Descending Projections From Auditory Cortex Modulate Sensitivity in the Midbrain to Cues for Spatial Position

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Nakamoto KT, Jones SJ, Palmer AR. Descending projections from auditory cortex modulate sensitivity in the midbrain to cues for spatial position. J Neurophysiol 99: 2347–2356, 2008. First published April 2, 2008; doi:10.1152/jn.01326.2007. The function of the profuse descending innervation from the auditory cortex is largely unknown; however, recent studies have demonstrated that focal stimulation of auditory cortex effects frequency tuning curves, duration tuning, and other auditory parameters in the inferior colliculus. Here we demonstrate that, in an anesthetized guinea pig, nonfocal deactivation of the auditory cortex alters the sensitivity of populations of neurons in the inferior colliculus (IC) to one of the major cues for the localization of sound in space, interaural level differences (ILDs). Primary and secondary auditory cortical areas were inactivated by cooling. The ILD functions of 46% of IC cells changed when the cortex was deactivated. In extreme cases, the ILD functions changed from monotonic to nonmonotonic during cooling and vice versa. Eight percent of the cells became unresponsive after deactivation of the auditory cortex. Deactivation of the cortex has previously been shown to alter the maximum spike count of cells in the IC; the change in normalized ILD functions is shown to be separate from this effect. In some cases, the ILD function changed shape when there was no change in the maximum spike count and in other cases there was no change in the shape of the ILD function even though there was a large change in the maximum spike count. Overall, the sensitivity of the IC neural population to ILD is radically altered by the corticofugal pathway.

INTRODUCTION

It has long been known that the cortico-collicular pathway (the descending projection from auditory cortex to the inferior colliculus or IC) can alter the responses of IC neurons (Amato et al. 1969; Massopust Jr and Ordy 1962; Syka and Popelar 1984), but until recently the functional implications of this descending modulation were largely unexplored. The descending projections are profuse and bilateral (Oliver 2005; Winer 2005; Winer et al. 1998), suggesting that the descending projections play a substantial role in auditory processing in the IC.

Descending projections to the inferior colliculus arise from all areas of the auditory cortex (Winer et al. 1998). The projections from the tonotopic and the nontonotopic cortical areas to the IC are anatomically ordered and focal (Winer et al. 1998) and are mostly excitatory. The projections are strongest to the dorsal cortex and external nucleus of the IC. However, this does not limit the descending effects to these areas since there are strong intracollicular and commissural connections from the dorsal cortex to both the central nucleus and the external cortex that are both excitatory and inhibitory. In addition, the projection patterns of the cortico-collicular connections mimic the topographical organization of the intracollicular connections (Saldana et al. 1996), suggesting that these connections also interact.

In vision, feedforward (ascending) and feedback (descending) connections have been recognized as forming a circuit, rather than isolated connections that can be logically segregated according to function. Layer 6 cells in primary visual cortex (V1) provide 30% of the synaptic input to lateral geniculate nucleus (LGN) relay cells (Sherman and Guillery 2002). The cells in the LGN send reciprocal connections back to V1 layers 4 and 6. This particular arrangement of connections suggests that layer 6 cells in V1 can regulate the transfer of retinal input to the central visual system. Functionally, the cells in the LGN that receive feedback have greater sensitivity and specificity to moving visual stimuli (Sillito et al. 2006; Wang et al. 2006).

Although such reciprocal anatomical connections have not been shown in the auditory system at the level of the IC (Fig. 1, hypothetical outline of connections), similar functional effects have been demonstrated. In the bat, repeated focal electrical stimulation of cells in the primary auditory cortex (AI) has been shown to alter the responses of frequency-matched IC cells. Alteration of frequency tuning, duration tuning, delay tuning, minimum threshold (Suga et al. 2000), and, most relevant to this study, spatial tuning (Zhou and Jen 2005) have been demonstrated. The spatial tuning of IC cells was modified toward the spatial tuning of the electrically stimulated AI cells, suggesting that activation of AI cells could adjust the spatial tuning of IC cells to match the spatial tuning of the activated AI cells. A key feature of these studies has been the use of focal stimulation and, in some cases, focal inactivation. When the entire auditory cortex is inactivated or strongly electrically stimulated no shifts in the frequency response of the IC cells were found (Suga et al. 2000), but the effects of such global cortical inactivation or activation have not been tested for IC spatial tuning.

