Thus, all three PTKs contribute to the enhanced tyrosine phosphorylation in irradiated DT-40 lymphoma B cells. Ionizing radiation or H_2O_2 do not have a direct activation effect on any of these three PTKs immunoprecipitated from DT-40 cells. Thus, radiation or H_2O_2 activation of BTK is mediated by as yet unknown mechanisms (*17*).
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29. Mutations in the human *btk* cDNA were introduced by polymerase chain reaction through use of Pfu polymerase (Strategene) and confirmed by sequencing. Wild-type and mutant *btk* cDNAs were subcloned into pApuro expression vector [M. Takata *et al.*, *EMBO J.* **13**, 1341 (1994)] and electroporated into BTK-deficient cells.
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38. Supported by National Institutes of Health grants R01-CA-42111 and R01-CA-42633. F.M.U. is a Stohlman Scholar of the Leukemia Society of America.

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Corticofugal Modulation of Time-Domain Processing of Biosonar Information in Bats

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The Jamaican mustached bat has delay-tuned neurons in the inferior colliculus, medial geniculate body, and auditory cortex. The responses of these neurons to an echo are facilitated by a biosonar pulse emitted by the bat when the echo returns with a particular delay from a target located at a particular distance. Electrical stimulation of cortical delay-tuned neurons increases the delay-tuned responses of collicular neurons tuned to the same echo delay as the cortical neurons and decreases those of collicular neurons tuned to different echo delays. Cortical neurons improve information processing in the inferior colliculus by way of the corticocollicular projection.

The processing of auditory information has been considered to be based on neural interactions occurring within the ascending auditory system (*1*). The contribution of the massive corticofugal system to auditory information processing has been given little consideration. Neurons in the deep layers of the auditory cortex (AC) project to the inferior colliculus (IC), the medial geniculate body (MGB) (*2–4*), or the subcollicular auditory nuclei (*5*). The corticofugal projections originating from the low- and high-frequency–tuned regions of the AC terminate at the low- and high-frequency–tuned regions of the MGB and IC, respectively (*3*). Electrical stimulation of the AC can inhibit or facilitate the auditory responses of neurons in the IC (*6–8*) and MGB (*6*, *9*). However, the response properties of neurons at the stimulation and recording sites were not examined in these studies. Therefore, it is not known how the inhibition and facilitation evoked by electrical stimulation contribute to auditory information processing.

In the visual system, however, an important functional role of the corticofugal projection in processing visual images has recently been identified. Through the corticothalamic projection, cortical visual neurons tuned to a particular orientation of a moving contour synchronize activities of thalamic visual neurons having receptive fields that are aligned appropriately to signal that particular orientation of a moving contour. This synchronized activity is hypothesized to facilitate the detection of the stimulus feature by the cortical visual neurons (*10*). Because corticofugal projections are part of the neural net shared by the auditory, visual, and somatosensory systems, the corticofugal projections in the auditory system presumably have a function similar to that of those found in the visual system.

The central auditory system of the Jamaican mustached bat (*Pteronotus parnellii parnellii*) is highly developed for processing different types of biosonar information in a parallel and hierarchical way. Its auditory cortex consists of many functional areas (*1*). Among these areas, the FM-FM area (FM, frequency-modulated) is particularly interesting because it has a map for a systematic representation of echo delays corresponding to target distances. Therefore, we studied the functional role of the corticofugal projections in the processing

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of target distance information.

The mustached bat emits orientation sounds (biosonar "pulses"). Each pulse consists of constant frequency (CF) and FM components (Fig. 1A). The CF and FM sounds are suited for measurements of target velocities and distances, respectively. Therefore, velocity information is carried by a difference in frequency between the pulse CF and echo CF components (that is, the Doppler shift), whereas distance information is carried by a delay of the echo FM components from the pulse FM components (that is, the echo delay). Echo delay is encoded by delay-tuned neurons, called FM-FM neurons in the IC, MGB, and AC. The responses of these neurons to an echo FM_n component (where n = 2, 3, or 4) are facilitated by the pulse FM_1 emitted by the bat when the echo FM_n returns from a target at a particular distance, that is, with a particular delay (*1*). The response properties of these neurons are most likely to be first created in the IC (*11–13*). Collicular FM-FM neurons project to the MGB, whereas thalamic FM-FM neurons project to the FM-FM area in the AC (*14*). Thalamic and cortical FM-FM neurons show stronger facilitative responses to pulse-echo pairs and sharper delay tuning curves than do collicular FM-FM neurons (*12, 13*). In the IC (*13*), MGB (*14*), and AC (*15*), FM-FM neurons form delay maps for the systematic representation of echo delays. Because a delay map does not exist in the auditory periphery and the subcollicular nuclei, the corticofugal influences on collicular FM-FM neurons reported here are not due to changes in the subcollicular nuclei and the periphery, but rather to changes in the IC.

