Corticofugal Modulation of Multi-Parametric Auditory Selectivity in the Midbrain of the Big Brown Bat

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Zhou X, Jen PH. Corticofugal modulation of multi-parametric auditory selectivity in the midbrain of the big brown bat. J Neurophysiol 98: 2509–2516, 2007. First published September 5, 2007; doi:10.1152/jn.00613.2007. Corticofugal modulation of subcortical auditory selectivity has been shown previously in mammals for frequency, amplitude, time, and direction domains in separate studies. As such, these studies do not show if multi-parametric corticofugal modulation can be mediated through the same subcortical neuron. Here we specifically studied corticofugal modulation of best frequency (BF), best amplitude (BA), and best azimuth (BAZ) at the same neuron in the inferior colliculus of the big brown bat, Eptesicus fuscus, using focal electrical stimulation in the auditory cortex. Among 53 corticofugally inhibited collicular neurons examined, cortical electrical stimulation produced a shift of all three measurements (i.e., BF, BA, and BAZ) toward the value of stimulated cortical neuron in 13 (24.5%) neurons, two measurements (i.e., BF and BAZ or BA and BAZ) in 19 (36%) neurons, and one measurement in 16 (30%) neurons. Cortical electrical stimulation did not shift any of these measurements in the remaining five (9.5%) neurons. Corticofugally induced collicular BF shift was symmetrical, whereas the shift in collicular BA or BAZ was asymmetrical. The amount of shift in each measurement was significantly correlated with each measurement difference between recorded collicular and stimulated cortical neurons. However, shifts of three measurements were not correlated with each other. Furthermore, average measurement difference between collicular and cortical neurons was larger for collicular neurons with measurement shifts than for those without shifts. These data indicate that multi-parametric corticofugal modulation can be mediated through the same subcortical neuron based on the difference in auditory selectivity between subcortical and cortical neurons.

INTRODUCTION

The auditory system consists of ascending and descending (corticofugal) pathways. The corticofugal pathway, originating from the deep layers of the auditory cortex (AC), projects to the medial geniculate body, inferior colliculus (IC), and subcollicular auditory nuclei (Andersen et al. 1980; Druga et al. 1997; Feliciano et al. 1995; Games and Winer 1988; Herbert et al. 1991; Huffman and Henson 1990; Saldana et al. 1996; Winer 2006). Previous electrophysiological studies in different animal species have shown that the corticofugal pathway not only adjusts and improves subcortical auditory signal processing (bats, Jen and Zhou 2003; Jen et al. 1998, 2002; Ma and Suga 2001a; Sun et al. 1989; Yan and Suga 1996; Zhang and Suga 1997; Zhang et al. 1997; Zhou and Jen 2000a,b, 2005; cats, He 1997; guinea pigs, He et al. 2002; Xiong et al. 2004; mice, Yan and Ehret 2001, 2002; Yan et al. 2005; rats, Popelar et al. 2003; Syka and Popelar 1984), but it also reorganizes sub-cortical auditory maps according to the acoustic experience (bats, Yan and Suga 1998; Zhang and Suga 2000).

Biologically relevant sounds, including human speech, have complex spectro-temporal structure and vary in several parameters such as frequency, amplitude, time, and direction, etc. Accordingly, central auditory neurons are tuned to these various signal parameters that characterize complex sounds. It might be expected that corticofugal modulation of subcortical auditory processing would also be multi-parametric, i.e., occurring not only in the frequency domain (Yan and Suga 1998; Yan et al. 2005; Zhang and Suga 2000) but also in amplitude (Jen and Zhou 2003; Yan and Ehret 2002), time (Ma and Suga 2001a; Yan and Suga 1996), and direction (Zhou and Jen 2005) domains. If this modulation only occurs in a single domain, the role of the corticofugal pathway in central auditory processing and reorganization would apparently be partial. However, most of the preceding studies only examined corticofugal modulation of subcortical signal processing for one signal parameter. As such, it remains unclear if corticofugal modulation of these different signal parameters is mediated through different subcortical neurons or can be mediated through the same neuron. It is also unclear if the multi-parametric corticofugal modulation is interrelated to each other.

