Corticofugal Modulation of Initial Sound Processing in the Brain

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The brain selectively extracts the most relevant information in top-down processing manner. Does the corticofugal system, a “back projection system,” constitute the neural basis of such top-down selection? Here, we show how focal activation of the auditory cortex with 500 nA electrical pulses influences the auditory information processing in the cochlear nucleus (CN) that receives almost unprocessed information directly from the ear. We found that cortical activation increased the response magnitudes and shortened response latencies of physiologically matched CN neurons, whereas decreased response magnitudes and lengthened response latencies of unmatched CN neurons. In addition, cortical activation shifted the frequency tunings of unmatched CN neurons toward those of the activated cortical neurons. Our data suggest that cortical activation selectively enhances the neural processing of particular auditory information and attenuates others at the first processing level in the brain based on sound frequencies encoded in the auditory cortex. The auditory cortex apparently implements a long-range feedback mechanism to select or filter incoming signals from the ear.

Key words: auditory cortex; corticofugal; cochlear nucleus; neural plasticity; neurophysiology; mouse

Introduction

Hearing in nature encounters noisy environment (Feng and Ratnam, 2000). Behavioral studies from the 1950s have described the brain's automatic selection of sound; one is able to selectively listen to one sound and reject or attenuate the perception of others (Broadbent, 1952; Cherry, 1953). The selection comprises top-down processing based on intention, experience and expectation (Grossberg, 1999; Alain, 2007; Gilbert, 2007). A fundamental issue that lies underneath the automatic sound selection is selective neural processing of auditory information. From the viewpoint of neurobiology, the crucial question is how the brain implements top-down selection. The behavioral characteristics of automatic sound selection determine that the underlying neural substrate must be a back projection system and is able to implement selective sound processing based on auditory information already registered in the higher auditory processing levels.

The corticofugal system is a back projection system capable of providing top-down information flow. There are six hierarchical information processing levels in the central auditory system. The highest level is the auditory cortex where the learned or experienced sounds are registered (Edeline et al., 1993; Recanzone et al., 1993; Bakin and Weinberger, 1996;

Pantev et al., 1998; Zhang et al., 2001, 2006; Ma and Suga, 2003; Yan and Zhang, 2005; Polley et al., 2006; Alain et al., 2007; Froemke et al., 2007; Ji and Suga, 2007). The lowest level is the cochlear nucleus (CN) that gates all incoming signals from the ear to the brain (Kiang et al., 1967; Evans, 1975; Liberman and Kiang, 1978; Feng and Vater, 1985; Taberner and Liberman, 2005). Neurons in the deep layers of the auditory cortex send descending (corticofugal) fibers directly to most subcortical nuclei including the CN (Winer et al., 2001; Doucet et al., 2002; Coomes and Schofield, 2004a; Schofield and Coomes, 2005; Meltzer and Ryugo, 2006; Bajo et al., 2007; Coomes Peterson and Schofield, 2007). The characteristics of the anatomical structures suggest that the central auditory system has the neural circuitry through which the auditory cortex could implement long-range feedback to control the incoming information from the ear.

Many studies in the visual, auditory and somatosensory systems have unveiled that sensory cortices differentially modulate subcortical neuron activities in a highly specific manner (Sillito et al., 1994; Yan and Suga, 1996; Zhang et al., 1997; Zhou and Jen, 2000, 2007; Yan and Ehret, 2002; Malmierca and Nuñez, 2004; Yan et al., 2005; Castellanos et al., 2007; Ma and Suga, 2007). In the auditory system, focal cortical activation enhances the thalamic and midbrain processing of auditory information that is encoded by activated cortical neurons (Suga and Ma, 2003). Cortical activation even modulates cochlear hair cells in a frequency-specific way (Xiao and Suga, 2002). Because the CN is the gate of the central auditory system, selective corticofugal modulation of CN neurons could be an important mechanism for controlling information flow to the brain, i.e., for early sound selection. Up to date, little is known how the auditory cortex improves or adjusts sound information processing in the CN.