Neural responses to acoustic stimuli were recorded from five mustached bats. The animal preparation, acoustic stimulation, and recording of action potentials were the same as those previously described (*13, 16*). Response properties of single neurons were first studied with the pulse (P) and echo (E) stimuli, which mimicked the essential components (FM_1 and FM_n) of the biosonar pulse and its echo (*17*). Then the responses of the neurons were studied with a computer-controlled acoustic stimulus, called a delay scan, which consisted of 13 time blocks (Fig. 2).

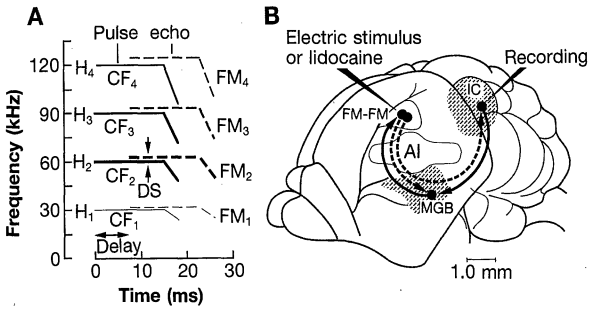

Fig. 1. (**A**) Schematized sound spectrogram of a mustached bat biosonar "pulse" (solid lines) and its Doppler-shifted (DS) echo (dashed lines), delayed 7.5 ms from the pulse. The pulse contains four harmonics (H_1 through H_4). Each harmonic consists of a long CF component and a short FM component. Therefore, each pulse consists of eight components, CF_1 through CF_4 and FM_1 through FM_4. The neurons described here were sensitive to a combination of pulse FM_1 and echo FM_n (where n = 2, 3, or 4). (**B**) A dorsolateral view of the bat brain from the left side. The FM-FM area is located anterodorsal to the primary auditory cortex (AI). The ascending and descending connections among the FM-FM area, medial geniculate body (MGB), and inferior colliculus (IC) are indicated by the solid and dashed arrows, respectively. Auditory responses were recorded from single FM-FM neurons in the IC before, during, and after activation or inactivation of cortical neurons in the FM-FM area.

