Corticofugal modulation of duration-tuned neurons in the midbrain auditory nucleus in bats

Xiaofeng Ma and Nobuo Suga*

Department of Biology, Washington University, One Brookings Drive, St. Louis, MO 63130

Contributed by Nobuo Suga, October 1, 2001

Animal sounds, as well as human speech sounds, are characterized by multiple parameters such as frequency, intensity, duration, etc. The central auditory system produces neurons tuned to particular durations and frequencies of sounds emitted by a species. In bats, ''duration-tuned'' neurons are mostly sensitive to short durations and high frequencies of sounds used for echolocation. They are scattered in the frequency maps of the inferior colliculus and auditory cortex. We found that electric stimulation of cortical duration-tuned neurons modulates collicular duration-tuned neurons in both duration and frequency tuning only when collicular and cortical neurons paired for studies are within ±4 ms in best duration and within ±6 kHz in best frequency. There are four types of modulations: sharpening or broadening of duration tuning, and lengthening or shortening of best duration. Sharpening is observed in ''matched'' collicular neurons whose best durations are the same as those of stimulated cortical neurons, and it is accompanied by augmentation of the auditory responses at their best durations. The other three types of modulations are observed in ''unmatched'' collicular neurons whose best durations are different from those of stimulated cortical neurons. Lengthening or shortening of best duration is linearly related to the amount of the difference in best duration between collicular and cortical neurons. Corticofugal modulation is specific and systematic according to relationships in both duration and frequency between stimulated cortical and recorded collicular neurons.

auditory cortex | descending system | hearing | inferior colliculus | plasticity

The descending (corticofugal) auditory system forms multiple feedback loops on the ascending auditory system (refs. 1 and 2; see ref. 3 for review) and is cochleotopically organized (3, 4). In the mustached bat (*Pteronotus parnellii parnellii*), focal activation of the auditory cortex (AC) with electric pulses augments auditory responses of thalamic and collicular auditory neurons matched in best frequency (BF) to the activated cortical neurons and sharpens the frequency tuning of these subcortical neurons without shifting their BFs. Therefore, corticofugal modulation can improve auditory signal processing in the frequency domain by the matched neurons. Such corticofugal modulation is highly specific to matched neurons, because it does not occur for unmatched neurons. On the other hand, focal activation of the AC suppresses the auditory responses of subcortical unmatched neurons at their BFs and shifts their BFs. The amount of BF shift is proportional to the amount of the difference in BF between the recorded and stimulated neurons. That is, the larger the BF difference, the larger the amount of the BF shift. Therefore, corticofugal modulation is systematic. BF shift results in the adjustment (i.e., reorganization) of the cochleotopic (i.e., frequency) map (5). Focal inactivation of the AC evokes the suppression of auditory responses and the broadening of frequency-tuning curves of matched subcortical neurons without shifting their BFs, whereas it evokes the augmentation of auditory responses of unmatched subcortical neurons at their BFs and shifts their BFs. The direction of BF shift is exactly opposite that evoked by focal cortical activation with electric pulses (6). These observations indicate that the corticofugal system improves auditory signal processing and adjusts the frequency map in the medial geniculate body and the inferior colliculus (IC), and that the auditory responses and the map in the normal condition result from the interaction between the ascending and corticofugal systems.

Highly specific and systematic corticofugal modulation for the improvement and adjustment of signal processing occurs not only in the frequency domain but also in the time domain. In the mustached bat, ''delay-tuned'' neurons specialized for processing target-distance information have been found in the AC (7, 8), medial geniculate body (9, 10), and IC (11, 12). Focal activation of the cortical delay-tuned area, called the FM-FM area, augments the auditory responses of subcortical delay-tuned neurons matched in best delay to the activated cortical neurons and sharpens their delay tuning without shifting their best delays, whereas it suppresses the auditory responses and shifts the best delays of unmatched subcortical delay-tuned neurons. Focal inactivation of the cortical delay-tuned area evokes changes of subcortical delay-tuned neurons that are exactly opposite those evoked by focal cortical activation (13). In the big brown bat, electric stimulation of the AC sharpens frequency-tuning curves and directional sensitivity curves (14, 15) and shifts the BFs of collicular neurons (16, 17). Therefore, the corticofugal system modulates auditory signal processing in multiple domains: frequency, time, and direction.

Animal and human speech sounds are characterized by frequency and other parameters, including duration. The central auditory system creates many physiologically distinct types of neurons tuned to behaviorally relevant acoustic parameters (see refs. 18 and 19 for review). ''Duration-tuned'' neurons showing bandpass duration tuning are one of these types and have been found in bats (20–23), cats (24), chinchillas (25), mice (26), and frogs (27–29). In cats, chinchillas, and mice, the importance of duration-tuned neurons in auditory signal processing is not obvious because of the lack of neuroethological studies of auditory behavior of these animals. On the other hand, in bats and frogs, the duration-tuned neurons are turned to the durations of acoustic signals used by the species, so that these neurons have been considered to play an important role in the processing of species-specific sounds. Duration-tuned neurons in the IC and AC of bats are mostly tuned to short-duration sounds used for echolocation. They are scattered within the frequency maps of the IC and AC (20–23). No duration map has been found.