Our recent studies in bats have shown that cortical electrical stimulation synchronized with acoustic stimulation produces shifts of the best amplitude (BA) (Jen and Zhou 2003) or the best azimuth (BAZ) (Zhou and Jen 2005) of IC neurons toward the values of stimulated AC neurons. Due to the fact that cortical electrical stimulation also produces the BF shifts of IC neurons (Yan and Ehret 2001, 2002; Yan and Suga 1998; Yan et al. 2005; Zhang and Suga 2000) and that the frequency, amplitude, and direction selectivities of IC neurons are interrelated to each other (Grothe et al. 1996; Jen and Zhang 2000; Jen et al. 1987; Poon et al. 1990), one may argue that the observed shift of BA or BAZ of IC neuron has been just due to the shift of BF rather than the influence of the corticofugal pathway. However, we did not study in detail the interrelationship among multi-parametric corticofugal modulation due to the time constrain and the holding of the recorded neurons in these studies. The main objective of the present study, therefore, was to study multi-parametric corticofugal modulation of the same neuron in the central nucleus of the IC of the big brown bat, Eptesicus fuscus, in frequency, amplitude, and direction domains. Specifically, we studied corticofugally in-
duced shifts of BF, BA, and BAZ in the same IC neuron and the relationship among these measurement shifts.

We report here that multi- parametric corticofugal modulation can be mediated through the same IC neuron based on the difference in auditory selectivity between IC and AC neurons in each signal parameter. The modulation of different parameters, however, is not correlated with each other. Some parts of this study have been presented in abstract form (Jen and Zhou 2005, 2006).

**METHODS**

The experiments were conducted in compliance with National Institutes of Health publication No. 85–23, “Principles of Laboratory Animal Care” and with the approval of the Institutional Animal Care and Use Committee (No. 1438) of the University of Missouri-Columbia.

Thirty *Eptesicus fuscus* (both sexes, body weight: 17–25 g) were used for this study. These bats were netted in Columbia, Missouri and housed in the animal care facility at the Division of Biological Sciences, University of Missouri-Columbia. Water and food (meal-worm) were available ad libitum. The condition of these bats was eye-checked daily to determine if they had any sign of weakness such as empty stomach or slow response to hand-handling.

The surgical procedures were basically the same as in previous studies (Jen and Zhou 2003; Zhou and Jen 2005). Briefly, a 1.8-cm nail was glued onto the exposed skull of each of pentobarbital sodium (Nembutal)-anesthetized (45–50 mg/kg body wt) bat 2 days before the recording session. Metofane and local anesthetic (Lidocaine) were used as supplements, when necessary, to minimize the pain and keep the animal motionless during the surgery. Exposed tissue was treated with antibiotic (Neosporin) to prevent inflammation. The bat was kept warm with a heating lamp during surgery and recovery from anesthesia. During recording, each bat was administered the neuroleptanalgesic Innovar-Vet (0.08 mg/kg body wt of fentanyl, 4 mg/kg body wt of droperidol) and was strapped to an aluminum plate with transparent plastic sheeting inside a double-wall, sound-proof room (temperature: 28–30°C). The ceiling and inside walls of the room were covered with 3-in convoluted polyurethane foam to reduce echoes. After immobilizing the bat’s head by fixing the shank of the nail into a mental rod using the bat’s head by fixing the shank of the nail into a mental rod by adjusting the metal rod. Small holes were bored in the skull above the IC and the AC for insertion of electrodes for recording of neural responses from the central nucleus of the IC, and for electrical stimulation and recording of responses from the primary AC. Additional doses of Innovar-Vet were administered during later phases of recording when the bat showed sign of discomfort. Each recording session typically lasted for 4–6 h to minimize the bat’s discomfort from being restrained. Typically each bat was used in one to five recording sessions on separate days. Between recording sessions, the scalp was treated with antibiotic cream, and the bat was housed individually.

Acoustic stimuli (4 ms with 0.5-ms rise-decay times) were generated with an oscillator (KH model 1200) and a custom electronic switch. These stimuli were then amplified after passing through a decade attenuator (HP 350D) before they were fed to a small condenser loudspeaker (AKG model CK 50, 1.5-cm diam, 1.2 g) placed 23.5 cm away from the bat. The loudspeaker could be positioned at 0° elevation and in any specific azimuth within 90° in the frontal auditory space through a remote control system driven by two small electric motors. To avoid potential influence of noises generated by the motors on response of a recorded neuron, the motors were always turned off after positioning the loudspeaker at each selected azimuthal angle. Calibration of the loudspeaker was performed with a 1/4 in microphone (B & K 4135) placed at the position where the bat’s head would be during recording. The output of the loudspeaker was expressed in dB SPL in reference to 20 μPa root mean square.