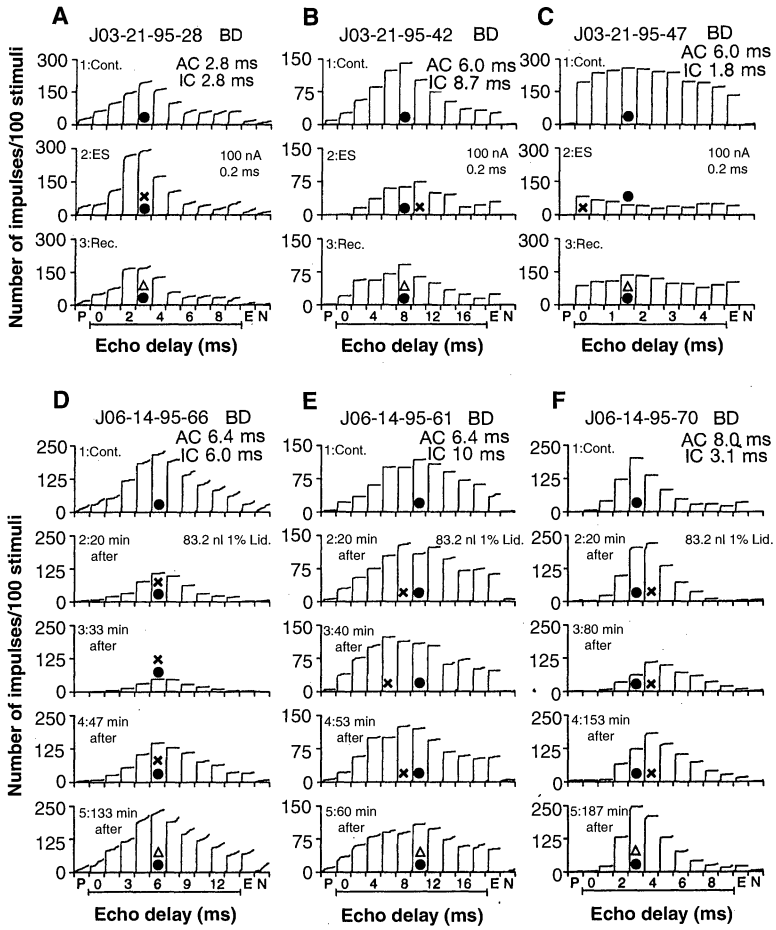

Fig. 2. Activation by electrical stimulation (**A** to **C**) or inactivation by lidocaine (**D** to **F**) of cortical FM-FM neurons modulates the auditory responses of collicular FM-FM neurons. Acoustic stimuli (delay scan) consisted of 13 time blocks. The duration of each block was 150 ms and was repeated at a rate of 6.7 per second. A 3.0-ms-long pulse (P) stimulus was delivered alone in the first block. A 3.0-ms-long echo (E) stimulus was delivered alone in the twelfth block. A P-E pair was delivered in each of the second to eleventh blocks, for which an echo delay was varied from $0\Delta t$ to $9\Delta t$. Δt was set at between 0.25 and 4.0 ms, depending on the best delay (BD) of E from P to excite a given collicular FM-FM neuron. No acoustic stimulus (N) was delivered in the thirteenth block so that background discharges could be counted. The P and E stimuli in the delay scan were FM sounds simulating the FM components of the species-specific biosonar pulse and its echo, respectively (Fig. 1A) (*17*). An identical delay scan was delivered 200 times. The auditory responses to these stimuli are displayed as peri-stimulus-time cumulative (PSTC) histograms. The BDs for collicular (IC) FM-FM neurons are identical (A and D), longer (B and E), or shorter (C and F) than those for cortical (AC) FM-FM neurons. The BDs of cortical and collicular FM-FM neurons are listed at the upper right corner of each panel. Cont., control data obtained immediately before electrical stimulation (ES) or lidocaine (Lid.) application; Rec., recovery data obtained after ES or lidocaine application. The filled circles, crosses, and open triangles indicate BDs before, during, and after ES or lidocaine application, respectively. The electrical stimulation was 100 nA, with a 0.2-ms single electric pulse synchronized with the P stimulus. Lidocaine applied was 1.0%, 83.2 ml.

Best delays (BDs) of multiple neurons were measured at four locations in the FM-FM area of the AC before activation with an electrical stimulus or inactivation with lidocaine (local anesthetic) of cortical FM-FM neurons (Fig. 1B). To activate cortical FM-FM neurons at a particular site in the delay map, we inserted a pair of tungsten wire electrodes (tip diameter, 10 μm) into the AC at one of the four cortical locations. An electrical stimulus was delivered through these electrodes 2.1 ms before the arrival of each P stimulus at the bat's ears (*18*). To inactivate cortical FM-FM neurons at a particular site, we inserted a glass pipette (tip diameter, 15 μm) filled with lidocaine solution into the AC at one of the four cortical locations (*19*). The responses of single neurons to delay scans were recorded from the central nucleus of the IC with a tungsten wire electrode (tip diameter, 6 to 8 μm) before, during, and after the electrical stimulation or lidocaine application (*20*).

FM-FM neurons recorded from the IC or AC usually responded poorly to a P stimulus (FM_1) and to an E stimulus (FM_n). They showed the best facilitative response to a P-E pair with a particular echo (FM_n) delay. The BDs of these neurons ranged from 1.8 to 13.2 ms. Three types of cortical and collicular FM-FM neurons were recorded: FM_1-FM_2, FM_1-FM_3, and FM_1-FM_4 (*13*, *15*, *16*). The effect of the activation or inactivation of cortical FM-FM neurons was studied on 31 and 18 collicular FM-FM neurons, respectively.

Electrical stimuli delivered to cortical FM-FM neurons increased the response to a P-E pair (hereafter called the auditory response) of collicular FM-FM neurons that had the same BD (within ±0.4 ms) as that of the cortical neurons (hereafter called "matched" collicular neurons) (Fig. 2A). The increase in the auditory response ranged from 11% to 192% of the control (47.5 ± 66.5%, N = 6; Fig. 3A, open circles). In contrast, electrical stimulation of cortical FM-FM neurons reduced the auditory responses of most collicular FM-FM neurons (20 of 25) that had a BD different from that of the cortical neurons (hereafter called "unmatched" collicular neurons) (Fig. 2, B and C). The decrease in auditory response ranged from 8% to 86% of the control (37.6 ± 24.4%, N = 20; Fig. 3A). However, some collicular neurons (5 of 25) showed an 8% to 29% increase in auditory response to unmatched cortical stimulation (18.9 ± 12.0%, N = 5; Fig. 3A). The mean change in response for all 25 neurons studied was −25.3 ± 31.8%. After the 2200 electrical stimuli delivered over 6.7 min, collicular neurons slowly recovered their responses over 34 to 87 min.