A major cue for sound localization in humans and other terrestrial mammals is the difference in sound level (interaural level differences [ILDs]) that results from the shadowing by the head of sounds coming from the opposite side. ILDs are...
Anesthesia and surgical preparation

In all, 12 pigmented guinea pigs of both sexes (weighing 400–1,000 g) contributed to this study. Anesthesia was induced with urethane (1.1 g/kg in 20% solution, intraperitoneal) supplemented as necessary by Hypnorm (fentanyl citrate, 0.315 mg/ml; fluanisone, 10 mg/ml, intramuscular) to maintain areflexia. A single dose of atropine sulfate (0.06 mg/kg, subcutaneous) was given to reduce bronchial secretions. All animals were tracheotomized and respired with oxygen to maintain normal end-tidal CO2 levels. Core temperature was maintained at 38°C by a heating blanket and rectal probe. The animals were placed in a stereotaxic frame, with hollow plastic specula replacing the ear bars, inside a sound-attenuating room. The bullae on both sides were vented using a polyethylene tube to equalize pressure across the tympanic membrane. Additionally, the posterior fossa was opened to reduce respiratory pulsations of the brain. A 7 × 7-mm craniotomy was performed over the right auditory cortex and a second 4 × 4-mm craniotomy was performed over the right inferior colliculus and the dura was removed. The craniotomy over the auditory cortex was large due to the size of the cooling loop. Multielectrodes were inserted into the IC and the auditory cortex. During recordings the surface of the brain was covered in 1.5% agar to stabilize the recordings and to prevent desiccation.

All experiments were performed in accordance with the 1986 UK Animals (Scientific Procedures) Act.

Stimulus presentation and recordings

Recordings were made in auditory cortex and the IC using four to eight individual glass-coated tungsten electrodes (Fig. 1) in a linear array attached to a single circuit board (Bullock et al. 1988), with tips aligned and separated by about 200 microns. The multielectrodes were fed into a Tucker Davis Technologies (TDT) Medusa headstage amplifier (Alachua, FL). All electrodes were advanced together. Spikes were analyzed with a TDT System 3 running Brainware (developed by J. Schnupp, University of Oxford, UK). Candidate spikes were amplified and discriminated from background noise on-line using a software level discriminator. Off-line, a Plexon (Dallas, TX) software spike sorter was used to isolate action potentials from single neurons and responses were checked for systematic shifts over time. Auditory stimuli were delivered dichotically through sealed acoustic systems, composed of modified Radio Shack 40-1377 tweeters joined via a conical section to a damped, 2.5-mm diameter probe tube that fitted into the speculum. The multiple electrode arrays could span large parts of the tonotopic axis and the choice of stimuli reflected this fact (wideband noise and tones over wide frequency ranges), ensuring that as far as possible we could simultaneously collect activity from as many electrodes as possible.

The search stimulus was a wideband noise (duration 100 ms) gated on and off with cosine-squared ramps lasting 8 ms and with a repetition period of 200 ms. All stimuli were generated by the TDT System 3. When a unit was isolated the minimum response threshold and the frequency response area were determined. For all units the frequency response areas were measured using 961 tone pips, randomly interleaved and presented at intervals of 800 ms. Attenuations of 10–100 dB in 3-dB steps (from a maximum of ~100 dB SPL) were used and the frequencies ranged over 6 octaves from 50 to 30,000 Hz in five steps per octave.

We previously observed and reported that the responses to temporally varying sounds (Rees and Palmer 1989) are often greater than those to static sound and we therefore used sinusoidally amplitude modulated (SAM) broadband noise signals, which additionally allowed us to assess the effects of cortical deactivation on temporal coding. The effects on temporal coding will be presented in a
subsequent paper. The depth of modulation was 100% and the duration was 1,000 ms. The modulation frequencies used for most cells was 50 Hz, although 29 cells were tested at 10, 50, and 100 Hz in a pseudorandom order. The broadband noise stimuli were presented over a natural range of ILDs (+20 to −20 dB) and the average binaural level was kept constant. These values would correspond to sounds that originate on the left side of the head (positive ILDs), directly in front (ILD of 0 dB) or on the right (negative ILDs). The majority of cells were tested at an average binaural level of 60 dB SPL. Each stimulus was repeated 15 times.