During experiments, a pair of custom-made tungsten-in-glass electrodes (tip diameter: <10 μm, inter-tip distance: 30–50 μm) was used for recording acoustically evoked responses of AC neurons as well as for cortical electrical stimulation. Electrodes were inserted into the primary AC at depths of 600–700 μm, which is the fifth layer of the AC where corticofugal fibers originate (Jen et al. 1997). On isolation of an AC neuron with 4-ms sound pulses delivered at 2 pulses/s from 40° contralateral to the recording site (hereafter abbreviated as c40°), the frequency and amplitude of acoustic stimuli were systematically varied to determine the BF, at which the neuron had the lowest threshold to sound stimulus (i.e., the MT). At the MT, the neuron responded to BFAC sounds with 50% probability.

A 3 M KCl glass micropipette electrode (tip diameter: 1 μm, impedance: 5–10 MΩ) was used for recording responses of neurons in the central nucleus of the IC ipsilateral to the recorded AC. After determining the BFIC and the MT of each isolated IC neuron, a BFIC sound delivered at 10 dB above the MT was used to obtain the neuron’s control response. To determine if the response of the recorded IC neuron was corticofugally modulated, the same BFIC sound was synchronized with an electrical stimulation (a train of 4 monophasic electric pulses of 0.1-ms duration at 1-ms interval) in the AC was delivered to the bat to obtain the IC neuron’s response. The electrical current and the intervals between electrical and acoustic stimulus onsets were systematically adjusted. If the IC neuron’s response to the BFIC sound was not affected by cortical electrical stimulation (change in number of impulses induced by cortical electrical stimulation was <20%), the IC neuron was abandoned (Jen et al. 1998). When the IC neuron’s response to the BFIC sound was modulated by cortical electrical stimulation, electrical current (5–50 μA, mostly 5–25 μA) and intervals between electrical and acoustic stimulus onsets (1–6 ms, mostly 1–3 ms) that modulated 30–50% of the control response were chosen for subsequent experiments. Corticofugal modulation was then studied with cortical electrical stimulation applied at 10 trains per second synchronized with a BFAC sound of AC neuron delivered at 10 dB above its MT for 30 min (hereafter referred to as cortical electrical stimulation).

Iso-amplitude frequency tuning curves, rate-amplitude functions, and directional selectivity curves were determined respectively for cortical neuron and for collicular neuron before and after cortical electrical stimulation. An iso-amplitude frequency tuning curve of each neuron was plotted with the number of impulses in response to sounds delivered at c40° and at 20 dB above its MT at several selected responsive frequencies. A rate-amplitude function was plotted with the number of impulses in response to BFIC sounds delivered at MT and at 10 dB increments above the MT. A directional selectivity curve was plotted with the number of impulses in response to BFIC sounds at 20 dB above MT against azimuth angles. Changes in BF, BA, and BAZ (i.e., frequency, amplitude, or azimuth angle which elicits the largest number of impulses of a neuron in each curve, as in previous studies) (Clarey et al. 1994; Jen and Zhou 2003; Phillips et al. 1995; Sutter and Schréiner 1995; Zhou and Jen 2005) of the same IC neuron determined before and after cortical electrical stimulation were then statistically compared using Student’s t-test at P < 0.01.

Recorded action potentials were amplified, band-pass filtered (Krohn-Hite 3500), and fed through a window discriminator (WPI 121) before being sent to an oscilloscope (Tektronix 5111) and an audio monitor (Grass AM6). They were then sent to a computer (Gateway 2000; 486) for acquisition of peristimulus time histograms (PSTHs; bin width: 500 μs, sampling period: 100 ms) to 32 stimulus presentations. PSTHs quantitatively described the discharge pattern of each neuron under different stimulation conditions. The number of impulses in each PSTH was used to quantify a neuron’s response under each stimulation condition.
RESULTS

A total of 119 corticofugally inhibited IC neurons was isolated in this study. As reported in our previous studies (Jen and Zhou 2003; Zhou and Jen 2005), the response of these neurons decreased and the latency lengthened to varying degrees during the cortical electrical stimulation. This corticofugal inhibition typically persisted up to ~30–35 min after the cessation of 30 min of cortical electrical stimulation.

Although recorded neurons were lost throughout the long course of study, we were able to determine the corticofugally induced shift in the BF, BA, and BAZ of 53 IC neurons. The BF, MT, and latency of these 53 neurons ranged between 21.6 and 73.4 kHz (average: 44.1 ± 13.3 kHz), 20 and 55 dB SPL (average: 34 ± 10 dB SPL), and 7.0 and 19.0 ms (average: 11.2 ± 3.1 ms).