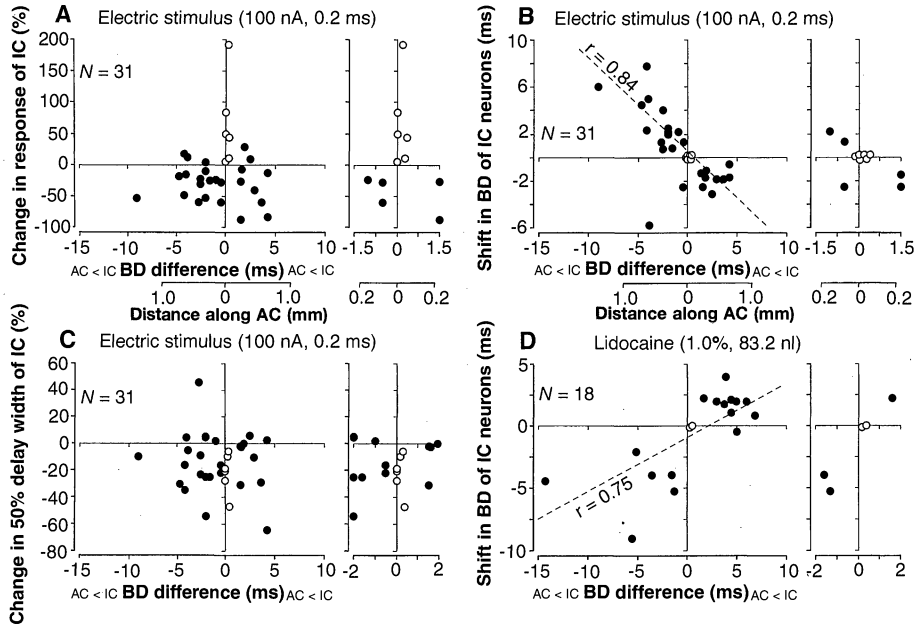

Fig. 3. Changes in response magnitude (**A**), BD (**B**), and 50% delay width (**C**) of collicular FM-FM neurons evoked by the electric stimulation of cortical FM-FM neurons. Changes in best delay (BD) of collicular neurons evoked by a lidocaine application to cortical FM-FM neurons are shown in (**D**). The abscissa represents the differences in BD between collicular (IC) and cortical FM-FM neurons (AC) paired for the experiments. The open circles represent the collicular neurons, which showed no shift in BD upon cortical electric stimulation or lidocaine application. In each panel, the right graph shows the data at and around 0 BD difference on the expanded abscissa. Because the FM-FM area has an echo-delay axis, the difference in BD values between collicular and cortical FM-FM neurons paired for the experiments can be expressed as a distance (millimeters) along the echo-delay axis, which is shown at the bottom of (A) and (B); *r*, correlation coefficient.

Changes in response magnitude were always associated with changes in BD, sharpness of a delay tuning curve, or both. In Fig. 2A, for example, the cortical stimulation sharpened the delay tuning of the matched collicular neuron without shifting its BD. This sharpening was due to an increase in auditory response at the BD and no change or a decrease in auditory responses around the BD.

In contrast, cortical stimulation reduced the auditory responses of unmatched collicular neurons at all echo delays and shifted their BDs in an orderly way: the BDs shifted toward longer echo delays after activation at shorter cortical BDs (Fig. 2B), but toward shorter echo delays after activation at longer cortical BDs (Fig. 2C). The shifts were due to a nonuniform decrease in response over different echo delays. The shift in collicular BD is linearly related to the difference between collicular and cortical BDs—a 0.76-ms BD shift per millisecond in BD difference (Fig. 3B). All six matched collicular neurons showed no shift in BD. Shifts in BD of unmatched collicular neurons occurred even when a BD difference was 9 ms. This large BD difference corresponds to a distance of ~1.4 mm along the delay axis in the FM-FM area, which is ~1.6 mm long (*21*). Therefore, it appears that neurons in the FM-FM area have an inhibitory influence on all unmatched collicular FM-FM neurons (*4*). This inhibitory influence is specific to the FM-FM area, because electrical stimulation of cortical areas just outside of the FM-FM area had no effect on collicular FM-FM neurons. Electrical stimulation of the cortical FM-FM area changed the sharpness of the delay tuning curves of almost all matched and unmatched collicular neurons (Fig. 3C). The changes in 50% delay width (*22*) for 30 neurons ranged between 5.9 and −64.2%, except for one which was 46.1%. The mean change was −14.6 ± 20.8% (N = 31). Therefore, the electrical stimulation of cortical neurons typically sharpened the collicular delay tuning.