Cortical cooling

We collected a full set of data before, during, and after inactivating the descending cortical inputs to the IC by reversibly cooling the auditory cortex. Over a 5-min period the surface of the right auditory cortex was cooled to 2–3°C using a 4-mm-diameter cryoloop (Lomber et al. 1999). The cryoloop was placed over the primary auditory cortex. The area cooled by a 4-mm cryoloop is large enough to cover primary and secondary auditory cortical areas (Wallace et al. 2000). Temperatures were recorded by a thermistor probe that protruded onto the cortical surface below the cryoloop. Temperatures as low as this at the cortical surface inactivate all six layers of the cortex (Lomber et al. 1999). This is important because the descending projections arise from the deeper layers (Winer and Prieto 2001; see Fig. 1). These temperatures did not affect the white matter below auditory cortex and, due to the distance from the cooling loop, are unlikely to affect areas below the white matter (Lomber et al. 1999). Cortical deactivation was confirmed by the cessation of activity in the deeper cortical layers of primary auditory cortex, as recorded by microelectrodes. Following the presentation of a battery of sounds (lasting ≤45 min), the cryoloop pump was turned off and the cortical surface returned to near normal temperature over a few minutes. Although normal temperature at the cortical surface was achieved in just a few minutes, cortical responses took longer to return to normal. We waited 20 min to ensure full recovery, which was confirmed by reappearance of stimulus-locked activity on the cortical electrodes that was similar to the precooling condition. We then repeated the recordings. In this way, each neuron acted as its own control. We do not report any data here from neurons whose responses failed to recover to control levels.

Histology

During the withdrawal of the electrodes from the IC, electrolytic lesions were made in the ends and a center track of the linear array by passing a 5-μA current for 10 s (electrode negative) through the electrode. At the end of the experiment, the animal was overdosed with pentobarbital and perfused with 4% paraformaldehyde. The brain was removed and sectioned at 50 μm on a vibratome. Sections were stained for cytochrome oxidase and Nissl substance. The electrode tracks were located using the electrolytic lesions to provide confirmation of the recording locations within the IC.

Location within collicular area

A combination of physiological and histological methods was used to identify the location of recorded IC cells. Physiological responses of the outer layers of the external cortex of the IC (ECIC) were marked by broad or patchy tuning curves and habituating responses, although the deep layers of the ECIC receive lemniscal projections and resemble more the response of the central nucleus of the IC (CNIC). Physiologically the response of the CNIC is marked by a clear ascending tonotopic progression with narrowly tuned frequency response areas. Responses that clearly resemble the outer layer ECIC response were classified as belonging to the ECIC and checked against the histology. CNIC-like responses were checked against the

histology and cells that could not be histologically identified as being in either were excluded from analysis of the collicular area.

Results

We recorded responses from 209 neurons in the right IC of 12 anesthetized guinea pigs to SAM broadband noise with different ILDs.

Effect of cortical cooling

An example of the full cycle of IC responses with the cortex active, inactive, and following recovery is shown for a cell in the CNIC in Fig. 2 in the form of poststimulus time histograms (PSTHs). Before cooling, there was a large sustained response to SAM noise at +20 and +10 dB ILD (Fig. 2, top row). At −20 and −10 dB ILD there was a large onset response and a weak sustained response (Fig. 2, top row). During cooling, the response at +20 and +10 dB ILD was primarily an onset response (Fig. 2, middle row). However, there was a sustained response to the stimulus at −10 and −20 dB ILD (Fig. 2, middle row). The response at +20 and +10 dB ILD was reduced during cortical inactivation, whereas the response at −10 and −20 dB ILD was greater when the cortex was inactivated. In both cases, the onset and the sustained response of this neuron were altered during cortical cooling. The response after recovery from cooling resembled the response before cooling (Fig. 2, bottom row). The mean discharge rate of the cell in Fig. 2, as a function of ILD, is shown in Fig. 3.

