter stimulus.

the signal and noise ( $F_{4,38} = 125.152$ ,  $P < 0.001$ ), which was shown by the more positive UI under the larger ITD disparity condition (the UI value is zero when ITD disparity is zero), regardless of whether the chatter was ipsilateral-ear leading or contralateral-ear leading. Pairwise comparisons reveal that (i) even 0.1-ms ITD disparity led to significant enhancement of rSNR regardless of the chatter-ITD (both  $P < 0.01$ ); (ii) 0.2-ms ITD disparity induced remarkably larger rSNR enhancement than 0.1-ms ITD disparity regardless of the chatter-ITD (both  $P < 0.001$ ) and (iii) the same ITD disparity induced significantly larger improvement of rSNR when the chatter was ipsilateral-ear leading than contralateral-ear leading (both  $P < 0.01$ ). These results indicate that FFRs in the rat IC can be improved by introducing an ITD disparity between the chatter and the noise masker, and the binaural unmasking of FFRs exhibits a marked advantage when the signal at the ipsilateral ear leads that at the contralateral ear.

#### Effects of blocking DNLL or IC on binaural unmasking of FFRs

The contribution of the contralateral DNLL or that of the contralateral IC to binaural unmasking of FFRs was examined by injecting either KYNA (Figs 7A and C, and 8A and C) or Locke's solution (Figs 7B and D, and 8B and D) into either of the two structures. The results are shown for conditions when chatter at the ipsilateral ear led the

contralateral ear (Fig. 7) or chatter at the contralateral ear led the ipsilateral ear (Fig. 8).

When the ipsilateral chatter led, for the DNLL/KYNA group (Fig. 7A), a 2 (testing time: pre-injection, post-injection) by 2 ( $|\text{ITD}_{\text{S+N}}|$ ) within-subjects, repeated-measures ANOVA shows that the main effect of testing time was significant ( $F_{1,12} = 13.286$ ,  $P < 0.05$ ), the main effect of  $|\text{ITD}_{\text{S+N}}|$  condition was significant ( $F_{1,12} = 29.797$ ,  $P < 0.001$ ), and the interaction between time and  $|\text{ITD}_{\text{S+N}}|$  was significant ( $F_{1,12} = 5.598$ ,  $P < 0.05$ ). Additional paired-sample *t*-tests show that blockade of glutamate receptors in the contralateral DNLL significantly reduced the binaural unmasking effect of FFRs under both 0.1-ms ( $P < 0.05$ ) and 0.2-ms ( $P < 0.01$ )  $|\text{ITD}_{\text{S+N}}|$  conditions.

Repeated-measures ANOVA for the IC/KYNA group (Fig. 7C) shows that the main effect of testing time was significant ( $F_{1,11} = 28.650$ ,  $P < 0.001$ ), the main effect of  $|\text{ITD}_{\text{S+N}}|$  condition was significant ( $F_{1,11} = 129.840$ ,  $P < 0.001$ ), but the interaction between testing time and  $|\text{ITD}_{\text{S+N}}|$  was not significant ( $F_{1,11} = 1.639$ ,  $P > 0.05$ ). Additional paired-sample *t*-tests confirm that blocking the glutamate receptors in the contralateral IC significantly reduced the binaural unmasking effect of IC FFRs under both  $|\text{ITD}_{\text{S+N}}|$  conditions (both  $P < 0.01$ ).

By contrast, for the two Locke's solution groups under ipsilateral chatter-led conditions, (Fig. 7B and D), separate repeated-measures ANOVA shows that the main effect of  $|\text{ITD}_{\text{S+N}}|$  condition was