As described above, cortical neurons facilitate the auditory responses of matched collicular neurons without changing their BDs. Cortical neurons also inhibit the auditory responses of unmatched collicular neurons and shift their BDs and sharpen the delay tuning curves of most collicular neurons, regardless of their BDs. Electrical stimulation of cortical neurons on collicular neurons has long-term effects (*4*).

Cortical FM-FM neurons tuned to a particular BD form a slab approximately 20 μm wide, 1000 μm long, and 900 μm thick. The slab stretches ventral to dorsal across three subdivisions of the FM-FM area: FM_1-FM_2, FM_1-FM_4, and FM_1-FM_3 (*15*, *21*). Therefore, each iso-BD slab also consists of three subdivisions. Electrical stimulation applied to different subdivisions along this 1000-μm-long

iso-BD slab evoked similar changes in the auditory responses of collicular neurons, regardless of whether harmonic combination sensitivity was matched between collicular and cortical neurons. Therefore, the critical factor for the functional descending connection between cortical and collicular FM-FM neurons is BD, not harmonic combination sensitivity.

In the FM-FM area of the Jamaican mustached bat, BD changes at a rate of 130 μs per 20-μm-wide iso-BD slab along the delay axis (*21*). Facilitation of auditory responses of collicular neurons evoked by matched cortical neurons can be overcome by inhibition evoked by many unmatched cortical neurons (*12*). Therefore, it is most likely that the electrical stimulus applied to the AC excited neurons within a radius of ~60 μm (three slabs wide) and that single collicular neurons received a facilitative influence from neurons in one cortical slab.

Inactivation of cortical FM-FM neurons with lidocaine produced an effect on collicular FM-FM neurons opposite that produced by electrical stimulation. Specifically, lidocaine applied to cortical neurons (N = 2 sites) reduced the auditory responses of matched collicular neurons by ~62% and broadened delay tuning curves by ~16% (Fig. 2D). On the other hand, it either augmented the auditory responses of unmatched collicular neurons (N = 2; Fig. 2E) or augmented those only in the initial 5 to 15 min and then suppressed those (N = 8; Fig. 2F) or suppressed those without initial augmentation (N = 6). The amount of lidocaine-induced suppression, measured at its peak, ranged between 6% and 93% of the control (52.9 ± 28.8%, N = 16). If the corticocollicular fibers were completely inactivated, the auditory response of collicular neurons might be as small as 10% of the control. Lidocaine suppressed not only the auditory responses, but also the background discharges of collicular neurons. Therefore, the corticocollicular fibers have a tonic excitatory influence on collicular neurons.

Inactivation of cortical neurons shifted the BDs of all 16 unmatched collicular neurons except one: BDs shifted toward shorter echo delays after inactivation at shorter cortical BDs (Fig. 2E), but toward longer echo delays after inactivation at longer cortical BDs (Fig. 2F). The data shown in Fig. 3D were obtained 30 to 60 min after a lidocaine application. The slope of the regression line is 0.47. Lidocaine application to cortical neurons slightly broadened (23.4 ± 47.8%, N = 18) the delay tuning curves of most collicular neurons regardless of differences in BD between cortical and collicular neurons. Therefore, the response properties of collicular FM-FM neurons are shaped by the corticocollicular projection. Those of cortical FM-FM neurons are also shaped accordingly.