Deactivating the auditory cortex altered ILD sensitivity functions of neurons in the IC. Before inactivation the cell in Figs. 2 and 3 responded with a sigmoidal ILD function, typical of the IC (Irvine and Gago 1990), responding best to stimuli with positive ILDs and progressively weaker as the stimulus levels were changed to negative ILDs (Fig. 3, dotted line). Such a neuron would be able to signal a change in ILD by altering its discharge rate over a 20-dB range of ILD. When the cortex was inactivated this cell responded best to stimuli with −10 and 0 dB ILD and responded weakly to stimuli with positive ILDs (Fig. 3, solid line), as was also evident from the PSTHs in Fig. 2. When the auditory cortex recovered from inactivation the responses became indistinguishable from those measured before cortical inactivation (Fig. 3, dashed line). Additional examples of changes in sensitivity to ILD are shown in Fig. 4. These effects of inactivating the auditory cortex can be quantified by two measures of ILD sensitivity: the 50% response point and the dynamic range (the range of ILDs between 10 and 90% of the maximum response; Irvine and Gago 1990). These measures are shown in Fig. 4A as dashed and dotted horizontal lines. Deactivating the cortex resulted in a shift toward negative ILDs for the cell in Fig. 4A. The 50% response point changed from 8 dB ILD precooling to −5 dB ILD during cooling, a decrease of 13 dB ILD (Fig. 4A, dotted line). The dynamic range was similar during cortical deactivation. Before cooling the dynamic range was 27 dB ILD wide (from 19 to −8 dB ILD) and during cooling it was 24 dB ILD wide (from 8 to −16 dB ILD), an increase of only 3 dB. The ILD function of the cell in Fig. 4B shifted toward positive ILDs. The 50% response point changed from −7 dB ILD...
precooling to 11 dB ILD during cooling, an increase of 18 dB ILD. The dynamic range changed from 16 to 24 dB ILD, an increase of 8 dB ILD. More extreme changes in the shape of the response functions also occurred during cortical deactivation. The cell in Fig. 4C changed from a monotonic ILD function to a nonmonotonic ILD function. The 50% response point changed from 2 to −11 dB ILD with little change in the dynamic range (from 10 to 12 dB ILD). The cell in Fig. 4D changed from a nonmonotonic ILD function to a monotonic ILD function. The 50% response point changed from −13 to 3 dB ILD.

**FIG. 2.** Poststimulus time histograms (PSTHs) of the responses of a single inferior colliculus cell, plotting the spike count (y-axis) against the time (x-axis) from stimulus onset to offset. Sinusoidally amplitude modulated (SAM) stimuli were played at 5 interaural level differences (20 to −20 dB ILD, columns), corresponding to stimuli arising from the left side of the head (20 dB ILD) to the right side of the head (−20 dB ILD). The response to these stimuli was recorded before, during, and after cortical inactivation by cooling (rows).

**FIG. 3.** The mean discharge rate as a function of the interaural level difference (ILD) for the neuron shown in Fig. 2. The ILD functions are plotted for cortex active (•, dotted line), during cortical cooling (●, solid line), and following recovery from cooling (□, dashed line). The ILD functions were normalized to the maximum and minimum for each condition to emphasize the shape of the function.

**FIG. 4.** Normalized ILD functions as in Fig. 3 for 4 other IC neurons. Deactivating the cortex resulted in a range of effects on ILD functions in the IC. There were shifts along the ILD axis, both toward negative ILDs (A) and toward positive ILDs (B). The most striking effect was a change from monotonic to nonmonotonic ILD functions (C) and vice versa (D). The dotted line in A represents the 50% point. The space between the dashed line represents the 10–90% dynamic range.
dB ILD and the dynamic range doubled from 16 to 33 dB ILD. Some neurons (8% of the population) were completely inhibited at all ILDs when the cortex was inactivated, even though they generally had stereotypical ILD functions when measured at the start. Two examples of such a response are shown in Fig. 5.

Two classes of cells were defined: “shifted” and “unshifted.” Cells in which the 50% point changed by \( \pm 5 \) dB ILD or the dynamic range changed by \( \pm 10 \) dB ILD were classified as “shifted” by cortical deactivation (36% of the population; Table 1). Note that some cells changed their dynamic range during cooling but not the 50% point (Fig. 6, black bars in the center) and there are cells that changed their 50% point but not their dynamic range (Fig. 7, black bars in the center). Cells were classified as “unshifted” if the 50% point did not change by \( \pm 5 \) dB ILD and the dynamic range did not change by \( \pm 10 \) dB ILD. The 50% point and the dynamic range were calculated only for the descending slope. For example, only the slopes descending toward negative ILDs were calculated for the nonmonotonic response in Fig. 4, C and D. A few cells had slopes descending toward positive ILDs and adding these slopes to the population analysis did not seem appropriate. Cells with little or no change in the ILD function were classified as “unshifted” (37% of the population; Table 1). The criterion for the categorization of “shifted” was chosen to highlight cells in which the ILD functions are altered by cortical cooling and is not meant to be a hard classification of cell type.