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Materials and Methods

The impact of the auditory cortex on the auditory information processing in the CN was examined by observing the changes of auditory responses and frequency tunings of CN neurons after focal electrical stimulation (ES) of the primary auditory cortex (Fig. 1A). Forty-one female C57 mice (Charles River Laboratories) aged 4–7 weeks and weighing 14.6–24.0 g were used in this study. Animal preparation, acoustic stimulation, electrical stimulation of the auditory cortex, recording of action potentials and data processing were mostly the same as those described previously (Yan and Ehret, 2002; Yan et al., 2005; Jafari et al., 2007; Wu and Yan, 2007). All protocols and procedures were in accordance with the Canadian Council on Animal Care and approved by the Animal Care Committee of the University of Calgary (protocol number: M04044).

Animal preparation. Under anesthesia with a mixture of ketamine (85 mg/kg, i.p.) and xylazine (15 mg/kg, i.p.), the mouse's head was fixed in a custom-made head holder by rigidly clamping between the palate and nasal/frontal bones. The mouth bar was adjusted to align the bregma and λ points of the skull in one horizontal plane. The scalp was incised along the midline and subcutaneous tissue and muscle were removed to expose the skull. Two holes measuring 2 mm in diameter were drilled in the skull to expose the right cerebellum above the CN (5.1–5.6 mm posterior to bregma, 2.3–2.8 mm lateral to the midline) and the left auditory cortex. The right CN and left auditory cortex were selected because the ascending auditory pathway runs from the CN to the contralateral cortex. During surgery and all recording sessions, the animal's body temperature was maintained at 37°C by a feedback-controlled heating pad. Anesthetic levels were maintained by additional doses of ketamine (17 mg/kg, i.p.) and xylazine (3 mg/kg, i.p.) when the animal exhibited responses to tail pinching. All experiments were performed in a soundproof chamber.

Acoustic stimulation. Tone bursts (60 ms duration with 5 ms rise and fall times) were used as acoustic stimuli. They were digitally synthesized and then converted into analog sinusoidal waves by an Enhanced Real-time Processor (RP2; Tucker-Davis Technologies). The signals were then fed to a tweeter via a digital attenuator (PA5) and power amplifier. The output amplitude of the tone bursts was expressed as decibel sound pressure level (dB SPL, ref. 20 μ Pa). The tweeter was placed 45° to the right of and 130 cm away from the mouse's right ear. During calibration, the tweeter was driven by 20 volt sinusoidal peak-to-peak bursts without attenuation. The amplitudes of tone bursts were measured and calibrated at the position of animal right ear with a condenser microphone (Model 2520; Larson-Davis Laboratories) and a microphone preamplifier (Model 2200C; Larson-Davis Laboratories). Frequencies and intensities of tone bursts were varied either manually or automatically with BrainWare software (Tucker-Davis Technologies).

Recording and electrical stimulation in the primary auditory cortex. A tungsten electrode of ~ 2 M Ω impedance was advanced, perpendicularly to the surface of the auditory cortex. The electrode was initially connected to the recording system. Signals recorded with the electrode were fed to a 16-channel preamplifier and were then amplified 10,000 times and filtered with a bandpass of 0.3–10 kHz with a RA16 module (Tucker-Davis Technologies). The output signals were observed on the oscilloscope and computer screen. During the electrode penetration, a tone burst with manual alteration of its frequency and amplitude was contin-

Figure 1. *A*, A schematic drawing of the mouse brain, including the corticofugal projection to CN as indicated by a solid dark line, and the sites of electrical stimulation and recording. *B*, Photomicrograph of the coronal section of the right brainstem at ~ 5.5 mm posterior to the bregma. *C*, Magnification of the area in a rectangle in *B*. A lesion site can be seen at the anteroventral cochlear nucleus (AVCN) as indicated by an arrowhead. AC, Auditory cortex; IC, inferior colliculus; MGB, medial geniculate body; MVN, medial vestibular nucleus; STN, spinal trigeminal nucleus; 4V, fourth ventricle; 5N, facial nucleus.