The corticofugal system improves collicular signal processing in the frequency domain and reorganizes the frequency map of the IC (5, 6, 16, 17), so that central auditory neurons are expected to be modulated in the frequency domain by the corticofugal system, regardless of whether they are specialized in processing auditory signals in nonfrequency domains. Duration-tuned neurons are tuned in both duration and frequency. Does

Abbreviations: AC, auditory cortex; IC, inferior colliculus; BF, best frequency; BDu, best duration.

*To whom reprint requests should be addressed. E-mail: suga@biology.wustl.edu.

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

 www.pnas.org/cgi/doi/10.1073/pnas.241517098

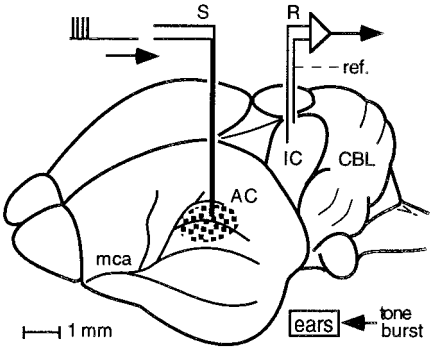

Fig. 1. Dorsolateral view of the brain of the big brown bat. A pair of stimulating electrodes (S) was inserted into the primary AC and a recording electrode (R) was inserted into the central nucleus of the IC. The ears were stimulated by tone bursts. CBL, cerebellum; mca, middle cerebral artery; ref., reference electrode.

the corticofugal system modulate collicular duration-tuned neurons in a specific and systematic way in duration, frequency, or both? We electrically stimulated cortical duration-tuned neurons and found that collicular duration-tuned neurons are modulated in a specific and systematic way according to relationships in both best duration (BDu) and BF between cortical and collicular neurons. Because corticofugal modulation of the frequency tuning of collicular neurons has been reported (refs. 5, 6, 14–17, and 30–32; see ref. 33 for review), we focused more on corticofugal modulation of duration tuning than on modulation of frequency tuning.

Materials and Methods

Materials, surgery, acoustic stimulation, cortical electric stimulation, recording of neural activity, and data acquisition and processing were similar to those described by Ma and Suga (17). Twelve adult big brown bats (*Eptesicus fuscus*) were used for the present experiments. Under neuroleptanalgesia and local anesthesia, a metal post was glued on the bat's skull. Physiological experiments were started 3–4 days after the surgery. The awake, nondrugged animal was placed in a polyethylene-foam body mold that was hung with an elastic band at the center of a soundproof room maintained at 31°C. The metal post glued on the skull was fixed to a metal rod with set screws to immobilize the animal's head, and the head was adjusted to face directly at a loudspeaker located 74 cm away. Holes (diameter, 50–100 μm) were made in the skull covering the AC and IC. Tungsten-wire electrodes (tip diameter, 6–8 μm) for recording action potentials or for electrically stimulating cortical neurons were inserted into the AC or the central nucleus of the IC through the holes (Fig. 1).

Acoustic Stimulation. A tone burst (0.5–100 ms with a 0.2- or 0.5-ms rise-decay time) was delivered at a rate of 5 per s. Its frequency, amplitude, and duration were varied manually for the measurements of BFs, minimum thresholds, and BDus of collicular and cortical neurons. To obtain a frequency-response curve, the tone burst was fixed at BDu and 10 dB above minimum threshold for a given neuron, and its frequency was varied around BF in 0.3- or 0.5-kHz steps. To obtain a duration-response curve, the tone burst was fixed at BF and the amplitude to which the duration-response curve was sharpest. On average, this amplitude was 18 $\pm$ 3.8 dB (n = 140) above minimum threshold for a given neuron. Then, the duration of the tone burst was varied around BDu in 0.5- or 1.0-ms steps.

Electric Stimulation. A 6-ms-long train of four monophasic electric pulses (100 nA, 0.2-ms duration, 2.0-ms interval) was delivered to cortical duration-tuned neurons at a rate of 10 per s for 30 min through a pair of tungsten-wire electrodes, the tips of which were 6–8 μm in diameter and were separated by 150 μm, one proximal to the other. Such electric stimulation would activate cortical neurons within a 60-μm radius (13). Electrodes were first used to measure BF and BDu of cortical neurons at a depth of 400–800 μm, and then used to stimulate them electrically. We do not know what types of neurons, other than the duration-tuned neuron electrophysiologically identified, were located within the 60-μm radius. What we do know is that in most orthogonal electrode penetrations, BDu and BF did not change with electrode depths, and that electric stimulation evoked specific changes in collicular duration-tuned neurons related to the BDu difference between the stimulated cortical and recorded collicular neurons. Therefore, we assumed that the electric stimulation stimulated cortical neurons with response properties similar to each other.

Definition of "Duration Tuning." According to our definition, a duration-tuned neuron showed a peak in its duration-response (impulse-count) function. Peak value at one duration (BDu) was $\geq$50% of the lowest value at durations longer than BDu and $\geq$30% of the lowest value at durations shorter than BDu. Long-duration-pass and short-duration-pass neurons (23) were excluded from our data.

Data Acquisition and Processing. Before and after cortical stimulation, responses of a duration-tuned collicular neuron to tone bursts varied in duration or frequency were recorded, and data were stored on a computer hard drive for off-line analysis. Duration-response curves used for data analysis were stable throughout the 3-h-long data acquisition period, because curves changed by cortical stimulation returned to the control condition (e.g., Fig. 2), and because duration-response curves not changed by cortical stimulation did not show any change more than 1.5 h after stimulation (Fig. 3, x).