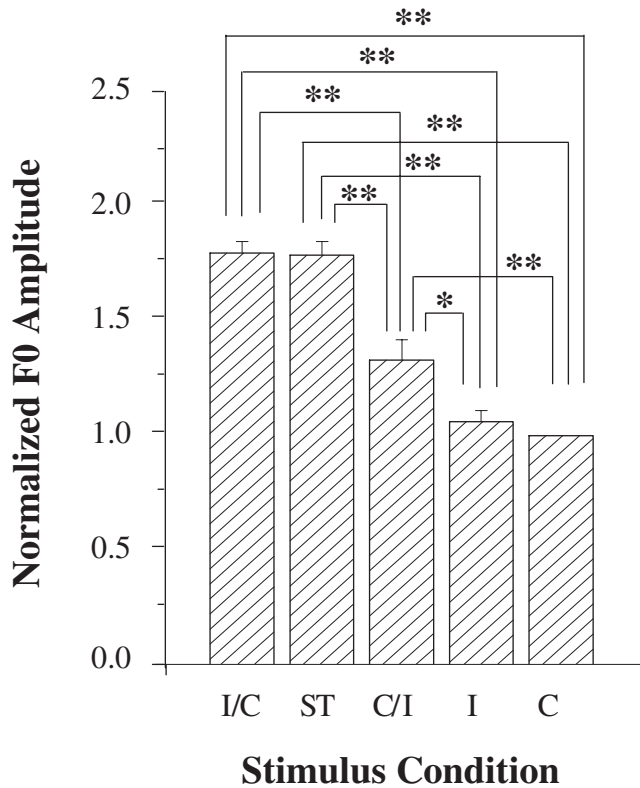


FIG. 3. Monaural and binaural IC FFRs. Mean normalized F0 spectral amplitudes in FFRs under various stimulation conditions are shown for 42 rats before injection manipulations. F0 amplitude evoked by contralateral stimulation only (C) served as the baseline condition (amplitude = 1) for amplitude normalization. Error bars in this and the following figures represent the standard error of the mean (SEM). I/C, binaural stimulation with ipsilateral (relative to recording site) chatter leading contralateral chatter; ST, simultaneous binaural stimulation; C/I, contralateral chatter leading ipsilateral chatter; I, chatter at ipsilateral ear only; C, chatter at contralateral ear only. \*\* $P < 0.01$ , \* $P < 0.05$ , repeated-measures ANOVA.

significant (both  $P < 0.01$ ), the main effect of testing time was not significant (both  $P > 0.05$ ), and the interaction between testing time and  $|ITD_{S+N}|$  was not significant (both  $P > 0.05$ ).

When the contralateral chatter led, for the two KYNA and the two Locke's solution groups (Fig. 8A–D), separate 2 (testing time) by 2 ( $|ITD_{S+N}|$ ) repeated-measures ANOVA shows that the main effect of  $|ITD_{S+N}|$  condition was significant (all  $P < 0.05$ ), the main effect of testing time was not significant (all  $P > 0.05$ ), and the interaction between testing time and  $|ITD_{S+N}|$  was also not significant (all  $P > 0.05$ ).

Therefore, both inputs from the contralateral DNLL and the contralateral IC contributed to the binaural unmasking effect of FFRs in rat auditory midbrain. However, these modulations of binaural unmasking effect occurred only when the signal at the ipsilateral ear led the contralateral ear.

## Discussion

### *Latencies to the chatter presented at the contralateral ear*

In our previous study using the same type of electrodes (Du *et al.*, 2009), for the onset response to the chatter presented at the contralateral ear, the latency of the first positive peak recorded in the lateral nucleus of the amygdala was 8.0 ms. By contrast, in the

present study, the latency of the first positive peak of the onset response recorded in the IC to the chatter at the contralateral ear was 6.3 ms. This latency value is within both the latency range (4–30 ms) of the first spike to clicks obtained in the young Long-Evans rat central nucleus of the IC as reported by Irvine *et al.* (1995) and the latency range (6.2–77.2 ms) of the first spike to tone bursts obtained in the young Fischer 344 rat central nucleus of the IC as reported by Palombi & Caspary (1996). Thus, although a high degree of spatial resolution of the intracranial recordings used in the present study was not particularly emphasized, the response-latency results indicate that the acoustically evoked responses with sufficiently large amplitude recorded with electrodes inside the IC were neural activities generated within the IC.