uously delivered at a rate of 1 per second. Tone-evoked action potentials were frequently found at ~ 300 μ m below the brain surface (layers III–IV) of the auditory cortex. The best frequency (BF) and minimum threshold of the recorded neurons were first measured. The minimum threshold was defined as the lowest sound amplitude across all frequencies and the BF was the frequency to which a neuron showed the largest response magnitude (spike number). The BF of the recorded neuron was first measured by manual alteration of tone frequency and amplitude. On the average, 5–8 electrode penetrations were made in each animal to determine the location of the primary auditory cortex. The electrode was then placed within the primary auditory cortex and penetrated until tone-evoked action potentials were observed. The BF and minimum threshold of the recorded cortical neurons were measured by manual alteration of tone frequency and amplitude. The responses of cortical neurons to tone bursts at different frequencies (10 dB above the minimum threshold) were then recorded and saved with BrainWare software. The BFs of the stimulated cortical neurons were determined based on the saved data. Thereafter, the electrode served as a stimulating electrode by switching the connection from the recording system to the output of an A360 constant current isolator (World Precision Instruments) of the stimulating system. The electrode was further advanced to a depth of ~ 700 – 800 μ m below the brain surface (deep layers) and was maintained in the same position throughout the experiment. The neurons at 700 – 800 μ m below the brain surface should have the same BFs as those at 300 μ m because of the columnar organization found in the auditory cortex (Abeles and Goldstein, 1970; Suga and Manabe, 1982). Negative pulses (monophasic, 0.1 ms, 500 nA constant current), generated by a Grass S88

Figure 2. *A*, Raster plotting of a typical change in auditory responses of a CN neuron before, during, and after ES. *B*, Magnification of the gray box in *A*, the initial development of the neuronal responses of this neuron to 10 kHz tone during ES. *C*, The change in the average latency is quantitatively illustrated. *D*, The time courses of changes in response magnitudes of this neuron to both 9 and 10 kHz tones. The asterisk indicates the best frequency of the stimulated cortical neurons.

stimulator (Astro-Medical) and the A360 constant-current unit (World Precision Instrument), were delivered to the primary auditory cortex through this electrode. An indifferent electrode for recording and electrical stimulation was placed on the brain surface just beside the stimulator.

Recording in the CN. Two tungsten electrodes of ~ 2 M Ω impedance separated by 100 μ m were connected to the TDT 16-channel preamplifier of the recording system and dorsoventrally advanced into the CN. During the electrode penetration, a tone burst with manual alteration of its frequency and amplitude was continuously delivered at a rate of 1 per second. Tone-evoked action potentials were commonly observed when the electrode tips were 2.5–3.6 mm below the surface of the cerebellum. The electrodes were then removed. Another penetration was made ~ 100 μ m anterior to the previous penetration and the same procedure continued until no tone-evoked action potentials were observed. Then the penetration was made 100 μ m either lateral or medial to previous penetrations and the above procedure repeated until the rostral boundary of the CN was determined. The electrodes were again removed. A final penetration was made in a range of 25–300 μ m caudal to the rostral boundary of the CN for recording the auditory responses of neurons in the anteroventral division of the CN. Once tone-evoked action potentials of CN neurons were observed, the BF and minimum threshold were audiovisually measured with various tone bursts delivered at a rate of 4 per second. The responses of CN neurons to various tone bursts were then recorded and saved with Brainware software (Tucker-Davis Technologies).

Experimental protocols. Once the BFs and minimum thresholds of CN neurons were measured, two experimental protocols were applied to evaluate the influence of the cortex on the activities of CN neurons.