Off-line data processing included plotting duration- and frequency-response curves: arrays of peristimulus-time cumulative histograms displaying responses of a collicular neuron to an identical sound repeated 100 times (Fig. 2). Magnitude of auditory responses was expressed by number of impulses per 100 stimuli. BF and BDu were defined as the frequency and duration, respectively, to which response magnitude of a neuron was largest. Width of a duration-tuning curve was defined as the width at which response magnitude was 30% less than maximum.

Results

Of 636 collicular and 109 cortical neurons studied, 140 and 40, respectively, were duration-tuned neurons. Their BDus ranged between 1.5 and 18 ms. Short- and long-duration-pass neurons (23) were also found in the IC and AC. They were saved for our future research because they are less specialized for responding to specific durations than duration-tuned neurons (26). In a dorsoventral electrode penetration across the IC, two to four single duration-tuned neurons were recorded at different depths and were studied without moving the pair of cortical stimulating electrodes (Fig. 1). Electric stimulation of cortical duration-tuned neurons evoked four types of changes in collicular duration-tuned neurons: (*i*) sharpening of duration tuning without changing BDu. Sharpening is associated with an increase (augmentation) of the auditory response at the BF of a given neuron (10 neurons); (*ii*) broadening of duration tuning (28 neurons); (*iii*) lengthening of BDu (17 neurons); and (*iv*) shortening of BDu (16 neurons). These changes were most prominent immediately after a 30-min-long cortical stimulation and gradually disappeared within 3 h after stimulation. Therefore, the collicu-

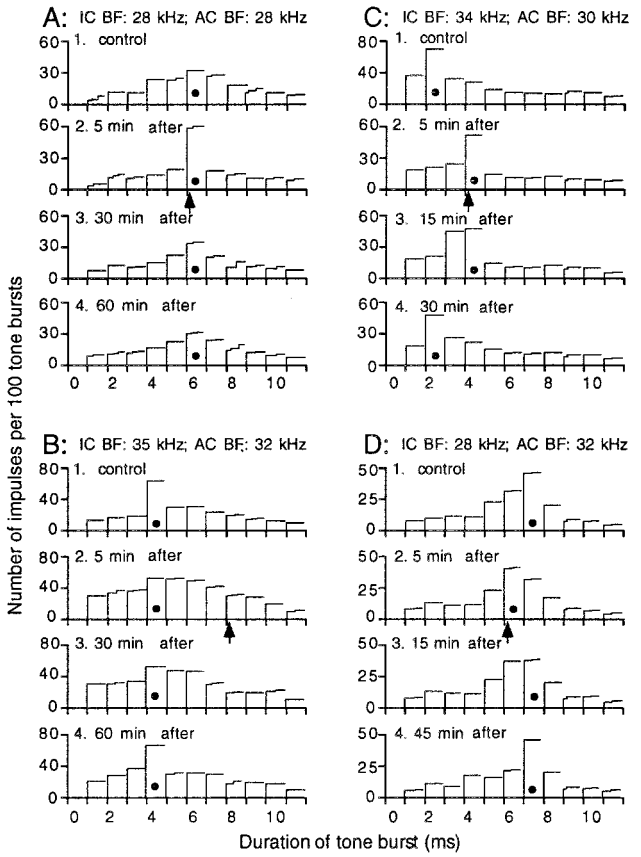

Fig. 2. Four types of changes in duration-response curves of collicular neurons (*A–D*) evoked by 30-min-long electric stimulation of cortical duration-tuned neurons. The stimulated cortical (AC) and recorded collicular neurons (IC) were ''matched'' (*A*) or ''unmatched'' (*B–D*) to each other in both BF and BDu. The filled circles and arrows indicate BDus of recorded collicular and stimulated cortical neurons, respectively. Their BFs are listed at the top of each panel. Cortical stimulation either sharpened (*A*), broadened (*B*), or shifted (*C* and *D*) duration-response curves. In *A–D*, *1–4*, respectively, show the array of peristimulus-time-cumulative histograms obtained before cortical stimulation, 5, 30 (or 15), and 60 (30 or 45) min after cessation of the cortical stimulation.

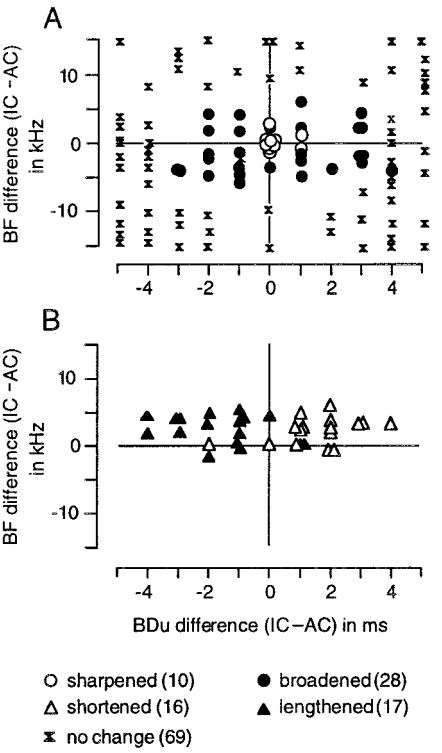

Fig. 3. Distributions of four types of changes in duration-response curves of collicular neurons evoked by cortical electric stimulation. The abscissae and ordinates, respectively, represent BDu and BF differences between recorded collicular (IC) and stimulated cortical (AC) neurons. (*A*) Sharpening (○) and broadening (●) in the duration-response curve. x, the neurons that changed neither width nor BDu. (*B*) Shortening (△) and lengthening (▲) in BDu.

lar changes were short-term. The remaining 69 collicular neurons showed no change in duration tuning.