**Corticofugally induced shift in BF, BA, or BAZ of IC neurons**

Cortical electrical stimulation produced different types of modulation of auditory selectivity in these IC neurons. Figure 1 shows the iso-amplitude frequency tuning curves, rate-amplitude functions, and directional selectivity curves of seven representative IC neurons plotted before (solid line) and after (dashed lines) cortical electrical stimulation. Cortical electrical stimulation sharpened the iso-amplitude frequency tuning curve, rate-amplitude function, and directional selectivity curve of neuron A and shifted its BF, BA, and BAZ toward the values of paired AC neuron (Fig. 1A, a–c, dashed vs. solid lines; unfilled vs. filled arrows). As a result, the $\text{BF}_{\text{IC}-\text{AC}}, \text{BA}_{\text{IC}-\text{AC}}$, and $\text{BAZ}_{\text{IC}-\text{AC}}$ differences of this neuron decreased from 3.5 to 2 kHz, 8 to 0 dB, and 14 to 6° after cortical electrical stimulation. For neurons B and C, cortical electrical stimulation shifted two measurements of each IC neuron (BF and BAZ for neuron B and BA and BAZ for neuron C) toward the values of paired AC neuron (Fig. 1, B, a and c, and C, b and c, unfilled vs. filled arrows) but did not change the third measurement (Fig. 1, Bb and Ca, unfilled vs. filled arrows). As a result, the $\text{BF}_{\text{IC}-\text{AC}}$ and $\text{BAZ}_{\text{IC}-\text{AC}}$ differences for neuron B decreased from 2.1 to 0.5 kHz and from 20 to 4°. Similarly, the $\text{BA}_{\text{IC}-\text{AC}}$ and $\text{BAZ}_{\text{IC}-\text{AC}}$ differences for neuron C decreased from 11 to 3 dB and from 20 to 8°.

Cortical electrical stimulation sharpened the iso-amplitude frequency tuning curve, rate-amplitude function, and directional selectivity curve of neurons D–F but only shifted one measurement of each neuron (BF for neuron D, BA for neuron E, and BAZ for neuron F) toward the value of paired AC neuron (Fig. 1, Da, Eb, and Fc, unfilled vs. filled arrows). As such, the $\text{BF}_{\text{IC}-\text{AC}}$ difference for neuron D decreased from 3.0 to 1.2 kHz, the $\text{BA}_{\text{IC}-\text{AC}}$ difference for neuron E decreased from 19 to 7 dB, and the $\text{BAZ}_{\text{IC}-\text{AC}}$ difference for neuron F decreased from 20 to 4°. Cortical electrical stimulation sharpened the iso-amplitude frequency tuning curve, rate-amplitude function, and directional selectivity curve of neuron G but did not produce any shift in any of these three measurements (Fig. 1G, a–c, dashed vs. solid lines).

The shift in BF, BA, and BAZ of all 53 IC neurons produced by cortical electrical stimulation was summarized in Table 1. It is clear that cortical electrical stimulation produced a shift of all three measurements (i.e., BF, BA, and BAZ) toward the values of paired AC neuron in 13 (24.5%, type I) neurons, two measurements in 19 neurons (type IIa: shift in BF and BAZ in 12, 23% and type IIb: shift in BA and BAZ in 7, 13%) and one measurement in 16 neurons (type IIIa: shift in BF in 5, 9.5%, type IIIb in BA in 7, 13% and type IIIc in BAZ in 4, 7.5%) but did not shift any of these measurements in the remaining 5 (9.5%, type IV) neurons. Average shifts in collicular BF, BA, and BAZ produced by cortical electrical stimulation were shown at the bottom row of Table 1.

Corticofugally induced BF shift was symmetrical such that the BF of IC neuron always shifted toward that of paired AC neuron regardless the BF of IC neuron was higher or lower than the BF of paired AC neuron (Fig. 1, Aa, Ba, and Da, unfilled vs. filled arrows). Among 30 IC neurons with BF shift after cortical electrical stimulation, the BF was lower than that of paired AC neuron in 13 (43%) neurons and higher than that...
of paired AC neuron in 17 (57%) neurons. Different from this observation, corticofugally induced shift in the BA and BAZ was asymmetrical. As such, cortical electrical stimulation only produced shift in collicular BA that was lower than cortical BA (n = 27; Fig. 1, Ab, Cb, and Eb, unfilled vs. filled arrows). Similarly, cortical electrical stimulation only produced shift in collicular BAZ that was more lateral than cortical BAZ (n = 36; Fig. 1, Ac, Bc,Cc, and Fc, unfilled vs. filled arrows).