One emphasized or highlighted how fast the changes were in CN auditory responses and how the response latency of the CN neuron was affected after cortical stimulation. In this protocol, a series of tone bursts separated by 500 ms was delivered to obtain frequency-dependent re-

sponses of recorded CN neurons. The tone frequency varied from 5 kHz below to 5 kHz above the BFs of given CN neurons with a 1 kHz increment. The tone amplitude was set at the minimum thresholds of given CN neurons so that neurons could only show responses to a few tone frequencies before cortical stimulation. A series of tone bursts was delivered every 10 s. The responses of CN neurons to the first 50 trials were recorded as control data. Starting from the 51st trial, a single electrical pulse was delivered to the primary auditory cortex 500 ms before the onset of the first tone burst. After 250 trials, the ES stopped but the tone bursts were continuously delivered until the ES-evoked changes in the auditory responses of CN neurons were recovered.

The second protocol focused on the frequency-dependent changes in CN auditory responses after cortical stimulation. Because this protocol was identical to what was used in our previous studies (Yan and Ehret, 2002; Yan et al., 2005), data were comparable with our previous findings. This protocol sampled the frequency tunings of CN neurons with a series of tone bursts separated by 250 ms. Tone frequency at 10 dB above the minimum thresholds of CN neurons varied from 3 to 40 kHz with a 1.0 kHz increment. The identical tone stimulation was repeated 15 times. After sampling the control data, electrical pulses were delivered to the primary auditory cortex at a rate of 4 per second for 7 min. Immediately after ES, the frequency tuning of the recorded CN neuron was continuously sampled with the same tone set every 30 min until the ES-evoked changes in frequency tuning were disappeared.

Data processing. Single-unit action potentials were isolated from the multiunit recording according to eight parameters of the waveform of action potentials; these parameters were peak, valley, spike height, spike width, peak time, valley time and two user-defined voltage values. The evaluated data included only neurons with stable spike waveforms over the entire recording session. Single-unit responses to a series of tone bursts were eventually displayed by dot rasters or peristimulus time histograms with a bin width of 1 ms.

In protocol one, the response latency, first-spike latency, and spike numbers were calculated based on 1 min time window (six-tone stimuli). The response latency of CN neurons was the average latency of all spikes, the first spike latency was the average latency of all first spikes and spike number was the count of spikes within the time window.

In protocol two, the excitatory frequency-response curve was derived from the response magnitudes of a neuron to a series of tone bursts.

Histology. On completion of the recording session, a 20-s-long and 1 mA electrical current was applied to the recording site in the CN through the recording and indifferent electrodes. The animal was given a cardiac perfusion with 10 ml of physiological saline and a mixture of 4% paraformaldehyde in 0.1 M phosphate buffer of pH 7.4. The brain was then removed from the cranium, fixed by immersion in 4% paraformaldehyde in a 0.1 M phosphate buffer and stored in phosphate buffered saline solution containing 20% sucrose at 4°C. After the brain was embedded with OCT (optimal cutting temperature) compound and frozen in 2-methylbutane, 40 μ m coronal brainstem sections were made with a cryostat. The tissue sections were mounted onto glass slides and stained using the Nissl method. The electrolytic lesion was examined under a light microscope. An example is shown in Figure 1, *B* and *C*.

Statistics. Data were expressed as mean $\pm$ SD. A *t* test was used to compare the differences between groups of data and numbers. A *p* value of <0.05 was considered to be statistically significant.