### TABLE 1. Categories of response type by percentage

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Inactivated</td>
<td>8</td>
</tr>
<tr>
<td>Shifted</td>
<td>36</td>
</tr>
<tr>
<td>Unshifted</td>
<td>37</td>
</tr>
<tr>
<td>Ascending slope shifted</td>
<td>7</td>
</tr>
<tr>
<td>Ascending slope unshifted</td>
<td>5</td>
</tr>
<tr>
<td>ILD insensitive during cooling</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
</tr>
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**Population data**

Although the effects of cortical cooling varied in magnitude there did not appear to be discrete classes of cells based on the magnitude of change. The change in the 50% response point of the ILD function for the population is plotted in Fig. 6 and the change in the dynamic range of the ILD function for the population is plotted in Fig. 7. The distribution of the change in the 50% point for “shifted” (black bars) and “unshifted” (gray bars) cells is centered at 0 dB ILD and decreases away from 0 dB ILD (Fig. 6). Although more “shifted” cells changed toward negative ILDs than positive ILDs (41 vs. 19 cells) the changes appear to make up a continuum rather than discrete classes of effects. Similarly, there do not appear to be discrete classes of change in dynamic range (Fig. 7), although more “shifted” cells increased their dynamic range than decreased (39 vs. 22 cells).
Another measure used to quantify ILD functions is the change in the spike rate across ILD (Semple and Kitzes 1993a). Spike rate measures of ILD sensitivity are not normalized; the dynamic range and the 50% response point are relative to the maximum and minimum responses of the cell (normalized). However, it is unclear whether the brain performs any kind of normalization as done when calculating the dynamic range and the 50% response point. Plotted in Fig. 8 is the change (cooling minus precooling) in the maximum spike rate of the population as a percentage (Fig. 8A) and as an absolute spike count (Fig. 8B). A negative value indicates a decrease in the response during cooling and a positive value indicates an increase in the response during cooling. Substantially more cells decreased their firing rate during cooling than increased their firing rate (82 vs. 50 cells). Unexpectedly, the effect of cortical deactivation on the change in spike rate between the “shifted” and “unshifted” categories was similar. There were many “unshifted” cells that changed their maximum spike count by >50% during cooling and yet retained a similar ILD function. The effect on the maximum spike rate seems to be partially separate from the degree of change in the ILD functions. A large change in the maximum spike rate does not necessarily accompany a change in the ILD function and vice versa. In Fig. 9 the change (cooling minus precooling) in the spike range (maximum spike rate minus the minimum spike rate) is plotted for the population. A negative value indicates that the difference between the maximum spike response and the minimum spike response decreased, indicating relatively smaller changes across ILD. More cells decreased in spike range than increased (86 vs. 46). Also, there was no apparent difference between the “shifted” and “unshifted” categories. The degree to which the spike range is compressed or expanded also does not seem to be related to the change in the ILD functions.

Twenty-nine cells were tested at an AM rate of 10, 50, and 100 Hz. Plotted in Fig. 9 is the response at the different AM rates for the measures used in this study. There was no significant difference (ANOVA, P < 0.05) in the 50% response point (Fig. 10A), the dynamic range (Fig. 10B), the percentage change in the maximum spike count (Fig. 10C), or the percentage change in the spike range (Fig. 10D).

A variety of cells were excluded from the population counts because their 50% point or the dynamic range could not be calculated. For example, 17 cells (8%, Table 1) that were completely inactivated by cortical cooling (Fig. 5, A and B) were excluded. Also excluded were 7 (3%, Table 1) cells that initially were sensitive to ILD and became insensitive during cooling (similar response across all ILDs; Fig. 11A) or vice versa.