Figure 2 compares the BFIC-AC, BAIC-AC, and BAZIC-AC differences before (refer to abscissa) and after (refer to ordinate) cortical electrical stimulation. It is clear that all data points were below the diagonal equal value line indicating a decrease in the BFIC-AC, BAIC-AC, and BAZIC-AC differences after cortical electrical stimulation. As shown in Table 2, the average BFIC-AC, BAIC-AC, and BAZIC-AC differences obtained after cortical electrical stimulation were significantly smaller than those obtained before cortical electrical stimulation (Table 2; paired Student’s t-test, all P < 0.0001).

IC neurons with and without corticofugally induced shift in the BF, BA, or BAZ

Because cortical electrical stimulation did not produce shift of BF, BA, or BAZ of all 53 IC neurons, we compared the BFIC-AC, BAIC-AC, and BAZIC-AC differences for IC neurons with or without measurement shift. As shown in Fig. 3, the BFIC-AC, BAIC-AC, and BAZIC-AC differences were larger and distributed over a wider range for IC neurons with (filled bars) than for IC neurons without (unfilled bars) measurement shifts. Most BFIC-AC (77%), BAIC-AC (89%), and all BAZIC-AC differences for IC neurons with measurement shifts were larger than 2 kHz, 10 dB, and 6°. Conversely, most BFIC-AC (96%), BAIC-AC (92%), and BAZIC-AC (88%) differences for IC neurons without measurement shifts were smaller than 2 kHz, 10 dB, and 6°. Unpaired Student’s t-test revealed these differences for measurement shifts were significantly larger than those without shifts (all P < 0.0001). In light of preceding findings, we further compared average BFIC-AC, BAIC-AC, and BAZIC-AC differences for different types of collicular neurons in Fig. 4. Here average differences for each type of neurons were arranged in row and separated by dashed lines. It is obvious that, for each type of neurons, the shift in certain measurement was coincident with large average difference in the same measurement and similarly, without shift in certain measurement was coincident with small average difference in this measurement (Fig. 4, A–C, filled vs. unfilled bars). The observation was also confirmed by one-way ANOVA analysis which revealed that, for each measurement, average differences of neuron types with measurement shifts were significantly larger than those without shifts (all P < 0.01).

Shift in BF, BA, or BAZ of IC neurons in relation to BF, BA, or BAZ of IC or AC neurons

To determine how the corticofugally induced measurement shift was related to the selectivity of IC and AC neurons, we obtained scatter plots of the shift in BF, BA, and BAZ in relation to BF, BA, and BAZ of IC and AC neurons as well as to the BFIC-AC, BAIC-AC, and BAZIC-AC differences (Fig. 5). Linear regression analyses did not reveal any significant cor-

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**Table 1. Summary of shifts in best frequency (BF), best amplitude (BA), and best azimuth (BAZ) of 53 IC neurons after cortical electrical stimulation**

<table>
<thead>
<tr>
<th>Types</th>
<th>n, %</th>
<th>BF</th>
<th>BA</th>
<th>BAZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>I [13 (24.5%)]</td>
<td>13 (24.5%)</td>
<td>w</td>
<td>w</td>
<td>w</td>
</tr>
<tr>
<td>II [19 (36%)]</td>
<td>19 (36%)</td>
<td>w</td>
<td>w</td>
<td>w</td>
</tr>
<tr>
<td>IIa</td>
<td>12 (23%)</td>
<td>w</td>
<td>w/o</td>
<td>w</td>
</tr>
<tr>
<td>IIb</td>
<td>7 (13%)</td>
<td>w/o</td>
<td>w</td>
<td>w</td>
</tr>
<tr>
<td>III [16 (30%)]</td>
<td>16 (30%)</td>
<td>w</td>
<td>w</td>
<td>w</td>
</tr>
<tr>
<td>IIIa</td>
<td>5 (9.5%)</td>
<td>w</td>
<td>w/o</td>
<td>w/o</td>
</tr>
<tr>
<td>IIIb</td>
<td>7 (13%)</td>
<td>w/o</td>
<td>w</td>
<td>w/o</td>
</tr>
<tr>
<td>IIIc</td>
<td>4 (7.5%)</td>
<td>w/o</td>
<td>w</td>
<td>w</td>
</tr>
<tr>
<td>IV [5 (9.5%)]</td>
<td>5 (9.5%)</td>
<td>w</td>
<td>w/o</td>
<td>w/o</td>
</tr>
<tr>
<td>Average shift</td>
<td>1.8 ± 0.9 kHz</td>
<td>9 ± 3 dB</td>
<td>14 ± 6 deg</td>
<td></td>
</tr>
</tbody>
</table>

n, number of neurons, w or w/o, with or without measurement shift after cortical electrical stimulation.