Results

We first examined the changes in response properties of CN neurons after focal ES of the auditory cortex in mice. Figure 2 shows an example of changes in responses of a CN neuron before, during and after the ES. This CN neuron originally showed strong response to a 9 kHz tone burst but no response to other tones including a 10 kHz tone burst (Fig. 2*A*, dots above zero). When 12-kHz-tuned cortical neurons were electrically stimulated, however, the response of this CN neuron to a 9 kHz tone burst gradually decreased and finally ceased. In contrast, its response to a 10 kHz tone burst emerged (Fig. 2*A*). The buildup of the response to the 10 kHz tone burst was closely observed. This CN neuron exhibited its first spike in response to the 10 kHz tone burst at the 12th cortical stimulus (120 s after the first ES). From the 12th stimulus to the 120th stimulus (first 20 min of ES), the number of spikes of this neuron in response to the 10 kHz tone burst gradually increased with extremely long spike latencies. After the 120th stimulus (20 min), this neuron showed much stronger response with greatly reduced response spike latencies (Fig. 2*B*). The changes in response latencies are quantified in Figure 2*C* in which the average latency of all spikes in a 1 min (six cortical stimuli) time window was calculated. The change in auditory response of this neuron slowly disappeared after the cessation of ES as shown in Figure 1*D* in which the average spike numbers in 1 min (six cortical stimuli) time windows were calculated. At 20 min after ES (120 cortical stimuli), this neuron showed equal response magnitudes to 9 kHz and 10 kHz. From this time point, the spike number in response to 10 kHz exceeded that to 9 kHz. As a result, the BF of this CN neuron shifted from 9 kHz to 10 kHz, i.e., toward the 12 kHz, the BF of the stimulated cortical neurons. The response to 9 kHz tended to cease at 31 min after the onset of ES (186 cortical stimuli). The responses of this neuron to 9 kHz and 10 kHz recovered at 158 min after the onset of ES (108 min after the cessation of ES).

Using the same procedure, we studied seven CN neurons in which the BFs were <1 kHz away from those of stimulated cortical neurons and another seven CN neurons in which the BFs were >1 kHz away from those of the stimulated cortical neurons. For simplicity, we called the former physiologically matched neurons and the latter physiologically unmatched neurons. Without exception, ES facilitated the auditory responses of matched CN neurons and suppressed those of unmatched CN neurons. In addition, the BFs of the unmatched neurons shifted toward the BFs of the stimulated cortical neurons (Fig. 2). Such BF-related changes in auditory response magnitudes and BFs of CN neurons will be addressed later with a procedure used in our previous studies (Yan and Ehret, 2002; Yan et al., 2005).

The data presented in Figure 2 also shows two additional phenomena. One is that the response latency increased at 9 kHz but decreased at 10 kHz after ES (Fig. 2*A*). The other is that the latency of ES-evoked changes in response magnitude was clearly shorter to the 10 kHz than to 9 kHz (Fig. 2*D*). This confirms that ES-evoked facilitation occurred more rapidly and was accompanied with a reduced response latency, whereas ES-evoked inhibition occurred at a later period, accompanied by an increased response latency. It was uncertain whether or not these two phenomena were applicable to the ES-evoked facilitation of the auditory responses of matched neurons and inhibition of unmatched neurons. To clarify this issue, the first-spike latencies of the recorded CN neurons were calculated in 1 min (six stimuli) time windows before, during and after the ES. Our data demonstrated that the averaged first-spike latency of seven matched

Figure 3. *A, B*, Changes in first spike latencies of matched (*A*) and unmatched (*B*) CN neurons as a function of time from the onset of ES.

Figure 4. Time required for 10% change, maximum changes, and 50% recovery in response magnitudes of the matched and unmatched neurons after ES. * $p < 0.05$, when matched and unmatched neurons were compared.

neurons gradually decreased (Fig. 3*A*) and that of seven unmatched neurons gradually increased (Fig. 3*B*) until the cessation of the ES.

We next calculated the periods of time required for a 10% change, the maximum change and a 50% recovery in the response magnitudes of CN neurons after the ES (Fig. 4). The time required for a 10% increase in the auditory response magnitudes of matched neurons was 2.6 ± 3.8 min ($n = 7$), which was significantly shorter than 14.6 ± 12.8 min ($n = 7$), the time required for a 10% decrease in response magnitudes of unmatched neurons ($p < 0.05$). The times of maximum change and 50% recovery were 54.7 ± 14.7 min and 93.0 ± 32.7 min ($n = 7$) for matched neurons, which were similar to 45.3 ± 22.9 min and 94.7 ± 43.0 min ($n = 7$) for unmatched neurons ($p > 0.05$). The ES influence occurred significantly earlier on matched CN neurons than that on unmatched ones.