A smaller population of cells was excluded from the population counts because they responded best to negative ILDs when the cortex was active. Fifteen (7%, Table 1) of these showed changes only on the ascending slope during cortical cooling (e.g., decreasing toward positive ILDs) (Fig. 11B) and 11 (5%, Table 1) were classified as “unshifted.”
Effects by collicular area

Seventy-seven cells were identified as being in the central nucleus of the IC (CNIC) and 76 cells were identified as being in the external cortex of the IC (ECIC). More cells in the ECIC (55%) were classified as “shifted” than in the CNIC (42%, Table 2). Fewer cells in the ECIC (37%) were classified as “unshifted” than in the CNIC (51%, Table 2). Cells that were completely inactivated by cortical deactivation were primarily found in the ECIC (6%, Table 2). The difference in the population classified as “shifted” and “unshifted” in the CNIC was small (9%, 7 cells); in the postanalysis it was noted that cells with similar classification tended to cluster. It is possible that the difference in the CNIC is due to sampling. However, there appears to be a greater percentage of “shifted” than “unshifted” cells in the ECIC.

DISCUSSION

There are a number of findings of the present study that are somewhat surprising, not least of which is the degree to which the descending projections actively modulate midbrain spatial sensitivity, even in this anesthetized preparation. We began this study after finding that deactivation of the auditory cortex had a profound effect on many cells in the auditory thalamus (Palmer et al. 2007). What was unexpected was that, in some neurons in the thalamus, inactivating the cortex had opposite effects on responses evoked by monaural contralateral stimuli.
TABLE 2. Categories of response type by nucleus

<table>
<thead>
<tr>
<th>Category</th>
<th>CNIC</th>
<th>ECIC</th>
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<tbody>
<tr>
<td>Unshifted</td>
<td>51% (39)</td>
<td>37% (28)</td>
</tr>
<tr>
<td>Shifted</td>
<td>42% (32)</td>
<td>55% (42)</td>
</tr>
<tr>
<td>Inactivated</td>
<td>1% (1)</td>
<td>8% (6)</td>
</tr>
<tr>
<td>Ascending slope shifted</td>
<td>6% (5)</td>
<td>0%</td>
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and monaural ipsilateral stimuli. Since we were unaware of any reports of the integration of inputs from the two ears occurring de novo at the level of the thalamus, this implied that the effects we saw were likely to be attributed to removal of the descending action of the cortex on nuclei below the thalamus. We therefore repeated the measurements at the auditory midbrain in the context of the present ILD paradigm. It is possible that the descending projections to the IC could directly affect ILD sensitivity that is generated at the level of the IC (Li and Kelly 1992; Pollak et al. 2002). However, some of the effects we show need not be generated at the IC because the auditory cortex also has descending projections to more subcortical nuclei. These effects could be inherited from the LSO, the dorsal nucleus of the lateral lemniscus, or possibly the cochlear nuclei, which are known to be the first levels at which cells show sensitivity to ILD (Ingham et al. 2006; Sumner and Shore 2004) and which do receive descending projections from the cortex (Saldana et al. 1993).

The complete cessation of firing of about 8% of our sample during cortical inactivation is also a little surprising. An active cortex is necessary for these cells to respond to stimuli. This would suggest that the cortico-collicular feedback is strong and can exert not only a modulating influence on ascending responses, but also a complete gating on or off of the activity of IC neurons.

For the cells that were completely inhibited during cooling it seems unlikely that we were recording from descending fibers passing through the IC, since the stimulus-driven activity of these neurons was, prior to cooling, indistinguishable from the rest of our sample.

The combination of the shifted ILD functions of 36% of our sample, the complete inactivation of 8%, and change in the ILD function of another 10% (cells similar to those depicted in Fig. 11) means that the population response in the IC to wideband stimuli from specific spatial positions is radically altered by the action of the descending projections from cortex.

Two effects of descending connections

The fact that the change in the shape of the ILD function does not seem to be related to the change in the spike rate suggests that two mechanisms are operating. The large changes in the spike rate that occur with little or no change in the ILD function are likely to arise from cells that inherit their ILD functions from lower auditory nuclei. The effect of the descending system on these cells primarily modulates the response magnitude of the cells (e.g., changes the number of spikes or the spike range). The shifts of the ILD function seem more likely to occur with ILD functions that are created de novo in the IC. Since this occurs when the maximum response is increased, decreased, or stays the same, it is likely that these effects are the result of a complex balance of excitation and inhibition.