### *Profile of major results*

The results of the present study show that in anaesthetized rats, a segment of species-specific pain call (rat chatter), presented either monaurally or binaurally, was able to elicit marked FFRs in the rat IC. In addition, noise masking of IC FFRs to the chatter can be reduced significantly by binaural processing. More importantly, KYNA blocking of either the contralateral DNLL or the contralateral IC weakened binaural unmasking of IC FFRs, even though the effects of blocking these two contralateral structures under quiet conditions were opposite: blocking of the contralateral DNLL generally enhanced FFRs while blocking of the contralateral IC generally reduced FFRs. The results suggest that binaural unmasking of FFRs recorded in the IC depends on the two contralateral inputs whose unmasking mechanisms are different.

### *Contribution of EE neurons to FFRs in the IC*

In rats, previous studies (e.g. Kelly *et al.*, 1991) have shown that the majority of auditory neurons in the IC are predominantly excited by stimuli at the contralateral ear and inhibited by stimuli at the ipsilateral ear, forming the so-called 'EI' neurons. Also, a small portion (about 20%) of IC neurons in rats are excited by stimuli at either ear (Kelly *et al.*, 1991), forming the so-called 'EE' neurons, which are sensitive to ITD. The remaining neurons are only excited by contralateral stimuli, forming the so-called 'EO' neurons. It is expected that FFRs to contralateral stimulation would be stronger than FFRs to ipsilateral stimulation, because contralateral stimulation drives all the three types of neurons (EE, EI, EO) in the IC but ipsilateral stimulation drives EE neurons only. However, the results of the present study show that when the noise masker was not present, although the chatter at the contralateral ear evoked much larger onset responses than the chatter at the ipsilateral ear, the normalized amplitude of IC FFRs to the contralateral chatter was similar to that to the ipsilateral chatter, without showing a marked contralateral dominance in eliciting IC FFRs. Moreover, IC FFRs to binaural-chatter stimulation exhibit a feature of ipsilateral predominance: FFRs were markedly stronger when the ipsilateral chatter either led or started simultaneously with the contralateral chatter than when the ipsilateral chatter lagged behind the contralateral chatter. These results suggest that EE neurons in the IC provide the major contribution to binaural FFRs.

### *Binaural unmasking of IC FFRs*

The present study shows for the first time that in rats with noise masker present, IC FFRs to the signal were improved by introducing an ITD disparity between the signal and the noise masker. The results