To obtain comparable data regarding the frequency-specific changes in auditory response magnitudes and BFs of CN neurons, we measured frequency response curves (receptive fields) of 55 CN neurons before and after the ES by using our second protocol.

Three examples in Figure 5 show how ES changed the frequency tunings of CN neurons. In Figure 5*A*, the BFs of both cortical and CN neurons were 15 kHz. The ES augmented the auditory responses but did not alter the BF of this CN neuron. Figure 5*B* shows that the BF of this CN neuron shifted from 17 to 19 kHz after 22-kHz-tuned cortical neurons were stimulated, which resulted from the inhibition of the responses to tone bursts <18 kHz and the facilitation of the responses to tone bursts >18 kHz (Fig. 5*B3*). The overall response magnitude of this neuron

Figure 5. Three examples of the ES effects on frequency tunings of CN neurons. **A–C**, The ES did not change the BF but augmented the auditory responses of the matched CN neurons (**A**), whereas the ES shifted the BFs of the unmatched CN neurons toward the cortical BF (**B**, **C**). The shift of BFs resulted from differential facilitation and inhibition (**B3**, **C3**). The gray bars in the top two panels represent the BFs of the stimulated cortical neurons. In the bottom, the dark gray area represents inhibition, whereas the light gray area represents facilitation.

was suppressed; the spike number in the peak response to 17 kHz tone bursts before the ES was larger than that to 19 kHz tone bursts after the ES. In contrast, the neuron in Figure 5C shifted its BF from 16 kHz down to 13 kHz after an 11-kHz-tuned cortical neurons were stimulated, which resulted from the inhibition of responses to tone bursts >15 kHz and the facilitation of responses to tone bursts <15 kHz (Fig. 5C3). These examples clearly demonstrate that the ES could lead to completely different changes in auditory response magnitudes and frequency tunings of CN neurons, i.e., either the facilitation or inhibition as well as BF changes in either direction that were largely dependent on the BFs of the stimulated cortical neurons.

Analysis of all 55 neurons confirmed that the ES-evoked changes in response magnitudes of CN neurons were closely related to the BF differences between the stimulated cortical and the recorded CN neurons. After the ES, the auditory response magnitudes of CN neurons increased when the BF differences between the cortical and CN neurons were <1.0 kHz (matched neurons), whereas they decreased when the BF differences between the cortical and CN neurons were larger than 1.0 kHz (unmatched neurons). On the average, the response magnitude of matched neurons increased by $2.2 \pm 10.1\%$ and those of unmatched neurons decreased by $17.9 \pm 14.5\%$ when CN BFs were higher than cortical BF and by $19.8 \pm 15.1\%$ when CN BFs were lower than cortical BF (Fig. 6A). The ES-evoked changes in response magnitude were significantly different between matched and unmatched CN neurons ($p < 0.001$). The ES-evoked BF shifts of CN neurons were also correlated to the stimulated cortical BFs (Fig. 6B). For unmatched CN neurons, ES shifted CN BFs either higher or lower depending on the BFs of the stimulated cortical neurons. This was particularly the case when the BF differences between cortical and CN neurons ranged from -5 to 7 kHz. In other words, ES shifted CN BFs toward the BFs of the stimulated cortical neurons. However, ES did not alter the BFs of matched CN neurons.