**Table 2. BFIC-AC, BAIC-AC, and BAZIC-AC differences before and after cortical electrical stimulation**

<table>
<thead>
<tr>
<th></th>
<th>BFIC-AC, kHz</th>
<th>BAIC-AC, dB</th>
<th>BAZIC-AC, deg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>3.4 ± 1.7</td>
<td>15 ± 5</td>
<td>21 ± 7</td>
</tr>
<tr>
<td>After</td>
<td>1.6 ± 1.2</td>
<td>6 ± 3</td>
<td>7 ± 5</td>
</tr>
<tr>
<td>n</td>
<td>30</td>
<td>27</td>
<td>36</td>
</tr>
<tr>
<td>P (paired Student’s t-test)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Because cortical electrical stimulation did not produce shift of BF, BA, or BAZ of all 53 IC neurons, we compared the BFIC-AC, BAIC-AC, and BAZIC-AC differences for IC neurons with or without measurement shift. As shown in Fig. 3, the BFIC-AC, BAIC-AC, and BAZIC-AC differences were larger and distributed over a wider range for IC neurons with (filled bars) than for IC neurons without (unfilled bars) measurement shifts. Most BFIC-AC (77%), BAIC-AC (89%), and all BAZIC-AC differences for IC neurons with measurement shifts were larger than 2 kHz, 10 dB, and 6°. Conversely, most BFIC-AC (96%), BAIC-AC (92%), and BAZIC-AC (88%) differences for IC neurons without measurement shifts were smaller than 2 kHz, 10 dB, and 6°. Unpaired Student’s t-test revealed these differences for measurement shifts were significantly larger than those without shifts (all P < 0.0001). In light of preceding findings, we further compared average BFIC-AC, BAIC-AC, and BAZIC-AC differences for different types of collicular neurons in Fig. 4. Here average differences for each type of neurons were arranged in row and separated by dashed lines. It is obvious that, for each type of neurons, the shift in certain measurement was coincident with large average difference in the same measurement and similarly, without shift in certain measurement was coincident with small average difference in this measurement (Fig. 4, A–C, filled vs. unfilled bars). The observation was also confirmed by one-way ANOVA analysis which revealed that, for each measurement, average differences of neuron types with measurement shifts were significantly larger than those without shifts (all P < 0.01). Shift in BF, BA, or BAZ of IC neurons in relation to BF, BA, or BAZ of IC or AC neurons

To determine how the corticofugally induced measurement shift was related to the selectivity of IC and AC neurons, we obtained scatter plots of the shift in BF, BA, and BAZ in relation to BF, BA, and BAZ of IC and AC neurons as well as to the BFIC-AC, BAIC-AC, and BAZIC-AC differences (Fig. 5). Linear regression analyses did not reveal any significant cor-
relation of the shift in BF, BA, and BAZ with the BF, BA, and BAZ of IC or AC neurons (Fig. 5, A–C; all $P < 0.05$).

Conversely, linear regression analyses did show that the shift in the BF, BA, and BAZ significantly increased with the BFIC-AC, BAIC-AC, and BAZIC-AC differences (Fig. 5, D–F; all $P < 0.0001$). We further determined if corticofugally induced shifts in the BF, BA, and BAZ of IC neurons were correlated with each other by obtaining scatter plots of these three measurement shifts. As shown in Fig. 6, linear regression analyses did not reveal any significant correlation of shifts in BF, BA, and BAZ (Fig. 6, A–C; all $P > 0.1$).

**DISCUSSION**

**Multi-parametric corticofugal modulation of subcortical auditory processing**

Corticofugal modulation of subcortical auditory processing has been shown in the multi-parametric domains in separate studies (Jen and Zhou 2003; Ma and Suga 2001a; Yan and Ehret 2001, 2002; Yan and Suga 1996, 1998; Yan et al. 2005; Zhang and Suga 2000; Zhou and Jen 2000a,b, 2005). However, because each of these studies mainly concentrated on studying corticofugal modulation of subcortical signal processing in only one signal parameter, these studies cannot conclude if corticofugal modulation of multi-parametric signal processing is mediated through different subcortical neurons or can be mediated through the same neuron.