In Fig. 2*A*, both recorded collicular and stimulated cortical neurons were tuned to 28.0 kHz and 6.0-ms duration (*A1*). They were ''matched'' to each other in BF and BDu. Stimulation of the cortical neurons augmented collicular response at 6.0-ms duration by 43%, but suppressed it at 5.0- and 7.0-ms durations by 39%. Therefore, the duration-response curve of the neuron became sharper (*A2*). In Fig. 2*B*, BF and BDu were 35.0 kHz and 4.0 ms, respectively, for the recorded collicular neuron (*B1*), and 32.0 kHz and 8.0 ms, respectively, for the stimulated cortical neurons. They were ''unmatched'' in both BF and BDu. Stimulation of the cortical neurons reduced the response of the collicular neuron at its BDu, and augmented responses at durations other than BDu. Accordingly, its duration-response curve became 300% broader in 30% width (*B2*). The changed curves shown in Fig. 2 *A2* and *B2* recovered ≈60 min after electric stimulation (Fig. 2 *A4* and *B4*).

In Fig. 2*C*, BF and BDu were 34.0 kHz and 2.0 ms, respectively, for the recorded collicular neuron (*C1*), and 30.0 kHz and 4.0 ms, respectively, for the stimulated cortical neurons. The neurons were unmatched in both BF and BDu. Stimulation of the cortical neurons reduced the response of the collicular neuron at 2.0-ms duration by 63% and increased the response at 4.0-ms duration by 108%, so that its BDu lengthened to 4.0 ms (*C2*). In Fig. 2*D*, BF and BDu were 28.0 kHz and 7.0 ms, respectively, for the recorded collicular neuron (*D1*), and 32.0 kHz and 6.0 ms, respectively, for the stimulated cortical neurons. Stimulation of the cortical neurons reduced the response of the collicular neuron at 7.0-ms duration by 39% and increased the response at 6.0-ms duration by 23% (*D2*). Accordingly, its BDu shortened to 6.0 ms. Shifted BDus in Fig. 2 *C2* and *D2* returned to the control BDus within 60 min after cortical stimulation (Fig. 2 *C4* and *D4*).

Sharpening of duration tuning accompanied with augmentation of the response at the BF was observed for 10 collicular neurons studied (Fig. 3*A*, open circles). The amounts of sharpening and augmentation were both 30 ± 8.0% (n = 10). Six of the ten neurons were matched in both BF and BDu, two were matched in BDu but unmatched in BF by 1 or 3 kHz, and the remaining two were unmatched in BDu by 1.0 ms and in BF by 1 kHz. Because sharpening accompanied with augmentation occurred in eight of ten collicular neurons matched in BDu with stimulated cortical neurons, this corticofugal modulation is specific to the matched neurons. Broadening of the duration-response curve was observed for 28 collicular neurons. Their BDus and BFs were, respectively, within ±4.0 ms and ±6.0 kHz of those of stimulated cortical neurons (Fig. 3*A*, filled circles).

Lengthening of BDu was observed for 17 collicular neurons. For 15 of the 17 collicular neurons, BDu was shorter than that of stimulated cortical neurons (Fig. 3*B*, filled triangles). Shortening of BDu was observed in 16 collicular neurons. For 14 of 16 collicular neurons, BDu was longer than that of stimulated cortical neurons (Fig. 3*B*, open triangles). These BDu shifts occurred when their BDus and BFs were, respectively, within

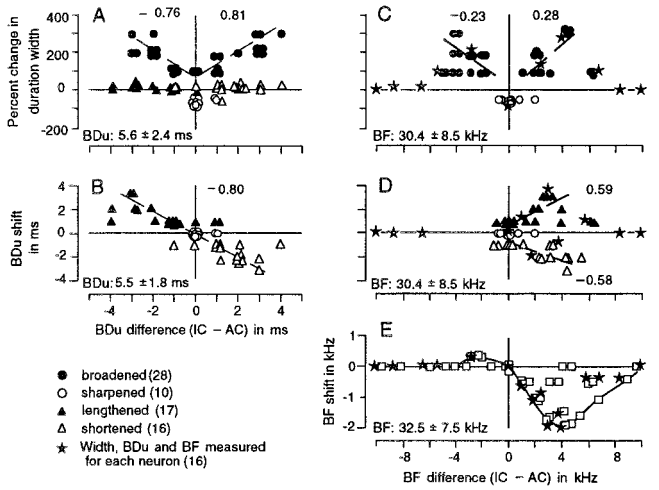

Fig. 4. Changes in width (*A* and *C*) and BDu (*B* and *D*) of duration-response curves of collicular neurons evoked by cortical electric stimulation. The amount of changes depend on BDu (*A* and *B*) and BF differences (*C* and *D*) between recorded collicular (IC) and stimulated cortical (AC) neurons. See Fig. 3 for symbols. *E* shows the BF shifts of collicular neurons evoked by cortical stimulation (17). Stars in *C–E* indicate changes or no changes in width, BDu and BF measured in each of 16 collicular neurons. The correlation coefficient (*r*) is shown above each regression line. Mean BDu or BF of stimulated cortical neurons is shown in each graph.