Although electrical stimulation of the AC evokes an unnatural excitation of a small cluster of cortical neurons, our data indicate that the corticocollicular projection is incorporated with neural circuits for sharply focused excitation and widely spread inhibition. Lidocaine applied to the AC evokes unnatural inactivation of a small cluster of cortical neurons. However, our data indicate that the auditory response and delay tuning of collicular neurons are weak and broad, respectively, in the absence of corticocollicular activities. When a particular acoustic signal is received by an animal, cortical neurons maximally excited by that signal increase the responses and selectivity of matched collicular neurons to the signal (*23*). In addition, these cortical neurons decrease the response and selectivity of unmatched collicular neurons to the signal. We name this feature-specific effect of cortical neurons on the ascending pathway "egocentric selection." Under natural conditions, acoustic signals received vary with time so that all cortical neurons tuned to particular acoustic parameters are probably in a semi-steady state. When an identical signal is frequently received by the animal, the egocentric selection will enhance the neural representation of this frequently occurring signal in the IC, MGB, and AC. Therefore, we hypothesize that egocentric selection is involved in the adjustment to long-term changes in the overall functional organization of the IC, MGB, and AC (*24*).

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4. Corticocollicular fibers directly terminate at all three subdivisions of the IC: the central, external, and dorsal nuclei in rats [E. Carrascal *et al.*, *Soc. Neurosci. Abstr.* **17**, 305 (1991); E. Saldana *et al.*, *J. Comp. Neurol.* **371**, 15 (1996)], guinea pigs [M. Feliciano and S. Polashner, *J. Neurochem.* **65**, 1348 (1995)], and monkeys [L. E. Leutheke *et al.*, *J. Comp. Neurol.* **285**, 487 (1989); A. Morel and J. H. Kaas, *ibid.* **318**, 27 (1992)]. Electrical stimulation of the AC evokes excitatory or inhibitory postsynaptic potentials or both in collicular neurons in the central nucleus of the IC (*7*). The neural circuits mediating these synaptic potentials remain to be studied. It is likely that the excitation is directly evoked by corticocollicular fibers and that inhibition is polysynaptically evoked through neurons in the IC that contain GABA (γ-aminobutyric acid) [(*7*); M. Vater *et al.*, *J. Comp. Neurol.* **325**, 183 (1992)]. Alternatively, inhibition may occur within the cortex to reduce the excitatory effect of the corticocollicular fibers on IC neurons.
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17. The frequencies of FM sounds were swept downward linearly with time by 6.0, 12, 18, and 24 kHz to generate the FM_1, FM_2, FM_3, and FM_4 sounds, respectively. The initial frequencies of these FM sounds were approximately 30, 60, 90, and 120 kHz, respectively. The duration and rise-decay time of the FM sounds were 3.0 and 0.5 ms, respectively. Acoustic stimuli were delivered from a condenser loudspeaker placed 72.4 cm in front of the bat's ears in an echo-attenuated soundproof chamber. The parameters of individual FM sounds and the time interval between paired sounds (hereafter called the echo delay) were manually varied to initially determine the best FM frequencies and best amplitudes of the FM sounds and the best delay (BD) to excite a neuron (*15, 16*). Then, the paired FM stimuli were fixed at the best FM frequencies and best amplitudes of the neuron, and echo delay was varied with a computer program.
18. For electrical stimulation, a tungsten wire electrode (negative pole) was placed at a depth of 600 to 700 μm from the cortical surface and another (positive pole) was placed on the cortical surface just above the negative pole. The thickness of the FM-FM area was ~900 μm. The BD of multiple neurons was again measured. Then, an electrical stimulus (100 nA, 0.2 ms) was delivered through these electrodes synchronously with each pulse stimulus in a delay scan; that is, the electrical stimulus was repeated every 150 ms, 11 times in each delay scan.
19. Two injections of 41.6 nl of 1.0% lidocaine solution were made at a depth of 600 to 700 μm with a mechanical microinjection unit (Picospritzer II, General Value Corp., Fairfield, NJ). Each injection lasted 700 ms and was separated by 1 s.
20. The change in auditory response during the 6.7-min period of electrical stimulation was small and was often obscured by the stimulus artifact. Therefore, all the data described in this paper were obtained after the termination of the electrical stimulus.
21. N. Suga and J. Horikawa, *J. Neurophysiol.* **55**, 776 (1986).
22. A 50% delay width is the width of a delay tuning curve at 50% of the maximum response (*21*).
23. This positive feedback mediated by cortical auditory neurons is similar to that mediated by cortical visual neurons. However, synchronized oscillatory discharges mediated by the corticofugal fibers appeared to be very rare and weak in the auditory system, because cortical FM-FM neurons show almost no oscillatory discharges [J. Horikawa *et al.*, *Hear. Res.* **76**, 45 (1994)].
24. It has been demonstrated that changes in sensory input evoke changes in cortical sensory maps [M. M. Merzenich *et al.*, *J. Comp. Neurol.* **224**, 591 (1984)].

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