In this study, we have shown that multi-parametric corticofugal modulation of collicular signal processing can be independently mediated through the same IC neuron. Supporting data include the following. 1) Cortical electrical stimulation produced shifts of all, two, one, or none of BF, BA, and BAZ of the same IC neuron toward the BF, BA, and BAZ of paired AC neuron (Fig. 1; Table 1). 2) Respectively, the amount of shift in the BF, BA, and BAZ of IC neurons was only significantly correlated with the BFIC-AC, BAIC-AC, and BAZIC-AC differences (Fig. 5, D–F; all $P < 0.0001$).

We further determined if corticofugally induced shifts in the BF, BA, and BAZ of IC neurons were correlated with each other by obtaining scatter plots of these three measurement shifts. As shown in Fig. 6, linear regression analyses did not reveal any significant correlation of shifts in BF, BA, and BAZ (Fig. 6, A–C; all $P > 0.1$).

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induced shifts in the BF, BA, and BAZ of IC neurons were not interrelated to each other (Fig. 6).

Previous studies have shown that neural tuning to one signal parameter is affected by other parameters such that the frequency, amplitude, and direction selectivities of IC neurons are interrelated to each other (Grothe et al. 1996; Jen and Zhang 2000; Jen et al. 1987; Poon et al. 1990). For this reason, one may argue that the corticofugally induced shift in the BA or BAZ of IC neurons may be simply a result of corticofugally induced BF shift. In agreement with our previous studies (Jen and Zhou 2003; Zhou and Jen 2005), our following data do not appear to support this notion. First, corticofugally induced BAZ shift of IC neurons (an average of 7.4° with BF shift of 1 kHz) is far larger than the BAZ shift due to BF shift (an average of 1.5° with BF shift of 1 kHz) (see Fig. 4 of Poon et al. 1990). Second, cortical electrical stimulation does not always produce shifts in both BF and BA or BF and BAZ of an IC neuron. For example, cortical electrical stimulation simply produces the shift in BF but not in BA and/or BAZ of some IC neurons (Table 1, types IIa and IIIa). For other IC neurons, however, cortical electrical stimulation produces shifts in the BA and/or BAZ even without producing a shift in BF (Table 1, types IIb, IIIb, and IIIc). Finally, corticofugally induced shifts in the BF, BA, and BAZ do not significantly correlate with each other (Fig. 6).

In the present study, we observed that cortical electrical stimulation produced a shift of none, one, two, or all three measurements (i.e., BF, BA, and BAZ) toward the value of stimulated cortical neuron (Fig. 1; Table 1). When cortical electrical stimulation produced shifts of two measurements, we observed shifts of BF and BAZ in 12 (23%) collicular neurons and shifts of BA and BAZ in 7 (13%) collicular neurons (Fig. 1, B and C; Table 1). However, we did not record collicular neurons with shifts of BF and BA after cortical electrical stimulation. We believe that the lack of such collicular neurons is simply due to small sampling size.

We observed that corticofugally induced shift in each measurement was correlated with measurement difference between recorded collicular and stimulated cortical neurons (Fig. 5, D–F), but shifts of three measurements were not correlated with each other (Fig. 6). These observations indicate that multi-parametric corticofugal modulation is based on the difference in auditory selectivity between sub-cortical and cortical neurons. A recent study by Ma and Suga (2007) showed that cortical electrical stimulation produced shifts in the BF, best duration, and BA of collicular neurons in *E. fuscus* when these...
measurements of collicular and stimulated cortical neurons were “unmatched.” However, their study did not examine whether the corticofugally induced measurement shift was correlated with each measurement difference between collicular and cortical neurons. They also did not study the relationship among these measurement shifts and thus could not conclude whether corticofugal modulation of a single collicular neuron in different domains is interrelated to each other. Nevertheless, their study and ours show that multi-parametric corticofugal modulation can be mediated through the same subcortical neuron.

Symmetrical BF shift versus asymmetrical BA and BAZ shifts

Previous studies have shown that cortical electrical stimulation produces two types of BF shifts, centripetal (i.e., BF shifts toward that of AC neuron) or centrifugal (i.e., BF shifts away from that of AC neuron), for these BF unmatched collicular neurons based on BF differences between collicular and cortical neurons (Ma and Suga 2001b; Suga and Ma 2003). Although centripetal shift occurs in a large area around the “matched” neurons, centrifugal shift only occurs in the narrow area surrounding the centripetal area. In E. fuscus, BF differences for these unmatched collicular neurons with centripetal BF shifts were less than ~10 kHz. By contrast, BF differences for these collicular neurons with centrifugal BF shifts were between ~10 and 15 kHz. Also the average amount of centrifugal BF shifts was much smaller than that of centripetal BF shifts (Ma and Suga 2001b; Suga and Ma 2003).