±4.0 ms and between −1.5 and 5.0 kHz of those of stimulated cortical neurons (Fig. 3*B*). Unlike broadening, most BDu shifts occurred for collicular BFs that were higher than the cortical BF.

The amount of broadening in duration-tuning curve related to the differences in both BDu (Fig. 4*A*, filled circles) and BF (Fig. 4*C*, filled circles) between stimulated cortical and recorded collicular neurons. The larger the BDu difference, the greater the broadening ($r = 0.81$ or -0.76). For large BF differences, broadening tended to be large ($r = 0.28$ or -0.23). Broadening was mainly due to a change in the tuning curve toward stimulated cortical BDu. The ratio between broadening toward and away from the cortical BDu was 2.80 ± 0.71 ($n = 28$). Mean and standard deviation of the increase in 30% width for 28 collicular neurons studied were 185 ± 67%. Of the 33 neurons showing BDu shift, 32 also showed slight broadening of a duration-tuning curve. The amount of broadening was 18 ± 8.5% in 30% width and was clearly different from that shown by the 28 neurons grouped as those showing broadening of a duration-tuning curve ($P < 0.0001$).

BDu shift toward cortical BDu is called "centripetal" BDu shift, whereas BDu shift away from cortical BDu is called "centrifugal" BDu shift (33). Centripetal and centrifugal BDu shifts were observed in 30 and 3 unmatched collicular neurons, respectively (Fig. 4*B*). Centripetal BDu shift occurred only for collicular BFs that were higher than the cortical BF (Fig. 4*D*). The amount of centripetal BDu shift depended on differences in both BDu (Fig. 4*B*, triangles) and BF (Fig. 4*D*, triangles) between recorded collicular and stimulated cortical neurons: the larger the BDu difference, the larger the BDu shift (Fig. 4*B*; $r = -0.80$), and the larger the BF difference, the larger the BDu shift (Fig. 4*D*; $r = 0.59$ or -0.58). Because the correlation between BDu difference and BDu shift is high ($r = -0.8$), corticofugal modulation is systematic for BDu shift.

In the big brown bat, BF shifts are asymmetrical and centripetal for BF differences (Fig. 4*E*). The largest BF shift occurs at ≈4 kHz above stimulated cortical BF (16, 17, 30, 34). The data shown in Fig. 4 *C* and *D* indicate that when the BFs of collicular duration-tuned neurons are slightly higher than those of stimulated cortical neurons, cortical stimulation evokes not only changes in duration tuning but also in frequency tuning. To substantiate this conclusion, changes in both duration- and frequency-response curves were measured for each of 16 collicular duration-tuned neurons. Of five collicular neurons showing broadening in duration-response curve, four showed centripetal BF shift (compare stars in Fig. 4*C* with those in Fig. 4*E*). Five collicular neurons showing BDu shift also showed centripetal BF shift. Their BFs were higher than cortical BF (compare stars in Fig. 4*D* with those in 4*E*). Of five collicular neurons showing neither broadening nor BDu shift, four showed no BF shift. The remaining one collicular neuron (matched neuron) showed no shift in BDu and BF, but sharpening in duration and frequency tuning. The corticofugal system apparently evoked centripetal reorganization in both frequency and duration domains. That is, it evoked multiparametric reorganization.

Discussion

Cortical Electric Stimulation for the Exploration of the Function of the Corticofugal System. The changes in collicular neurons evoked by focal electric stimulation of the AC last up to 3 h after the stimulation. Some neurophysiologists have been arguing that, because cortical electric stimulation is unnatural, the changes evoked by the electric stimulation is epiphenomena and even something pathologic, and that the short-term subcortical changes are insignificant and not at all related to normal brain function. This article reports the effects of cortical electric stimulation on collicular duration-tuned neurons. Therefore, we point out that there are many observations indicating that focal electric stimulation of the AC is an efficient and adequate method for the exploration of the function of the corticofugal system and that the collicular short-term changes are important for the production of long-term cortical changes. (*i*) Auditory fear conditioning evokes long-term cortical and short-term collicular changes (31). It, however, fails to evoke the collicular changes when the AC is inactivated by muscimol during the conditioning (30, 31). (*ii*) The conditioning evokes the collicular change even when the cortical change is abolished by atropine applied to the AC (32). Observations *i* and *ii* indicate that the corticofugal system evokes the collicular change with neither cortical electric stimulation nor the cortical change. (*iii*) The cortical long-term change, which would be evoked by the conditioning, is significantly reduced in amount and becomes short-term when the collicular change is abolished by atropine applied to the IC (32). This observation indicates that the collicular short-term change evoked by the corticofugal system plays an important role in producing the cortical long-term change. The cortical long-term change greatly depends on both the subcortical short-term change and an increase in acetylcholine level in the AC (31, 32). (*iv*) The collicular change evoked by cortical electric stimulation is very similar in amount and time course to that evoked by the conditioning (31). (*v*) Repetitive acoustic stimulation alone evokes a collicular change similar to that evoked by cortical electric stimulation (16, 17, 30). Observations *iv* and *v* indicate that the conditioning causes the collicular change by means of the corticofugal system, that the collicular change evoked by cortical electric stimulation is not epiphenomena, and that cortical electric stimulation is an adequate method for the exploration of the function of the corticofugal system. (*vi*) Auditory fear conditioning evokes plasticity of the frequency-tuning curves of cortical neurons in guinea pigs (35, 36). Cortical plasticity greatly depends on the activity of the cholinergic basal nucleus in the forebrain (see refs. 37 and 38 for review). Electric stimulation of the basal forebrain paired with tone bursts evokes BF shift of cortical auditory neurons in the guinea pig (39) and rat (40). In the big brown bat, both the cortical and collicular BF shifts evoked by electric stimulation of the AC are augmented by