Area of effect

With our current method the entire auditory cortex was likely to be inactivated along with its entire system of descending connections. It is therefore likely that the effects shown here are rather extreme. Those cells that were completely inhibited might show more subtle ILD changes in a normal situation where the descending pathway is likely to be modulating rather than gating the ascending responses.

Since cortico-collicular projections from tonotopic areas in the auditory cortex target frequency-matched cells in the IC (Lim and Anderson 2007; Saldana et al. 1996)—i.e., low-frequency cells target low-frequency cells and high-frequency cells target high-frequency cells—the feedback is normally specific to a focal and organized frequency-matched neural population. Projections from nontonotopic cortical areas are also anatomically well organized (Winer et al. 1998). In this study, we showed that cortical cooling altered responses across the entire IC; however, it is likely that in normal conditions the effects would be specific to discrete neural populations. Activation of discrete neural populations in the IC of the bat have been shown to occur when the auditory cortex is focally stimulated electrically (Lim and Anderson 2007; Suga et al. 2000) and discrete activation of the neural population of the guinea pig auditory cortex has been shown to occur when the IC is electrically stimulated (Lim and Anderson 2007).

Comparison to other studies

Previous studies using electrical stimulation have shown that electrical stimulation of AI cells causes the spatial tuning of frequency-matched IC cells to shift toward the spatial tuning of the electrically stimulated AI cell (Zhou and Jen 2005); this can be considered to be complementary to the present study. There are two possible reasons for this. First, the ILD functions in the IC may be created by a combination of ascending and descending binaural inputs. Electrical stimulation of AI cells may increase their influence on ILD functions in the IC, such as by sharpening their spatial tuning. Removal of this descending influence by cortical cooling may allow the IC cells’ response to more closely resemble their ascending input. Second, in this study both primary and secondary auditory cortical areas were likely to be deactivated, as opposed to cells in AI alone. The effect on the ILD functions noted may be caused by deactivation of secondary auditory areas, which also have large descending projections to the IC (Winer et al. 1998) and have been shown to be necessary for spatial localization (Malhotra et al. 2004).

Repeated focal stimulation or focal deactivation of AI cells is necessary to cause a change in frequency-matched cells in the IC (Suga and Ma 2003). Deactivation of the entire auditory cortex does not affect the frequency tuning of IC cells (Nwabueze-Ogbo et al. 2002; Yan and Suga 1999), although this is not the case for ILD tuning of IC cells as we have shown here. ILD functions in the IC are altered by nonfocal deactivation of the auditory cortex. This suggests that ILD functions in the IC are strongly affected by the corticofugal system. The differ-
ences between the frequency tuning and the ILD tuning may be due to the different nature of the stimuli. Frequency tuning originates monaurally. ILDs are created in the LSO and IC by combining input from both ears. Potentially, integration of responses between the two ears could be under greater descending control than monaural auditory responses.

**Adaptation**

The changes in the responses of collicular neurons to particular ILD cue values appear at first sight to be consistent with at least one function that has been proposed for the cortico-collicular pathway. Ferrets and humans trained in a localization task make large errors when one ear is plugged, thereby disrupting the binaural localization cues. However, after about a week of further testing both ferrets and humans can regain the preplugging localization accuracy (Hofman et al. 1998; Kacelnik et al. 2006). When the earplug is removed both are able to recover to preear plug performance after a few trials. Additionally, reinserting the earplug weeks later had a significantly less disruptive effect on localization performance compared with the initial ear plugging. After the initial adaptation, the subjects are capable of quickly switching between the two modes, suggesting a relatively fast adaptation of their use of the spatial cues. This adaptation process has been described as a reweighting of the available localization cues (Kacelnik et al. 2006). When the descending cortical inputs to the midbrain are lesioned, ferrets lose the ability to adapt to the monaural earplug (King 2007). Thus the descending pathway must be capable of changing the responses in the midbrain to localization cue values, as indeed we have demonstrated here. However, the pathway in the ear-plugged ferrets appears capable of deemphasizing altered ILD cues in favor of unaltered interaural time differences and monaural cues. The changes in ILD functions we show here would not seem consistent with this action, although the complete gating of many ILD-sensitive cells could be.

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**References**