In the present study, the BF differences for unmatched collicular neurons were ~8 kHz, and the BFs of these neurons were always shifted toward those of AC neurons after cortical electrical stimulation (i.e., centripetal BF shifts). In addition, we showed that cortical electrical stimulation produced symmetrical shift of the BF of IC neurons (Fig. 1, Aa, Ba, and Da), in agreement with previous studies in bats and mice (Jen and Zhou 2003; Yan and Ehret 2001, 2002; Yan et al. 2005; Zhou and Jen 2005). Different from these findings, Yan and Suga (1998) reported that cortical electrical stimulation produced asymmetrical BF shift in E. fuscus such that BF shift only occurred when IC neurons had higher BF than paired AC neurons. We do not know if these inconsistent observations are due to different stimulation conditions or sampling bias.

Different from symmetrical shift in the BF of IC neurons, we observed asymmetrical shift in the BA or BAZ of IC neurons such that cortical electrical stimulation only produced shift in collicular BA that was lower than cortical BA (Fig. 1, Ab, Ch, and Eb) or a shift in collicular BAZ that was more lateral than cortical BAZ (Fig. 1, Ac, Bc, Cc, and Fc). Previous studies have shown that corticofugal modulation is both amplitude- and azimuth-dependent (Jen et al. 1998; Zhang et al. 2000; Zhou and Jen 2000b, 2005). For example, the degree of corticofugal modulation of auditory selectivity of IC neurons decreases with increasing sound amplitude (Jen et al. 1998; Zhang et al. 2000; Zhou and Jen 2000b) and with the movement of sound source from lateral to middle angles (Zhou and Jen 2005). It then follows that the strength of corticofugal modulation of collicular rate-amplitude function would be greater for the low- than for the high-amplitude limb. Similarly, the strength of corticofugal modulation of collicular directional sensitivity curve would be greater for lateral than for the medial limb. Conceivably, this uneven strength of corticofugal modulation of the rate-amplitude function and directional selectivity curve of IC neurons may contribute to the asymmetrical shift of BA and BAZ of IC neurons after cortical electrical stimulation.

Functional significance

The processing of auditory information is considered to be based on neural integration occurring within the ascending auditory pathway through excitatory and inhibitory interaction (Suga 1997). Many studies have shown that this ascending information processing is modulated by the corticofugal system in multi-parametric domains (for review, see Suga and Ma 2003). This multi-parametric corticofugal modulation may be mediated through different subcortical neurons or through the same neuron or a combination of both. Our study shows that multi-parametric corticofugal modulation may be mediated through the same subcortical neuron although we do not rule out the other two possibilities.

As almost all biological meaningful sounds are complex sounds, multi-parametric corticofugal modulation can certainly plays an indispensable role in the improvement of sub-cortical processing of these complex sounds. We have shown that the corticofugal system modulates the BF, BA, and BAZ of the same IC neuron in a specific and systematic way that is based on the difference in auditory selectivity between IC and AC neurons (Figs. 1 and 5). As a result, collicular BA, BA, and BAZ shift toward those of stimulated cortical neuron (Figs. 1 and 2). Such modulation leads to more collicular neurons tuned to sounds that maximally excite the paired AC neurons and thus an “over-representation” of the modulated signal parameters in the IC. This improvement of multi-parametric subcortical auditory signal processing is considered as one of most important functions of the corticofugal system (He 2003; Suga et al. 2000). Neural basis underlying the corticofugal modulation of tuning for same IC neuron to multiple stimulus parameters such as the cellular mechanism and involved synaptic transmitter, however, remains to be explored.

It should note that here we used bats as a mammalian model to study the multi-parametric corticofugal modulation of collicular auditory signal processing. Bats rely heavily on acoustic signal processing for survival and thus have prominent auditory nuclei that facilitate electrophysiological study of central auditory signal processing. Most importantly, the ascending and descending auditory systems of bats are fundamentally similar to other nonecholocating mammals. It is therefore conceivable that multi-parametric corticofugal modulation of signal processing in the same IC neuron may be common across all mammals. Indeed, recent studies in mice have shown that cortical electrical stimulation also produces shifts of collicular BF and MT toward cortical BF and MT (Yan and Ehret 2001, 2002; Yan et al. 2005).

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