electric stimulation of the basal forebrain,[†] as expected from the data obtained from the guinea pig and rat. This observation indicates that cortical electric stimulation is an adequate method to explore the function of the corticofugal system for plasticity of the central auditory system (see ref. 33 for review). In general, focal electric stimulation of the brain has contributed significantly to the understanding of brain function and functional neural connections in the brain (see ref. 41 for review). Therefore, the use of electric stimulation to explore the brain function has been well accepted.

Multiparametric Corticofugal Modulation. Animal sounds, including human speech sounds, are characterized by multiple acoustic parameters. If corticofugal modulation occurs only in the frequency domain, the improvement and adjustment (or reorganization) of the central auditory system for auditory signal processing would be partial. Our present data and those obtained by others indicate that corticofugal modulation simultaneously occurs in a specific way according to the relationship in tuning between stimulated cortical and recorded subcortical neurons for not only frequency (5, 6, 16, 17, 30–32) and duration (this article), but also for other parameters (13, 42) characterizing behaviorally relevant sounds. Therefore, corticofugal modulation is apparently ''multiparametric.''

This article indicates that cortical duration-tuned neurons modulate both duration and frequency tuning of collicular duration-tuned neurons, and that the modulation in duration tuning occurs only when the BF difference between paired recorded collicular and stimulated cortical neurons is smaller than 6 kHz. Why does corticofugal modulation of duration tuning occur only for the collicular duration-tuned neurons showing a BF difference less than 6 kHz? Different types of animal sounds and the different harmonics of an animal sound are characterized with different values of parameters, so that corticofugal modulation should not occur for all duration-tuned neurons regardless of their BFs, but only for those with BFs within a particular range of frequencies including the BF of activated cortical neurons. The BF difference of 6 kHz may be related to the fundamentals of sounds produced by the big brown bat. If the fundamentals of bat's sounds are higher than 6 kHz, a group of neurons responding to each harmonic in a complex sound will be separately modulated by the corticofugal system. This speculation remains to be tested by neuroethological studies.

If collicular and cortical neurons are tuned in three domains—the frequency, intensity, and time (duration and time interval) characterizing particular sounds or particular components of a complex sound—the cortical neurons may modulate the tunings of the collicular neurons in these three domains. This hypothesis is favored by the recent findings in mice by Yan and Ehret[‡] that the minimum threshold and the best frequency of collicular neurons are modulated by electric stimulation of cortical neurons. The shifts in BF and minimum threshold both are centripetal and systematic: the larger the difference in BF or minimum threshold, the larger the shift. Multiparametric corticofugal modulation, which remains to be examined further, must play an important role in auditory information processing and reorganization of the central auditory system.

Specific and Systematic Corticofugal Modulations and Neural Maps. Corticofugal modulation of the frequency tuning of subcortical neurons is highly specific and systematic (5, 6, 16, 30). One may have no problem in accepting this finding because the auditory system is tonotopically organized. However, one may have a problem in accepting specific and systematic corticofugal modulation of duration tuning, because no duration map for systematic representation of durations has been found (20, 22, 23). Therefore, an intriguing problem is how the corticofugal system can modulate subcortical duration-tuned neurons in a highly specific and systematic way without the duration map.

In the mustached bat, echo delay is systematically mapped in the FM-FM area of the AC (7, 43). The medial geniculate body (9) and IC (12) seem to have a delay map. However, a recent study failed to find the delay map in the IC (44). Corticofugal modulation of delay tuning of collicular and thalamic neurons is highly specific and systematic (13). Therefore, how the corticofugal system performs the specific and systematic modulation of collicular delay tuning is also an intriguing problem.

It has been physiologically demonstrated that the IC of the big brown bat has an array of neurons tuned to different values of durations (22). One may consider that such an array is created by the neural mechanisms based on some sort of anatomical and/or physiological gradients along iso-BF laminae in the IC and that a duration map emerges as a consequence of the mechanisms. If a lack of a map in the IC and AC means that collicular neurons tuned to different values of durations are randomly produced in the IC and that cortical neurons tuned to them also randomly exist in the AC, a neural net for specific and systematic corticofugal modulation will be difficult to imagine. Corticofugal modulation of duration tuning, as well as delay tuning, thus raises a question of how the IC is actually organized for the representation of durations or delays.