Discussion

Our data clearly suggest that the auditory cortex specifically modulates the neural processing of auditory information in the cochlear nucleus in two ways. One is that cortical stimulation increased the auditory responses and shortened response latencies of the matched CN neurons but decreased and lengthened those of the unmatched neurons. The second involves the enhancement of the CN representation of the sound frequencies that are

Figure 6. **A**, **B**, ES-evoked changes in response magnitudes (**A**) and BFs (**B**) of CN neurons as the function of BF difference between the stimulated cortical and recorded CN neurons. These changes were clearly different between the matched and unmatched CN neurons. The gray boxes and bars in **A** represent the mean $\pm$ SD of BF shifts of all neurons in its representing range of BF difference, and the line in **B** is regression line.

emphasized in the auditory cortex, i.e., the shift of the BFs of unmatched CN neurons toward those of the activated cortical neurons. These findings support a recent report that musical experience enhanced human brainstem encoding of linguistic pitch presumably via corticofugal feedback (Wong et al., 2007). Such corticofugal modulation is consistent with our previous work involving the mouse midbrain. The mouse study reveals that focal cortical activation suppresses auditory responses and shifts BFs of unmatched midbrain neurons toward the BFs of the activated cortical neurons (Yan and Ehret, 2002; Yan et al., 2005). An important distinction here is that, for unmatched neurons, the ES suppresses auditory responses by up to 80% in the midbrain comparing with up to 43% in the CN (Fig. 6A). Similarly, the ratio of ES-evoked BF shift over BF difference is 0.58 in the midbrain but 0.41 in the CN (Fig. 6B). Earlier bat studies have already

demonstrated that the ES-evoked changes in auditory responses and BFs are larger in the auditory thalamus than those in the midbrain (Zhang et al., 1997; Zhang and Suga, 2000). Interestingly, the auditory cortex also implements highly specific modulation of auditory receptors in the cochlea via olivocochlear neurons; such modulation is probably smaller than corticofugal modulation of central nuclei (Xiao and Suga, 2002; Perrot et al., 2006). This suggests that corticofugal modulation cascades from the auditory thalamus down to the auditory periphery.

With all of these findings considered, a framework of a physiological model of top-down selection emerges in the central auditory system. The auditory cortex is an adaptive processor of auditory experience and learning (Dahmen and King, 2007). Because of the impact of top-down modulation through the corticofugal system, the auditory cortex automatically selects incoming signals from the ear based on cortical information that is emphasized through previous auditory learning and experience. The incoming signals are amplified if they match the emphasized information in the auditory cortex. Conversely, the incoming signals are attenuated or suppressed if they are not or are relatively less emphasized (Fig. 6). The differential changes in various information (frequency) channels are likely based on cortical impact on dynamics of auditory nerve-to-CN synaptic transmission and/or inhibitory modulation of CN neurons (Figs. 2A, B, 3A, 5). This top-down selection enhances step by step through corticofugal projections to other subcortical nuclei along the ascending auditory system. It should be noted here that cortical neurons also send descending fibers to the inferior colliculus and superior olivary complex that in turn project to the CN (Horváth et al., 2000; Doucet et al., 2002; Coomes and Schofield, 2004a,b; Bajo et al., 2007; Coomes Peterson et al., 2007). Therefore, the ES-evoked CN changes observed in this study can be a summation of direct and indirect corticofugal influences.

There are three fundamental requirements for the selective sound processing for hearing in nature. First of all, selective processing is directed by higher-order information processes. This requires a top-down mechanism that compares the registered information with incoming signals. Only the matched signal is selected and amplified, whereas others are suppressed (Cherry, 1953; Grossberg, 1999; Ahveninen et al., 2006; Gilbert and Sigman, 2007; Knudsen, 2007). Second, the higher-order processing levels should have efficient feedback pathways to lower-order processing levels. Because the top-down mechanism was originally proposed for the impact of higher-order cortical areas to lower-order cortical areas, the focus has been primarily on the intracortical feedback pathway. Recent evidence suggests that the impact of the cortex on subcortical nuclei must also be taken into account (Grossberg, 1999; Alain, 2007). Last, selective processing should ideally take place as early as possible so that the brain receives less irrelevant sound information and neural selective processing can be more efficient. Our work allows us to propose with considerable certainty that the corticofugal system, the top-down selection, is an effective neural substrate that comprises these elements or satisfies these requirements of automatic sound selection in the brain for hearing in nature.

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