## KYNA                      Locke's Contralateral DNLL Injection

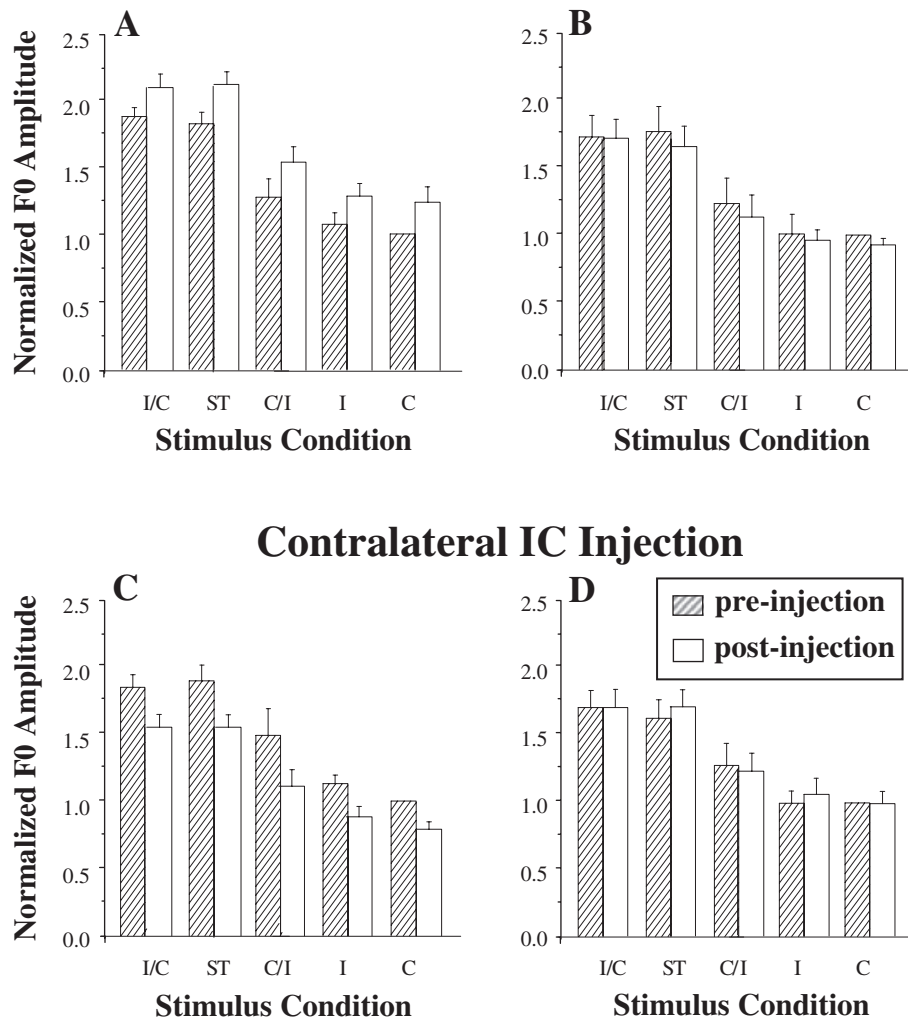


FIG. 4. Effects of blocking of the contralateral DNLL or the contralateral IC on IC FFRs. Normalized F0 amplitudes of FFRs under various monaural/binaural stimulation conditions are shown before (hatched bars) and after (open bars) either kynurenic acid (A and C) or Locke's solution (B and D) was injected into the contralateral DNLL (A and B) or the contralateral IC (C and D). F0 amplitude under Condition C before injection served as the baseline condition (F0 amplitude = 1) for normalization. See Fig. 3 for abbreviations. Note that F0 amplitudes were significantly enhanced across conditions after blocking of glutamate receptors in the contralateral DNLL (A,  $P = 0.023$ ), and generally reduced after blocking of glutamate receptors in the contralateral IC (C,  $P = 0.001$ ), which are revealed by repeated-measures ANOVAS.

are generally in agreement with the notion that introducing a difference between signal and masker in binaural configurations improves auditory representations of the signal, as shown by previous reports on binaural unmasking/spatial unmasking of auditory responses in the IC in laboratory animals (e.g. Caird *et al.*, 1991; Mandava *et al.*, 1996; McAlpine *et al.*, 1996; Jiang *et al.*, 1997; Ratnam & Feng, 1998; Palmer *et al.*, 2000; Lin & Feng, 2003; Lane & Delgutte, 2005) and previous reports on binaural unmasking of brainstem FFRs in humans (Wilson & Krishnan, 2005).

It would be of interest to know whether the binaural unmasking of FFRs recorded in the rat IC shares similar mechanisms with the binaural masking level difference (BMLD) as measured in the IC of other species. The BMLD is a well-studied psychophysical phenomenon showing that the signal, presented at both ears and masked by a noise masker presented at both ears, becomes more easily detected

when either the interaural phase of the signal or that of the masker is reversed (Hirsh, 1948). Thus, the BMLD measures the ability of listeners to use a difference between signal and masker in binaural attributes to improve their detection of the signal against the masking noise. The BMLD has been demonstrated on single neurons in both the guinea-pig IC (e.g. Caird *et al.*, 1991; McAlpine *et al.*, 1996; Jiang *et al.*, 1997; Palmer *et al.*, 1999, 2000; Palmer & Shackleton, 2002) and the chinchilla IC (Mandava *et al.*, 1996). In general, the BMLD is considered to be a low-frequency phenomenon, because it has been found to be efficient when the frequency of the signal is below 1–2 kHz (e.g. Hirsh, 1948; Caird *et al.*, 1991; Mandava *et al.*, 1996). Either reducing the interaural correlation of the masking noise or introducing a signal (e.g. 500-Hz tone) to the fully correlated masking noise is able to weaken the quasiperiodic noise delay functions (NDFs), which are modulations of neural responses to interaurally correlated noise with

... is resistant to noise masking & is unmasked by binaural processing (Wilson & Krishnan, 2005).