In the past, auditory physiology has given a wrong conclusion: a large number of single-unit data sampled from the ACs of several cats indicated that there was no tonotopic (i.e., frequency) map in the AC (45). Therefore, one should be cautious not to easily accept a negative conclusion that there is no duration or delay map.

Functional Significance of Corticofugal Modulation of Duration Tuning. We found four types of corticofugal modulations of duration tuning: sharpening of duration tuning, broadening of duration tuning, lengthening of BDu, and shortening of BDu. What kind of advantage in auditory signal processing results from these modulations? Sharpening of duration tuning accompanied with the augmentation of the response at the BF occurs only in matched collicular neurons. Such modulation would make them respond more selectively and strongly to a sound with a particular duration represented by activated cortical neurons. Broadening of duration tuning of unmatched collicular neurons occurs mostly toward the BDu of activated cortical neurons. Such modulation would make them respond more strongly to a sound with the particular duration. Two types of BDu shifts, lengthening and shortening, may be put into one type, centripetal BDu shift. Centripetal BDu shift of unmatched collicular neurons would increase the number of duration-tuned neurons responding strongly to a sound with the particular duration. Therefore, one of the functions of corticofugal modulation of duration would be the improvement of the subcortical processing of an auditory signal that repetitively excites cortical duration-tuned neurons. In other words, one of the functions of the corticofugal system is to improve the input of cortical neurons.

Broadening of duration tuning occurred for collicular neurons whose BFs were within a range from −6 kHz to +6 kHz relative to the BF of activated cortical neurons, whereas centripetal BDu shift occurred for collicular neurons whose BFs were within a range from −1.5 kHz to +5 kHz relative to the cortical BF. There is no explanation about why these two types of modulations occur and why the BF difference related to the modulation of duration tuning is different between the neurons showing broadening or BDu shift.

[†]Ma, X. & Suga, N. (2000) *Soc. Neurosci. Abstr.* **26,** 1475.

[‡]Yan, J. & Ehret, G. (2001) *Int. Congr. Neuroethology Abstr.*, 151.

Importance of Short-Term Collicular Modulation in Evoking Long-Term Cortical Modulation. Corticofugal modulation of collicular duration tuning is short-term as that of frequency tuning (refs. 5, 16, 17, and 30–32; see ref. 33 for review) and delay tuning (13). As described in this article, duration-tuned neurons are corticofugally modulated not only in duration tuning, but also in frequency tuning. Therefore, we may propose a hypothesis by using the findings made about corticofugal modulation of frequency tuning (refs. 30–32; see ref. 33 for review). Namely, as in frequency tuning, the short-term subcortical changes in duration tuning evoked by the corticofugal system and an increase in the cortical acetylcholine level are both essential for the production of the cortical long-term changes in duration tuning that would be caused by auditory conditioning (associative learning). Thus, the short-term collicular modulation of duration tuning plays an important role in creating memory for improved auditory signal processing in the time domain as well as in the frequency domain. Weinberger (46) stated that "physiological memory is enduring neuronal change sufficiently specific to represent learned information" and hypothesized that "physiological memory in the auditory cortex is not procedural memory, i.e., is not tied to any behavioral conditioned responses, but can be used flexibly." We completely agree with his definition and hypothesis of physiological memory.

Corticofugal Modulation in Bats and Non-Bat Species. Corticofugal reorganization of the subcortical auditory nuclei has been studied only in bats. One may wonder whether auditory neural mechanisms found in bats are relevant to those operating in non-bat species. Duration-tuned neurons adapted for processing behaviorally relevant sounds in bats (20–23) have also been found in several other species of animals (24–29). Many other types of auditory neurons found in bats have also been found in non-bat species (see ref. 18 for review). In the visual (47, 48) and somatosensory systems (49, 50), the corticofugal system modulates thalamic neurons in a specific way and is involved in reorganization. Comparative neurophysiology and neuroanatomy suggest that the basic function of the corticofugal system found in bats is shared with different species of animals and with different sensory systems, although certain differences in corticofugal reorganization of the AC have been found between different species of mammals and between specialized and nonspecialized cortical areas of an identical species (51).

We thank J. H. Casseday, A. S. Feng, and J. H. Kaas for their comments on this paper and N. Laleman for editing this paper. This work was supported by National Institute on Deafness and Other Communication Disorders Grant DC 00175.