By contrast, IC neurons receive inhibitory (GABAergic) influence from the contralateral DNLL (Burger & Pollak, 2001; Faingold *et al.*, 1993; Kelly & Li, 1997; Kidd & Kelly, 1996; Li & Kelly, 1992; Van Adel *et al.*, 1999; Zhang *et al.*, 1998; for a review see Li & Yue, 2002). Clearly, ipsilateral stimulation drives EE neurons in the (recorded) IC, all types of neurons in the contralateral IC, as well as neurons in the contralateral DNLL. Both the present study and our previous study (Ping *et al.*, 2008) confirm that the contralateral DNLL plays a role in suppressing IC FFRs in quiet because IC FFRs were enhanced by blocking of the contralateral DNLL when no masker was presented. Interestingly, in the present study when the masker was presented and the ipsilateral chatter led the contralateral chatter, binaural unmasking was reduced significantly by blocking of excitatory glutamate transmissions in the contralateral DNLL, suggesting that GABAergic projections from the contralateral DNLL play a role in forming binaural unmasking in the IC. It is well known that inhibitory inputs to the IC shape binaural responses of IC neurons (Li & Kelly, 1992; Ito *et al.*, 1996; Kidd & Kelly, 1996; Kelly & Li, 1997; Van Adel *et al.*, 1999; Burger & Pollak, 2001). In addition, Lin & Feng (2003) have reported that iontophoretic application of bicuculline, a GABA<sub>A</sub> receptor antagonist, into the frog IC markedly degraded binaural processing involved in spatial unmasking of the IC. Thus, the results of the present study suggest that ipsilateral stimulation (relative to the recorded IC) drives the contralateral DNLL, which not only inhibits IC FFRs but also facilitates binaural unmasking of FFRs in the IC. The unmasking effect may be caused by the function of the DNLL in both facilitation of binaural responses to the signal and suppression of responses to the noise masker. Klug *et al.* (2002) and Xie *et al.* (2005) have shown that in the free-tailed bat IC, neural selectivity to species-specific calls is primarily attributed to local GABAergic inhibition. Thus, in the present study, the interruption of GABAergic innervations from the contralateral DNLL might also disrupt the response selectivity of IC neurons to the tail-pain chatter, leading to a reduction of FFRs to the chatter against noise masking.

As both enhancement of signal inputs and suppression of masker inputs can improve the signal-to-masker ratio in neural representation of acoustic stimuli, the functional integration of excitatory inputs from the contralateral IC and inhibitory inputs from the contralateral DNLL is a critical issue for future studies of binaural unmasking of FFRs. As mentioned in the introduction, scalp-recorded FFRs in humans can be used to study the neural coding of critical features of speech sounds (Hall, 1979; Krishnan, 2002; Krishnan *et al.*, 2004; Russo *et al.*, 2004), top-down regulation of brainstem auditory responses (Galbraith *et al.*, 2003) and language-experience-related neural plasticity (Galbraith *et al.*, 2004; Krishnan *et al.*, 2005; Xu *et al.*, 2006; Swaminathan *et al.*, 2008). The resistance of human brainstem FFRs to noise masking (Russo *et al.*, 2004) and binaural unmasking of FFRs (Wilson & Krishnan, 2005) may be also useful for studying mechanisms underlying the 'cocktail party problem' as proposed by Cherry (1953). Thus, investigation of mechanisms underlying binaural unmasking of IC FFRs (the present study) and higher-level structure FFRs (Du *et al.*, 2009) to species-specific calls in rats is important for building animal models in this line of research.

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## Abbreviations

BMLD, binaural masking level difference; C, contralateral; C/I, contralateral chatter leading; DNLL, dorsal nucleus of the lateral lemniscus; FFR, frequency-following response; FFT, fast Fourier transform; I, ipsilateral; I/C, ipsilateral chatter leading; IC, inferior colliculus; ISI, inter-stimulus interval; KYNA, kynurenic acid; NDF, noise delay function; rSNR, response signal-to-noise ratio; SNR, signal-to-noise ratio; sSNR, stimulus signal-to-noise ratio; UI, unmasking index.

## References

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