1. Kelly, J. P. & Wong, D. (1981) *Brain Res.* **212,** 1–15.
2. Saldana, E., Feliciano, M. & Mugnaini, E. (1996) *J. Comp. Neurol.* **371,** 15–40.
3. Huffman, R. F. & Henson, O. W., Jr. (1990) *Brain Res. Rev.* **15,** 295–323.
4. Malmierca, M. S., Le Beau, F. E. N. & Rees, A. (1996) *Hear. Res.* **93,** 167–180.
5. Zhang, Y. & Suga, N. (2000) *J. Neurophysiol.* **84,** 325–333.
6. Zhang, Y., Suga, N. & Yan, J. (1997) *Nature (London)* **387,** 900–903.
7. Suga, N. & O'Neill, W. E. (1979) *Science* **206,** 351–353.
8. O'Neill, W. E. & Suga, N. (1979) *Science* **203,** 69–73.
9. Olsen, J. F. & Suga, N. (1991) *J. Neurophysiol.* **65,** 1275–1296.
10. Wenstrup, J. J. & Grose, C. D. (1995) *J. Neurosci.* **15,** 4693–4711.
11. Mittmann, D. H. & Wenstrup, J. (1995) *Hear. Res.* **90,** 185–191.
12. Yan, J. & Suga, N. (1996) *Hear. Res.* **93,** 102–110.
13. Yan, J. & Suga, N. (1996) *Science* **273,** 1100–1103.
14. Jen, P. H. S., Chen, Q. C. & Sun, X. D. (1998) *J. Comp. Physiol. A* **183,** 683–697.
15. Sun, X., Jen, P. H. S., Sun, D. & Zhang, S. (1989) *Brain Res.* **495,** 1–8.
16. Yan, W. & Suga, N. (1998) *Nat. Neurosci.* **1,** 54–58.
17. Ma, X. & Suga, N. (2001) *J. Neurophysiol.* **85,** 1078–1087.
18. Suga, N. (1988) *Auditory Function*, eds. Edelman, G. M., Gall, W. E. & Cowan, W. M. (Wiley, New York), pp. 679–720.
19. Covey, E. & Casseday, J. H. (1999) *Annu. Rev. Physiol.* **61,** 457–476.
20. Pinheiro, A. D., Wu, M. & Jen, P. H. S. (1991) *J. Comp. Physiol. A* **169,** 69–85.
21. Casseday, J. H., Ehrlich, D. & Covey, E. (1994) *Science* **264,** 847–850.
22. Ehrlich, D., Casseday, J. H. & Covey, E. (1997) *J. Neurophysiol.* **77,** 2360–2372.
23. Galazyuk, A. V. & Feng, A. S. (1997) *J. Comp. Physiol. A* **180,** 301–311.
24. He, J., Hashikawa, T., Ojima, H. & Kinouchi, Y. (1997) *J. Neurosci.* **17,** 2615–2625.
25. Chen, G. D. (1998) *Hear. Res.* **122,** 142–150.
26. Brand, A., Urban, R. & Grothe, B. (2000) *J. Neurophysiol.* **84,** 1790–1799.
27. Feng, A. S., Hall, J. C. & Gooler, D. M. (1990) *Prog. Neurobiol.* **34,** 313–329.
28. Gooler, D. M. & Feng, A. S. (1992) *J. Neurophysiol.* **67,** 1–22.
29. Potter, H. D. (1965) *J. Neurophysiol.* **28,** 1155–1184.
30. Gao, E. & Suga, N. (1998) *Proc. Natl. Acad. Sci. USA* **95,** 12663–12670.
31. Gao, E. & Suga, N. (2000) *Proc. Natl. Acad. Sci. USA* **97,** 8081–8086.
32. Ji, W., Gao, E. & Suga, N. (2001) *J. Neurophysiol.* **86,** 211–225.
33. Suga, N., Gao, E., Zhang, Y., Ma, X. & Olsen, J. F. (2000) *Proc. Natl. Acad. Sci. USA* **97,** 11807–11814.
34. Chowdhury, S. A. & Suga, N. (2000) *J. Neurophysiol.* **83,** 1856–1863.
35. Bakin, J. S. & Weinberger, N. M. (1990) *Brain Res.* **536,** 271–286.
36. Edeline, J. M., Pham, P. & Weinberger, N. M. (1993) *Behav. Neurosci.* **107,** 539–551.
37. Weinberger, N. M. (1995) *Annu. Rev. Neurosci.* **18,** 129–158.
38. Rasmusson, D. D. (2000) *Behav. Brain Res.* **115,** 205–218.
39. Bakin, J. S. & Weinberger N. M. (1996) *Proc. Natl. Acad. Sci. USA* **93,** 11219–11224.
40. Kilgard, M. P. & Merzenich, M. M. (1998) *Science* **279,** 1714–1718.
41. Parker, A. J. & Newsome, W. T. (1998) *Annu. Rev. Neurosci.* **21,** 227–277.
42. Yan, J. & Suga, N. (1999) *J. Neurophysiol.* **81,** 817–824.
43. O'Neill, W. E. & Suga, N. (1982) *J. Neurosci.* **2,** 17–31.
44. Portfors, C. V. & Wenstrup, J. J. (2001) *Hear. Res.* **151,** 95–105.
45. Evans, E. F., Ross, H. F. & Whitfield, I. C. (1965) *J. Physiol.* **179,** 238–247.
46. Weinberger, N. M. (1998) *Neurobiol. Learn. Mem*. **70,** 226–251.
47. Murphy, P. C., Duckett, S. G. & Sillito, A. M. (1999) *Science* **286,** 1552–1554.
48. Sillito, A. M., Jones, H. E., Gerstein, G. L. & West, D. C. (1994) *Nature (London)* **369,** 479–482.
49. Ergenzinger, E. R., Glasier, M. M., Hahm, J. O. & Pons, T. P. (1998) *Nat. Neurosci*. **1,** 226–229.
50. Krupa, D. J., Ghazanfar, A. A. & Nicolelis, M. A. (1999) *Proc. Natl. Acad. Sci. USA* **96,** 8200–8205.
51. Sakai, M. & Suga, N. (2001) *Proc. Natl. Acad. Sci. USA* **98,** 3507–3512. (First Published March 6, 2001; 10.1073/pnas.061021698)